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Nasal mucoadhesive in situ gelling liquid crystalline fluid precursor system of polyene antibiotic for potential treatment of localized sinuses aspergillosis post COVID infection

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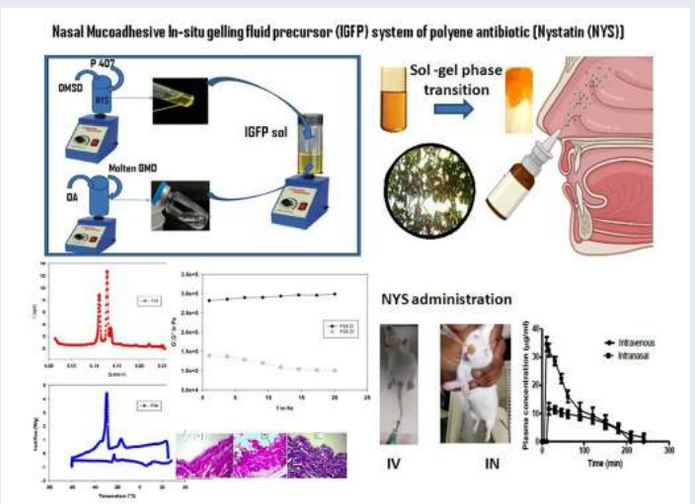
ABSTRACT

Nasal mucoadhesive in situ gelling liquid crystalline precursor system (IGFPS) of nystatin was developed for localized treatment of nasal aspergillosis post COVID infection. The stimuli-sensitive sol system comprising of Monoolein (60%w/w), Oleic acid (10%w/w), Dimethyl sulfoxide (15%w/w), Poloxamer 407 (9%w/w), and the drug (2.23%w/w) exhibited a faster sol–gel transformation in situ with good swelling ability. The small angle X-ray scattering study identified the coexistence of Im3m cubic phase with hexagonal closed pack P63/mmc structures. The subzero differential scanning calorimetry studies identified entrapped interphasal water and free water in the gels with confirmation of gelation due to micellization. Mucoadhesive properties of the gel indicate these systems to prolong the residence time at the site of absorption. The gels followed Non-Newtonian flow pattern characteristic of pesudoplastic type. The oscillatory rheology revealed that high complex viscosity and lower tanδ value provided superior adhesiveness and mucoadhesion ability to the gel. The gel exhibited a drug release of 86% at the end of 8h and of Higuchi kinetics with anomalous transport. The IGFPS exhibited better in vitro antifungal activity in comparison to drug solution. The system demonstrated permeation enhancing effect undamaged cilia and no serious histological changes. Post intranasal administration the maximum concentration (11.79 ± 2.31 μg/ml) was realized in 20 min and the curve showed a decline similar to intravenous. The storage stability of the IGFPS was found to be within acceptable limits for stability. Thus, a nasal mucoadhesive in situ gelling fluid liquid crystalline precursor formulation may represent a promising novel alternative for the localized and systemic delivery of nystatin.

GRAPHICAL ABSTRACT



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Nystatin; polyene antibiotic; in situ gelling fluid precursor system (IGFPS); nasal; aspergillosis; COVID

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Anti-Cancer Agents in Medicinal Chemistry

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Research Article

Discovery of new quinazoline derivatives as VEGFR-2 inhibitors: Design, Synthesis, and anti-proliferative studies

Author(s): Sachin A. Dhawale, Pratap S. Dabhade and Santosh N. Mokale*

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Abstract

Background: In cancer, Receptor tyrosine kinases (RTKs) are powerful oncoproteins that can lead to uncontrolled cell proliferation, angiogenesis, and metastasis when mutated or overexpressed, making them crucial targets for cancer treatment. In endothelial cells, one of them is vascular endothelial growth factor receptor 2 (VEGFR2), a tyrosine kinase receptor that is produced and is the most essential regulator of angiogenic factors involved in tumor angiogenesis. So, a series of new N-(4-(4-amino-6,7-dimethoxyquinazolin-2-yloxy)phenyl)-N-phenyl cyclopropane-1,1-dicarboxamide derivatives as VEGFR-2 inhibitors have been designed and synthesized.

Methods: The designed derivatives were synthesized and evaluated using H-NMR, C13-NMR, and Mass spectroscopy. The cytotoxicity was done with HT-29 and COLO-205 cell lines. The potent compound was further studied for Vegfr-2 kinase inhibition assay. Furthermore, the highest activity compound was tested for cell cycle arrest and apoptosis. The molecular docking investigation was also done with the help of the Glide-7.6 program interfaced with Maestro-11.3 of Schrodinger 2017. The molecular dynamics simulation was performed on the Desmond module of Schrodinger.

Results: Compound SQ2 was observed to have promising cytotoxic activity (IC50 = 3.38 and 10.55 μM) in comparison to the reference drug Cabozantinib (IC50 = 9.10 and 10.66 μM) against HT-29 and COLO-205, respectively. The synthesized compound SQ2 showed VEGFR-2 kinase inhibition activity (IC50 = 0.014 μM) compared to the reference drug, Cabozantinib (IC50 = 0.0045 μM). Moreover, compound SQ2 strongly induced apoptosis by arresting the cell cycle in the G1 and G2/M phases. The docking study was performed to understand the binding pattern of the new compounds to the VEGFR-2 active site. Docking results attributed the potent VEGFR-2 inhibitory effect of the new compounds as they bound to the key amino acids in the active site, Asp1044, and Glu883, as well as their hydrophobic interaction with the receptor's hydrophobic pocket. The advanced computational study was also done with the help of molecular dynamics simulation.

Conclusion: The findings show that the developed derivatives SQ2 and SQ4 are equally powerful as cabozantinib at cellular and enzymatic levels. The apoptosis and cell cycle results show that the proposed compounds are potent. This research has provided us with identical or more potent VEGFR-2 inhibitors supported by the results of docking studies, molecular dynamics simulation, cytotoxic actions, in vitro VEGFR-2 inhibition, apoptosis, and cell cycle arrest.

Keywords: Quinazoline, Molecular modeling, Anti-proliferation, VEGFR-2, Cell Cycle, Apoptosis

"INNOVATIVE DRUG DELIVERY STRATEGIES: UNVEILING THE POTENTIAL OF SELF-EMULSIFICATION"

Preeti Sable[1*], Swaroop Lahoti[2], Shyam Ghadalinge[3], Jaiprakash Sangshetti[4]

Abstract

Challenges encountered in the efficient delivery of drugs are multi-dimensional ranging from solubility issues to the first-pass biotransformation to P-gp efflux-based removal of drugs. Most drugs suffer from one or more of these problems. There are varieties of ways to overcome them. This article provides a comprehensive review of one such approach called "selfies". Selfies are self-emulsifying systems that have the ability to convert into an emulsion with extremely fine droplets of micron or nano sizes. Thereby they give all the benefits of emulsions without the inherent stability issues associated with the dosage form. This review is designed to help formulators see the multifaceted personality of these systems. It is going to highlight the differences between the different selfies, elaborate on the various excipients that are available to make a system as you envision functioning, reflecting on the various applications for which these versatile systems have been used thus far, the assortment of dosage forms into which they have been converted for ease of delivery and lastly, it would focus on the opportunities that lay ahead if one opts for these systems. This would also provide unique areas of research which are hitherto still questions largely unanswered.

Keywords: Bioavailability, Nano formulations, Self-emulsifying system; Self-micro emulsifying; Self-nanoemulsifying; Solubility

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A COMPREHENSIVE REVIEW OF POLYMERIC MICELLES

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1. ABSTRACT

One of the most widely studied subjects in nanoscience technology is related to the creation of supramolecular architectures with well-defined structures and functionalities. These supramolecular structures are generated as a result of the self-assemblage of amphiphilic block polymers. Self-assembly of block polymers via hydrophobic and hydrophilic effects, electrostatic interactions, hydrogen bonding, and metal complexation has shown tremendous potential for creating such supramolecular structures with a wide array of applications. Polymeric micelles have gathered considerable attention in the field of drug and gene delivery due to their excellent biocompatibility, low toxicity, enhanced blood circulation time, and ability to solubilize a large number of drugs in their micellar core. In this article, we have reviewed several aspects of polymeric micelles concerning their general properties, preparation and characterization techniques, and their applications in the areas of drug delivery. Polymeric micelles can be used as 'smart drug carriers' for targeting certain areas of the body by making them stimuli-sensitive or by attachment of a specific ligand molecule onto their surface.

KEYWORDS: Micellization, polymeric micelles, solubilization, targeting, stimuli-sensitivity, polymers.

2. INTRODUCTION

The versatility of micelles produced from amphiphilic copolymers as self-assembled nanostructures (≈10 to 200 nm) has signaled significant advances in the biomedical area due to their varying functions and clinical success.[1] The enormous progress in polymer science has enabled the design of these colloidal systems that can selectively accumulate in solid tumors, and have improved loading capability, better therapeutic efficacy, and superior targeting ability by surface modification with tumor homing ligands and aptamers. Polymeric micelles that can form above the critical micellar concentration (CMC) are composed of

"INNOVATIVE DRUG DELIVERY STRATEGIES: UNVEILING THE POTENTIAL OF SELF-EMULSIFICATION"

Preeti Sable[1*], Swaroop Lahoti[2], Shyam Ghadalinge[3], Jaiprakash Sangshetti[4]

Abstract

Challenges encountered in the efficient delivery of drugs are multi-dimensional ranging from solubility issues to the first-pass biotransformation to P-gp efflux-based removal of drugs. Most drugs suffer from one or more of these problems. There are varieties of ways to overcome them. This article provides a comprehensive review of one such approach called "selfies". Selfies are self-emulsifying systems that have the ability to convert into an emulsion with extremely fine droplets of micron or nano sizes. Thereby they give all the benefits of emulsions without the inherent stability issues associated with the dosage form. This review is designed to help formulators see the multifaceted personality of these systems. It is going to highlight the differences between the different selfies, elaborate on the various excipients that are available to make a system as you envision functioning, reflecting on the various applications for which these versatile systems have been used thus far, the assortment of dosage forms into which they have been converted for ease of delivery and lastly, it would focus on the opportunities that lay ahead if one opts for these systems. This would also provide unique areas of research which are hitherto still questions largely unanswered.

Keywords: Bioavailability, Nano formulations, Self-emulsifying system; Self-micro emulsifying; Self-nanoemulsifying; Solubility

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molecules

MDPI

Article

Antifungal Properties of Biogenic Selenium Nanoparticles Functionalized with Nystatin for the Inhibition of *Candida albicans* Biofilm Formation

Shivraj Hariram Nile [1,†], Dipalee Thombre [2,†], Amruta Shelar [3], Krithika Gosavi [2], Jaiprakash Sangshetti [4], Weiping Zhang [1], Elwira Sieniawska [5], Rajendra Patil [2,*] and Guoyin Kai [1,*]

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† These authors contributed equally to this work.

Abstract: In the present study, biogenic selenium nanoparticles (SeNPs) have been prepared using *Paenibacillus terreus* and functionalized with nystatin (SeNP@PVP_Nystatin nanoconjugates) for inhibiting growth, morphogenesis, and a biofilm in *Candida albicans*. Ultraviolet–visible spectroscopy analysis has shown a characteristic absorption at 289, 303, and 318 nm, and X-ray diffraction analysis has shown characteristic peaks at different 2θ values for SeNPs. Electron microscopy analysis has shown that biogenic SeNPs are spherical in shape with a size in the range of 220–240 nm. Fourier transform infrared spectroscopy has confirmed the functionalization of nystatin on SeNPs (formation of SeNP@PVP_Nystatin nanoconjugates), and the zeta potential has confirmed the negative charge on the nanoconjugates. Biogenic SeNPs are inactive; however, nanoconjugates have shown antifungal activities on *C. albicans* (inhibited growth, morphogenesis, and a biofilm). The molecular mechanism for the action of nanoconjugates via a real-time polymerase chain reaction has shown that genes involved in the RAS/cAMP/PKA signaling pathway play an important role in antifungal activity. In cytotoxic studies, nanoconjugates have inhibited only 12% growth of the human embryonic kidney cell line 293 cells, indicating that the nanocomposites are not cytotoxic. Thus, the biogenic SeNPs produced by *P. terreus* can be used as innovative and effective drug carriers to increase the antifungal activity of nystatin.

Keywords: antibiofilm; nanoparticles; morphogenesis; biogenic selenium; *Candida albicans*

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1. Introduction

Candida albicans is an opportunistic pathogenic yeast commonly associated with superficial and systemic infections [1]. *C. albicans* has become difficult to kill due to its virulence factors and increasing antifungal resistance [2,3]. The virulence factors include yeast-to-hyphae transition and biofilm formation [2,4,5]. Although yeast and hyphal forms have a role in the pathogenicity of *C. albicans*, the hyphal form of *C. albicans* is the main invasive form [6]. The transition from yeast to hyphae is known as dimorphism [7]. Various factors induce dimorphism, which includes pH, starvation, serum, N-acetylglucosamine, temperature, and CO_2 [8]. Dimorphism is the first committed step by which *C. albicans* invade the host [5]. The hyphal protrusions formed during dimorphism help *C. albicans* invade the host tissue. Generally, under the appropriate conditions, and after dimorphic, biofilm formation starts; the latter increases the survival rates and traits of multidrug resistance in *C. albicans*, which has become a challenge for therapeutic intervention [9]. A

Polycyclic Aromatic Compounds ›
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Research Articles

Docking Simulations and Primary Assessment of Newly Synthesized Benzene Sulfonamide Pyrazole Oxadiazole Derivatives as Potential Antimicrobial and Antitubercular Agents

Ramesh Shingare, Yogesh Patil, Jaiprakash Sangshett... Madje

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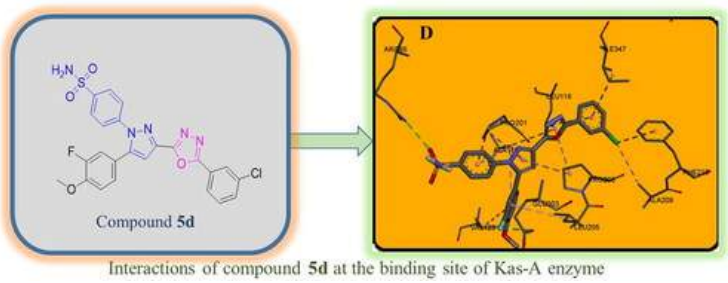
Abstract

A novel series of benzene sulfonamide pyrazole oxadiazole derivatives have been synthesized by reaction of 4-(5-(3-fluoro-4-methoxyphenyl)-3-(hydrazinecarbonyl)-1H-pyrazol-1-yl) benzene sulfonamide with different substituted benzoic/pyridinyl/indolyl acids in phosphorous oxychloride, characterized by IR, ^{1}H NMR, ^{13}C NMR, MS analytical data and evaluated for their antimicrobial as well as antitubercular activity. Molecular docking studies against *Mycobacterium tuberculosis* β-ketoacyl-acyl carrier protein synthase A, (Kas-A) was carried out to understand the possible mode of its inhibition and potential of synthesized compounds as antitubercular agents. Antibacterial activity of compounds **5d (**3-Cl**)** and **5f** (2,4-diCl) were found good against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* as compared to standard Ampicillin. Compound **5d** was found active antitubercular agents against *M. tuberculosis* H_{37}Rv.



Interactions of compound **5d** at the binding site of Kas-A enzyme

Keywords: Antimicrobial Antitubercular activity Benzene sulfonamide pyrazole Molecular docking Oxadiazole

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Surface decorated quantum dots: Synthesis, properties and role in herbal therapy

Mirza Shahed Baig[1], Ravikiran Maheshrao Suryawanshi[2], Mehrukh Zehravi[3], Hitendra S. Mahajan[2], Ritesh Rana[4], Ahemadi Banu[5], Muthukumar Subramanian[6], Amit Kumar Kaundal[7], Sachin Puri[8], Falak A. Siddiqui[9], Rohit Sharma[10], Sharuk L. Khan[9]*, Kow-Tong Chen[11,12]* and Talha Bin Emran[13,14]

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Quantum dots are the serendipitous outcome of materials research. It is the tiny carbonaceous nanoparticles with diameters ranging from 1 to 10 nm. This review is a brief discussion of the synthesis, properties, and biomedical applicability of quantum dots, especially in herbal therapy. As quantum dots are highly polar, they can be surface decorated with several kinds of polar functionalities, such as polymeric molecules, small functional molecules, and so on. The review also consists of the basic physical and optical properties of quantum dots and their excitation—dependent properties in the application section. We focus on therapeutics, where quantum dots are used as drugs or imaging probes. Nanoprobes for several diagnostics are quite new in the biomedical research domain. Quantum dot—based nanoprobes are in high demand due to their excellent fluorescence, non-bleaching nature, biocompatibility, anchoring feasibility for several analytes, and fast point—of—care sensibility. Lastly, we also included a discussion on quantum dot—based drug delivery as phytomedicine.

KEYWORDS

quantum dots, nanoprobe, nanomaterials, biomedical, nanotechnology, herbal medicines

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ANALYSIS OF PHYTOCHEMICALS BY QTOF-MS AND ASSESSMENT OF ANTIOXIDANT ACTIVITY FOR THE ETHYL ACETATE FRACTIONS OF LEAVES OF *CHROZOPHORA PLICATA*

Mohd Mukhtar Khan [1]* Syed Ayaz Ali [2] and Subur W Khan [3]

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Abstract

This study presents the analysis of phytochemicals by QTOF-MS and the assessment of antioxidant activity for the ethyl acetate fractions of leaves of *Chrozophora plicata*. A QTOF Mass Spectrometer equipped with a HiP Sampler, Binary Pump, Column Comp., DAD, and Q-TOF Mass Spectrometer was employed for the analysis of phytochemicals. The QTOF-MS analysis was conducted using the Default Method (metabolite_ESI_+VE_MSMS.m) specifically designed for metabolite analysis on TOF/Q-TOF Mass Spectrometer. The Dual AJS ESI Ion Source was used in both positive and negative ionization modes for comprehensive compound detection. The analysis was divided into time segments from 0 to 25.00 minutes to group compounds with similar elution characteristics. The MS Abs. threshold and MS/MS Abs. threshold were set at 200 and 5, respectively. The Fast Polarity was set to 0.010, enabling rapid polarity switching. The in vitro antioxidant activity of the ethyl acetate fractions was assessed using DPPH Inhibition, FeCl3 Radical Scavenging, and Phosphomolybdenum Assay. The results revealed a diverse array of phytochemicals in *Chrozophora plicata* leaves. The ethyl acetate fractions exhibited significant antioxidant activity in all three assays, indicating their potential as a rich source of natural antioxidants. Further investigations, including compound identification and in vivo studies, are warranted to fully understand the medicinal and therapeutic potential of *Chrozophora plicata* leaves as a promising natural antioxidant resource.

Keywords: Phytochemicals, QTOF-MS, Antioxidant Activity, Ethyl Acetate Fractions, *Chrozophora Plicata* Leaves.

INTRODUCTION

Phytochemicals, bioactive compounds derived from plants, have gained significant attention due to their diverse therapeutic properties and potential health benefits. Analyzing the phytochemical composition of medicinal plants can provide valuable insights into their chemical profile and contribute to understanding their medicinal properties. *Chrozophora plicata*, a plant with traditional medicinal uses, has been recognized for its potential pharmacological activities. However, a comprehensive analysis of its phytochemical constituents is essential to unlock its full therapeutic potential. [1,2]

In recent years, advances in analytical techniques have enabled in-depth investigations of plant metabolites. One such technique is Quadrupole-Time-of-Flight Mass Spectrometry (QTOF-MS), which allows for high-resolution and accurate mass measurements, facilitating the identification of a wide range of phytochemicals present in complex plant extracts. The use of QTOF-MS can provide detailed molecular information and enhance the understanding of the chemical complexity of plant materials. [3,4]

Section A-Research paper
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"*Chrozophora plicata* Leaves: A Treasure Trove of Medicinal Compounds Revealed through Pharmacognostic Exploration"

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Abstract:

Chrozophora plicata, a traditional medicinal plant, is known for its potential therapeutic properties and has been used in various herbal remedies. This research aimed to conduct a pharmacognostic and phytochemical evaluation of the leaves of *Chrozophora plicata* to provide valuable insights into its medicinal potential and chemical composition. The physicochemical analysis of the powdered leaves revealed favorable results, indicating the quality and purity of the plant material for medicinal use. The presence of glycosides, tannins, flavonoids, resins, steroids, proteins, fats & oil, and saponins in the phytochemical investigation suggests its potential antioxidant, antimicrobial, anti-inflammatory, expectorant, and anti-inflammatory properties, validating its traditional use. However, alkaloids, phenol, diterpens, and amino acids were absent, further clarifying the chemical profile of the plant extract. These findings support the traditional use of *Chrozophora plicata* and provide scientific evidence for its potential therapeutic benefits. Nevertheless, further research is warranted to explore its pharmacological activities, efficacy, and safety in various disease models. Standardization of the extract's active compounds and optimization of its dosage forms will be crucial to ensure its safe and effective use in modern healthcare practices. In conclusion, the pharmacognostic and phytochemical evaluation of *Chrozophora plicata* leaves offers a comprehensive understanding of its chemical composition and medicinal properties. Embracing this traditional herbal remedy, along with appropriate scientific

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Nasal mucoadhesive in situ gelling liquid crystalline fluid precursor system of polyene antibiotic for potential treatment of localized sinuses aspergillosis post COVID infection

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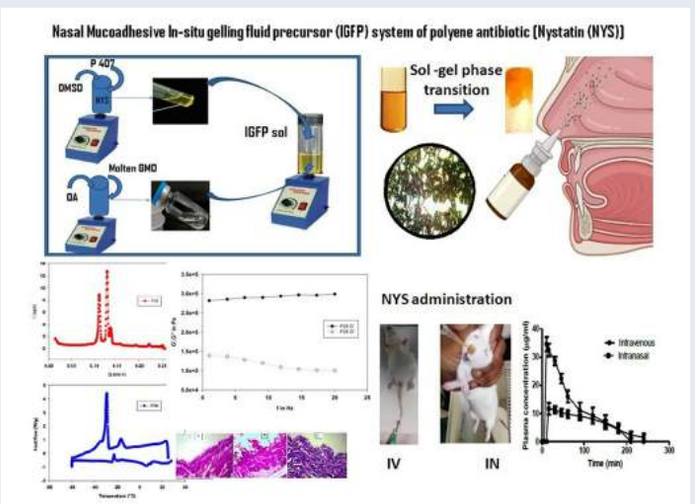
ABSTRACT

Nasal mucoadhesive in situ gelling liquid crystalline precursor system (IGFPS) of nystatin was developed for localized treatment of nasal aspergillosis post COVID infection. The stimuli-sensitive sol system comprising of Monoolein (60%w/w), Oleic acid (10%w/w), Dimethyl sulfoxide (15%w/w), Poloxamer 407 (9%w/w), and the drug (2.23%w/w) exhibited a faster sol–gel transformation in situ with good swelling ability. The small angle X-ray scattering study identified the coexistence of Im3m cubic phase with hexagonal closed pack P63/mmc structures. The subzero differential scanning calorimetry studies identified entrapped interphasal water and free water in the gels with confirmation of gelation due to micellization. Mucoadhesive properties of the gel indicate these systems to prolong the residence time at the site of absorption. The gels followed Non-Newtonian flow pattern characteristic of pesudoplastic type. The oscillatory rheology revealed that high complex viscosity and lower tanδ value provided superior adhesiveness and mucoadhesion ability to the gel. The gel exhibited a drug release of 86% at the end of 8h and of Higuchi kinetics with anomalous transport. The IGFPS exhibited better in vitro antifungal activity in comparison to drug solution. The system demonstrated permeation enhancing effect undamaged cilia and no serious histological changes. Post intranasal administration the maximum concentration (11.79 ± 2.31 μg/ml) was realized in 20 min and the curve showed a decline similar to intravenous. The storage stability of the IGFPS was found to be within acceptable limits for stability. Thus, a nasal mucoadhesive in situ gelling fluid liquid crystalline precursor formulation may represent a promising novel alternative for the localized and systemic delivery of nystatin.

GRAPHICAL ABSTRACT



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Nystatin; polyene antibiotic; in situ gelling fluid precursor system (IGFPS); nasal; aspergillosis; COVID

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Publications of 2022

"STUDIES ON METHANOLIC EXTRACT OF *MOMORDICA CYMBALARIA* FENZL ROOTS FOR NEUROPROTECTIVE ACTIVITY IN VINCRISTINE- INDUCED PERIPHERAL NEUROPATHY"

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Review Article

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A COMPREHENSIVE REVIEW ON MEDICINAL PLANT: *AEGLE MARMELOS (LINN) CORREA*

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ABSTRACT

The plants are the good substitution for the medicines because of their less or no side effect and their ability to cure the problem from their root. The present study gives the complete profile of aegle marmelos belongs to family *Rutaceae*, commonly known as a bael in India. This review gives the detailed information about the phytochemistry and pharmacological activity of aegle marmelos. A number of biologically active compounds (Alkaloids, Terpenoids, Vitamins, Coumarins, Tannins, Carbohydrates, Flavonoids, Fatty Acids, and Essential Oils) isolated from various parts of aegle marmelos, which belongs to various chemical groups. This plant is having great prospective to cure the disease like diabetes, cholesterol, peptic ulcer, inflammation, diarrhea, and dysentery, anticancer, cardio protective, anti bacterial, anti fungal, radio protective, anti pyretic, analgesic, constipation, respiratory infection, antioxidant, hepatoprotective, wound healing and many more. Hence, this review may be a good reference for the researchers who are willing to commence further investigation about aegle marmelos.

KEYWORDS: Aegle marmelos, Ehanobotanical description, Phytochemistry, Pharmacological activity.

INTRODUCTION

The universal role of plants in the treatment of disease is exemplified by their employment in all the major system of medicine irrespective of the underlying philosophical premise. Plants have at one time supplied virtually all cultures with food, clothing, shelter and medicine. It is estimated that approximately 10 to 15 percent of roughly 300,000 species of higher plant, have a history of use in traditional medicine. In terms of both quantity and value of the medicinal plant exported India ranks second in the world. Plants are the very important for the human, because they possess several active constituents, which are the precursor for the synthesis of many drugs. Humans are considered as most developed among all living species on earth. They are adopting plants not only as an origin of food but also to delight various ailments of humankind since ancient age. Several plants or plant parts are used to heal a number of physical and mental disturbances and helps us to withstand successfully.

Aegle marmelos, "Fig 1"a plant of Indian origin having tremendous therapeutic potential, belongs to family Rutaceae. This plant is familiar with several names like Bael, Bengal quince, Golden apple, Wood apple, etc. Every part of plant such as fruit, seed, bark, leaves and root is used as an ingredient of several traditional formulations. Due to its curative properties, it is one of the most useful medicinal plants of India. The product obtained from bael, being highly therapeutic and is being popularized in India and international market. It is a subtropical plant, which grows in the dry forest of hilly and plain area and found in Bihar, Chhattisgarh, Uttar Pradesh, Uttarakhand, Jharkhand and Madhya Pradesh. Bael is a scared tree of Hindus as its leaves are offered to Lord Shiva for fulfillment of wishes. The tree is symbol of fertility.

It is cultivated as temple garden plant and the leaves of *Aegle marmelos* L. are use for praying Lord Shiva "Fig 2". Its fruits are use as food as well as traditional medicine "Fig 3".

The special focus of this review highlights the morphology, phytochemistry, traditional use and medicinal uses of *Aegle marmelos* for its further investigation and development of active constituents.

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Phytochemical and Pharmacological Evaluation of Ethanolic Extract of *Moringa Oleifera* as Neuroprotective Agent in Vincristine Induced Peripheral Neuropathy

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Abstract:*The objective of this study was to phytochemically analyze the ethanolic extracts of the leaves of Moringa oleifera and thereafter to evaluate its neuroprotective activity in vincristine induced peripheral neuropathy.The fresh leaves of Moringa oleifera were collected, powdered and extracted with ethanol. Thereafter the dried ethanolic extract was subjected to phytochemical analysis using various analytical techniques primarily GC-MS to identify the bioactive phytochemical components. Acute toxicity studies were also carried out on the extract. After overnight fasting peripheral neuropathy was induced in Wistar rats by intraperitoneal injection of vincristine 100µg/kg/day body weight dissolved in saline (0.1ml/kg/day). Group A served as normal control while group B was considered as neuropathy control. Group C was standard receiving methylcobalamin (50µg/kg i. p) and Group D & E neuropathy animals were treated with the extract, dose of 250 and 500 mg/kg/b. w p.o. respectively. During the investigations, studies were carried out by in-vivo models such as tail flick, acetone spray method, pain sensation test, nerve conduction test as well as proinflammatory and antioxidant studies. At the end of study, animals in all groups were sacrificed, the sciatic nerve was dissected and histopathology was performed. The interpretation of the results was done after subjecting the data obtained from various studies to statistical analysis which included descriptive statistics, ANOVA followed by Tukey's test. Ethanolic extract of Moringa oleifera leaves were phytochemically analyzed and showed presence of bioactive chemicals. The ethanolic extracts produced significant neuroprotective activity it was effective in anti-nociceptive activity, and caused changes in in-vivo anti-oxidants enzyme and nerve conduction. Further significant improvements were noted in pro-inflammatory markers. Histopathology studies indicated amelioration of histological features. In conclusion, the ethanolic extracts of Moringa oleifera leaves showed potential neuroprotective activity against vincristine induced peripheral neuropathy.*

Key Word*:Moringa oleifera, GCMS, Vincristine, Pro-inflammatory, Anti-oxidant enzyme, Nerve Conduction.*

I. Introduction

Moringa Oleifera is a valuable plant because of its multiple uses such as a food source in the tropics as well as its medicinal uses. The leaves of Moringa are reported to be of utility in the treatment of eye and ear infections, skin diseases, flu, headaches, scurvy, heart burn, asthma, bronchitis, hyper-glycemia, malaria, dyslipidaemia, syphilis,

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DUAL TARGETING OF VEGFR-2 AND C-MET KINASES VIA THE DESIGN AND SYNTHESIS OF SUBSTITUTED BENZYLIDENE-6-(5-CHLOROPYRIMIDIN-2-YL)-9H-PURINE-2,6-DIAMINE DERIVATIVES AS ANGIOGENESIS INHIBITORS

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ABSTRACT

We have designed and synthesized a unique library of benzylidene-6-(5-chloropyrimidin-2-yl)-9H-purine-2,6-diamine derivatives as angiogenesis inhibitors. The designed scaffolds were subjected to docking and ADME prediction studies so as to guage the particular interaction. Further anti-proliferative activity was allotted by employing the SRB method as a target for colorectal cancer on HT-29 and COLO-205 cell lines. The SM-6 derivative showed good anticancer activity and was subjected to in-vitro enzyme inhibition activity using a flow cytometer to test the enzyme inhibition potential. It also induced apoptosis and cell cycle arrest at the G0/G1 phase on HT-29 cells supported by DAPI staining and propidium iodide (PI) staining followed by flow cytometry analyses. These compounds exhibited slight inhibitory effects against VEGFR and c-Met kinases, so their active skeletons warrant further study and will have a positive effect on the event of small anticancer inhibitors of dual-target VEGFR/c-Met kinase.

Keywords: Synthesis, Anti-Proliferative Activity, Cell Cycle Analysis, Apoptosis Assay, VEGFR-2 Inhibitory Assay, Molecular Docking, In-silico ADME Study, MM/GBSA.

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INTRODUCTION

Tumors can be a multi-stage, complex process with life-threatening consequences for people's health and lives.[1] For tumor spread, growth, and survival (RTK) a variety of signal transduction pathways including receptor tyrosine kinases are required for cell differentiation, proliferation, angiogenesis, and apoptosis.[2] In response to ligands, RTK primarily activates transcription factors that mediate target organic phenomenon. RTK signaling pathways are complicated including a wide range of metabolic events and molecular mediators in complex signaling networks.[3] Vascular endothelial protein receptor-2 (VEGFR-2) is taken into account because of the main effector of VEGF/ VEGFR signal transduction in promoting tumor angiogenesis.[4,5] The phosphorylation of VEGFR-2 activates the Raf-1/MAPK/ERK signaling pathway, which results in angiogenesis and improves vascular permeability and tumor migration.[6] Therefore, inhibition of the VEGFR-2 signaling pathway is taken into account in the concert of the foremost important pathway within the development of tumor chemotherapy.[7,8] Mesenchymal epithelial transfer factor tyrosine kinase (c-MET) may be a crucial member of the receptor tyrosine kinases (RTK) family.[9] c-MET is activated by extracellular binding of its ligand, hepatocyte growth factor/ scatter factor (HGF/SF).[10] The aberrant expression of c-MET/ HGF signaling arises from c-MET mutations or overexpression or genomic amplification, which may promote proliferation, migration, invasion, and tumor angiogenesis.[11] The role of c-MET and VEGFR-2 have a synergistic role within the angiogenesis of human cancer. The utilization of dual targets i.e., c-MET and VEGFR-2 inhibitor may act as a necessary element within the development of targeted therapy.[12,13] c-MET is up-regulated in response to VEGFR pathway inhibition and so plays a vital role in tumor angiogenesis and progression.[14] However, the matter of drug resistance frequently arises within the research of single-target drugs and combination drugs. It is found that multi-target drugs may

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Design and Synthesis of N-4-(substituted benzylidene)-N-2-(4-chloropyrimidin-2-yl)-6, 7-dimethoxyquinazoline-2, 4-diamines as Anticancer Agents

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A novel series of N-4-(substituted benzylidene)-N-2-(4-chloropyrimidine-2-yl)-6,7-dimethoxyquinazoline-2,4-diamine compounds were designed, synthesized and evaluated for their anti-cancer properties. The structures of the target derivatives were elucidated using spectral techniques like ^{1}H NMR, ^{13}C NMR and mass spectroscopy. All the designed compounds were tested for their probable anti-cancer activity on human colon-rectal cell lines (HT-29 and COLO-205), followed by cell-cycle analysis, apoptosis assays, and enzyme inhibitory assays. VEGFR-2 kinase inhibitory assays and cell cycle analyses were performed to validate the target selectivity of the designed compounds. Among the synthesized derivatives, **SM-8 (GI_{50}= 10.64 µM)** showed good inhibition activity against HT-29 cell lines. Cellular mechanism studies confirmed that compound SM-8 could induce apoptosis in HT-29 cells in G1 phase, which was concentration-dependent. In order to evaluate the specific interaction with tyrosine kinase, designed scaffolds were subjected to docking, *in-silico* physicochemical properties and ADME prediction studies. MM/GBSA was performed to calculate the ligand binding free energies.

Key words: Quinazoline; *in-vitro* activity; molecular Docking; *in-silico* ADME study

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Receptor Tyrosine Kinases (RTKs) play a vital role in various cellular processes and signal transduction pathways. In the current era RTKs have been found to have divergent roles in different chemo-therapeutic medications. RTKs play an important role in phosphorylating the tyrosine amino acid in several proteins with the help of ATP (ɣ-phosphoryl group donor). Phosphorylation ultimately leads to activation of a signalling pathway at the cellular level which includes crucial processes for differentiation, proliferation, migration, and antiapoptotic pathways. The c-mesenchymal epithelial transition factor (c-MET) is a widely over-expressed RTK in human tumours and a receptor for hepatocyte growth factor (HGF). HGF binding to c-Met causes phosphorylation of tyrosine residues on c-Met, which activates the downstream signalling pathway involved in cell proliferation, invasion, metastasis, and angiogenesis in a variety of cancers. c-Met activation has been linked to poor clinical outcomes in a variety of human solid tumours and haematological cancers [1,2]. Additionally, c-Met overactivation leads to therapeutic resistance. As a result of resistance, inhibiting c-Met activity could be a promising treatment option for malignancies. Small molecule inhibitors of c-Met can be divided into several types based on their binding mechanisms. Multikinase inhibitors, for example, are a common form of c-Met inhibitor that also inhibits VEGFR and other Homologous kinases. Endothelial cells contain a tyrosine kinase receptor known as vascular endothelial growth factor receptor 2 (VEGFR-2, also known as KDR). When VEGF binds to VEGFR, it causes a conformational shift in the receptor, which is followed by dimerization and phosphorylation of tyrosine residues [3]. VEGFR-2-mediated VEGF signalling has been found to play a key role in tumour angio-genesis regulation. VEGF expression is increased in a variety of human cancers, and high levels of VEGF are linked to a poor prognosis and clinical stage in patients with solid tumours. As a result, VEGF/VEGFR-2 signalling represents a promising therapeutic target in cancer treatment. The synergistic collaboration of c-Met and VEGFR-2 has been shown to promote angiogenesis in the development and progression of several human malignancies [4, 5, 11]. As a result, compounds that inhibit both c Met and VEGFR-2 at the same time may be preferable to c Met- or VEGFR-2-specific inhibitors because they can disrupt numerous signalling pathways involved in tumour proliferation, metastasis, and angiogenesis. Several kinase inhibitors, such as cabozantinib and foretinib, have been shown to suppress both c-Met and VEGFR-2 kinases at the same time. Consequently, we began developing dual c-Met and VEGFR-2 TKIs with substantial anti-tumour effectiveness using the quinazoline nucleus, which is widely used in drug development, particularly in RTK inhibitors [6].

Original Article

Formulation And Development Of Nanosuspension For Solubility Enhancement Of Gefitinib

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Abstract

Gefitinib (GFT) is a BCS class II tyrosine kinase inhibitor with limited solubility and bioavailability. In the present investigation, nanosuspensions (NSPs) were formulated to overcome these pitfalls. The GFT-NSPs nine batches were prepared by nanoprecipitation method using Poloxamer-188 (Polo-188) and Tween-80. The developed formulations were subjected to determine percent drug content, percent drug entrapment, particle size, polydispersity index, zeta potential, x-ray diffraction pattern, formulation morphology, solubility and *in vitro* drug release. Following the percent drug content and entrapment, NSP-6 was selected as an optimized batch. In the study's outcomes, it was observed that NSP-6 showed 96.71 percent drug content and 96.61 percent drug entrapment. In particle size analysis, NSP-6 explored 357.6.4 nm dimensions, 0.325 polydispersity index and -26.5 zeta potential. X-ray diffractogram of NSP-6 indicated characteristics peak of both GFT and Polo-188. Morphological photomicrographs of NSP-6 explored small spherical structures. In the solubility study, it was observed that NSP-6 showed higher solubility enhancement than pure GFT in purified water, methanol and pH 7.4 phosphate buffer. *In vitro* dissolution study of pure GFT and NSP-6 exhibited 97.23% and 99.14% drug dissolution. NSP showed a maximum drug dissolution rate; therefore, NSP was considered a suitable approach for the solubility enhancement of GFT. The developed NSP significantly increased the water solubility and bioavailability of GFT, suggesting its potential as a nanocarrier in the delivery of GFT for future clinical application.

Keywords: Gefitinib, Nanosuspension, Solubility, Tuberculosis, Tyrosine kinase inhibitors

1. INTRODUCTION

Low aqueous solubility is one of the significant challenges during the formulation of new chemical entities and generics. In drug discovery, most new candidates share this undesirable physicochemical property[1]. Due to the slow dissolution of these compounds, absorption and bioavailability are limited when administered orally. Some of the most common technologies applied to enhance biopharmaceutical properties of drugs are micronization, nanosizing, crystal engineering, application of solid dispersions, molecular or lipid encapsulations, and other colloidal drug delivery systems such as formulation of microemulsions and self-emulsifying drug delivery systems[2]. The biopharmaceutics classification system is a scientific classification designed for actives based on their aqueous solubility and *in vivo* bioavailability. BCS takes two fundamental factors: solubility and intestinal permeability, into account, predicting oral drug absorption of solid dosage forms[3]. GFT is BCS class II drug demonstrating poor water solubility and high permeability. GFT is a type of drug called a tyrosine kinase inhibitor (TKI). Kinases are proteins in the body that regulate how the cells grow and divide. GFT restricts mycobacterium tuberculosis growth through increased lysosomal biogenesis and modulation of cytokine signalling [4]. The GFT inhibit target protein (EGFR) is a family of receptors which includes Her 1 (erb-B1), Her 2 (erb-B2), and Her 3(erb-B3).GFT is absorbed slowly after oral administration with a mean bioavailability of 60%[5]. It is metabolised by CYP 3A4, primarily eliminated by the liver, and faces 48 hours elimination half-life. As aforesaid, GFT is a poorly water-soluble drug; hence various technologies have been developed to enhance its solubilities, such as solid dispersion, crystal engineering, salt formation, and complexation. All methods are utilized to attack universal applicability to all drugs[2]. Nanotechnology is one of the emerging fields in pharmaceutical development to enhance the solubility of poorly soluble drugs. In nanotechnology nanoemulsion, nanoparticles and NSPs are the most commonly used methods [6]. Regarding NSPs, submicron colloidal dispersions of nanosized drug particles stabilized by surfactants and poorly water-soluble drugs are without any matrix material suspended in dispersion. NSPs help in enhance solubility as well as the bioavailability of drugs. Precipitation, high-pressure homogenization, and solvent evaporation techniques using stabilizers and co-stabilizer are the most common methods for NSP development[7]. As previously mentioned, GFT is a

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Research Article

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RP-HPLC method development and validation for quantification of letrozole solid lipid nanoparticle

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ABSTRACT: A sensitive, simple, rapid, stability-indicating reverse-phase high-pressure liquid chromatographic method was developed for the estimation of letrozole in solid lipid nanoparticles. The developed method was validated as per the International Council of Harmonization (ICH guideline) concerning system suitability, linearity, accuracy, precision, specificity, robustness, and range. The chromatographic separation was achieved on the Zorbax C18 column (250 x 4.6 mm ID; 5.0 µm particle size). Isocratic elution was performed using methanol: 0.1% orthophosphoric acid (60:40) at 0.7 mL/min flow rate. The detection was done using a UV-Vis detector at 240 nm. Linearity for the analytical method was observed at the concentration range of 10 to 50 µg/mL having a correlation coefficient of 0.999. The method was precise, accurate with a relative standard deviation (RSD) ≤ 2.0. The developed validated analytical method can be used as a quality control tool for the quantitative estimation of letrozole in a novel formulated solid lipid nanoparticle.
KEYWORDS: Letrozole; RP-HPLC; Solid lipid nanoparticle; ICH; Validation.

1. INTRODUCTION

Letrozole (Figure 1) is chemically known as 4-[{4-cyanophenyl)-(1, 2,4-triazol-1-yl) methyl] benzonitrile [1]. Letrozole is a third-generation non-steroidal aromatase inhibitor used in the treatment of hormone-responsive positive and metastatic breast cancer in postmenopausal women [2]. Breast cancer is the leading cause of death in women worldwide [3]. Nearly 30% of breast cancer are hormone-responsive and requires hormone for growth. Breast cancer cells have receptors/protein for the hormone estrogen (ER-positive cancer) which acts as a catalyst for the growth and spread of cancer cells. Hence hormone deprivation is the most preferred therapy leading to regress [4, 5]. Estrogen plays a major role in breast cancer [6].

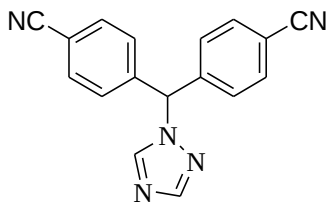

Figure 1. Chemical structure of letrozole.

Before menopause, most estrogen is produced by ovaries. After menopause when the ovary stops functioning a small amount of estrogen is produced by the aromatase enzyme in fat tissues surrounding breast cells [7]. The mechanism of action of an aromatase inhibitor is to block aromatase from producing estrogen [7-8]. Aromatase inhibitors such as letrozole are prescribed as hormone therapy for the treatment and management of breast cancer.

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Original Article

Pazopanib Colon Targeted Liposomal Drug Delivery for Colorectal Cancer: High-pressure Homogenization Process Optimization and *in-vivo* Evaluation

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ABSTRACT

Background: Pazopanib is second-generation tyrosinekinase inhibitor used in Colorectal cancer (CRC) which is effective orally. Targeted liposomal drug delivery will reduce the unwanted side effects of the drug. The application of High-pressure homogenizers for the preparation of systems like liposomes and lipid dispersions is rising because of its ability of vesicle disruption. **Aim:** Major objective of present research work was to optimize high pressure homogenization process for formulation of colon targeted liposomal drug delivery system of Pazopanib and its *in-vivo* evaluation. To study the influence of homogenization Pressure and number of cycles on some parameters, such as vesicle size and polydispersity index (PDI). **Materials and Methods:** The liposomes were formulated with HSPC (Hydrogenated Phosphotidylcholin from Soybean) m-PEG DSPE-2000 (Phospolipid) and Cholesterol using Ethanol injection method followed by downsizing by EmilsiFlex High pressure Homogenizer. **Results and Conclusion:** The liposomes were evaluated for entrapment efficiency, *in-vitro* drug release, osmolality, particle size, size distribution, polydispersity index, FEG-SEM and stability studies. Optimization studies concluded that the optimized formulation with homogenization pressure of 1000, 1500, 2000 psi and number of cycle 9, 6, 6 respectivly gives particle size of 109 nm with PDI 0.998 and desirability 0.975. *In-vivo* studies in wrister rats in which carcino genesis was done using 1,2- dimethylhydrazine (DMH), indicated that Pazopanib liposomes caused significant tumors growth suppression in terms of tumor volume and weight as compared to control. Histo-pathological evaluation showed that the animals treated with pazopanib liposomes had moderate dysplasia where as untreated animals had severe dysplasia.

Key words: Liposome, Pazopanib, High-pressure homogenizer, Colon targeted, Colorectal.

INTRODUCTION

Colorectal cancer (CRC) is the third recurrently diagnosed tumor worldwide in society. Presently conventional approaches like targeted chemotherapy, surgery, and radiotherapy are being used for the treatment of CRC. The targeted delivery of chemotherapeutics to their site of action increases efficiency with reduced side effects.[1] The conventional non-targeted chemotherapy produces untoward effects like anemia, neutropenia, liver toxicity gastrointestinal (GI) toxicity, mucositis, fatigue, and hematologic disorders.[2] In CRC, there is need to develop targated drug delivery to the required site of the colon in a expected and reproducible manner.[3]

Pazopanib is an orally bio-available second generation tyrosine-kinase inhibitor. It acts on VEGFR1, VEGFR2, VEGFR3, PDGFR alpha, PDGFR beta, FGFR1, FGFR2, c-kit, and with moderate activity against c-FMS.[4] It significantly reduces progression and prolongs lifespan of the patient of complex cancer. In preclinical evaluation Pazopanib has shown excellent anti-angiogenic and anticancer activity in relapsed colorectal cancer.[5,6]

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Original Article

Quality by Design: Optimization of Letrozole Solid Lipid Nanoparticle for Breast Cancer

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ABSTRACT

Aim: Hormone responsive breast cancer is the most prevalent cancer worldwide. Letrozole is a third-generation aromatase inhibitor widely used for the treatment of advanced breast cancer. The primary objective of the present work is to develop and optimize an injectable solid lipid nanoparticle incorporating letrozole to circumvent the side-effects of a marketed conventional formulation and thereby improve patient compliance. **Materials and Methods:** Emulsification solvent evaporation and melt dispersion techniques were used for formulating the said solid lipid nanoparticles. Quality by design concept was used for the development and optimization of formulation and process variables. **Results:** The optimum level selected is 60 mg lipid, 30 mg surfactant, and co-surfactant, 15000 psi HPH pressure, and 15 HPH passes. **Conclusion:** Glyceryl dibehenate was selected as suitable lipid based on solubility and partition coefficient. With an increase in lipid content there is increase in particle size and PDI and decrease in entrapment efficiency. Higher surfactant and co-surfactant concentrations result in lower particle size, PDI, higher zeta potential, and lower entrapment efficiency. An increase in HPH pressure reduced particle size and PDI up to a certain level, however, the increase in HPH pressure from 15000 to 20000 psi increased particle size. An increase in the number of HPH passes reduces particle size and PDI. The drug release mechanism for LTR-SLN was found to follow the first order and higuichi model.

Keywords: Solid lipid nanoparticle, Letrozole, Ishikawa diagram, Plackett burman design, Central composite design, Mathematical modeling.

INTRODUCTION

Cancer is one of the major reasons of mortality across the world. Breast cancer is the most leading type of cancer in females taking a significant toll on life across the globe.[1] Hormone receptor breast cancer is the most prevalent type of breast cancer that requires hormones for growth.[2] Hormone deprivation using aromatase inhibitors is recommended for the treatment of estrogen receptor positive breast cancer. The mechanism of action of an aromatase inhibitor is to block aromatase from producing estrogen.[3-4] Letrozole is a third-generation non-steroidal aromatase inhibitor widely used for the prophylaxis of hormone receptor positive breast cancer.[5-6] Letrozole is approved and marketed as a conventional tablet dosage form. A major barrier of conventional chemotherapy is poor specificity, side effects, and drug resistance leading to a reduction in the therapeutic window. Hence a novel delivery system is recommended for the delivery of letrozole.[7]

Solid lipid nanoparticles (SLN) were utilized as an alternate drug delivery system to traditional carrier systems. SLN were developed combining advantages and nullifying disadvantages of colloidal carrier such as liposomes, emulsions, polymeric nanoparticles.[8] Solid lipid nanoparticle is an aqueous colloidal dispersion consisting of solid biodegradable lipid as matrix and stabilized with the aid of surfactant.[9]

Pharmaceutical development of novel solid lipid nanoparticles includes complex

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ORGANOGELS IN TOPICAL DRUG DELIVERY SYSTEM: A SYSTEMATIC REVIEW

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ABSTRACT

In topical drug delivery system, the gel has gained increasing attention due to the ease of fabrication methods, provides local and systemic effect, greater drug loading capacity, ability to penetrate into deeper skin layers, easy to apply, minimum side effects etc. Organogels are gels formulated with organic liquid phases, which are distinguished from hydrogels infiltrated with water/aqueous solutions in a three-dimensional network. In this review fundamental understandings of organogels, their basic composition, different types of organogelators, factors affecting organogel, gelation mechanisms, types of organogels fabrication methods, various bioactive agents that can be incorporated inorganic gels, evaluation parameters and applications in drug delivery and recent advancements are summarized. Finally, the remaining challenges and prospects of organogel are addressed.

KEYWORDS: Topical drug delivery, organogels, Hydrogels.

INTRODUCTION

Topical drug delivery system is a way to deliver medication that is applied on to a particular part of the body typically on the skin. Topical drug delivery is an interesting option because it is convenient and safe. This offers several potential advantages over conventional routes like avoidance of first pass metabolism, minimizing undesirable side effects, and most significantly it provides patient compliance as the drug delivery is painless. Topical gels are semisolid dosage forms in which a liquid phase is constrained within three-dimensional polymeric metrics derived from natural or semi synthetic sources. Gels are defined as semi-solid system in which liquid solvent phase immobilised within a 3D network structure formed by the gelator molecules by physical or chemical manner. Depending upon the nature of the dispersed solvent phases gels can be typically classified into hydrogels and organogels.

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RESEARCH ARTICLE

The Anti-leukemic Potential of *Cyclea peltata* as Validated by Phytochemical and Cell Line Studies

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ABSTRACT:

Hematological malignancies for a very large percentage of cancers occurring the world over and lead to a very large number of deaths each year. It is not just the disease but also the currently available cure which are equally responsible for the side effects and discomfort experienced by the patients. The side effects of the current chemotherapeutic agents' available range from mouth ulcers, diarrhea, temporary hair loss, rashes, nausea, vomiting, and fatigue to low blood cell counts, increased risk of infections, graft versus host disease, tumor lysis syndrome, differentiation syndrome, and difficulty in conceiving. Due to these myriad side effects researchers and on a continuous lookout for newer treatment alternatives. For most developing countries one of the most attractive options is offered by herbals or plant-based medicines. One such herb is *Cyclea peltata.* It is a climbing shrub found aplenty in southern and eastern India. It has been used traditionally to cure lots of minor ailments. This paper explores the possibility of using the root extract for the treatment of leukemia. To do this, the extracts of the roots were prepared in different organic solvents to ensure complete extraction of all phytoconstituents fractions. The extracts were then tested on 3 different human cell lines. The potential cause of the antileukemic potential of the plant was also hypothesized and proven by carrying out antioxidant studies using the DPPH free radical scavenging assay. The probable active constituents were identified using the liquid chromatography-mass spectrometry assessment, wherein the responsible fractions were successfully identified. The studies showed that the alkaloid and phenolic phytoconstituents were responsible for the antileukemic potential via their antioxidant activity. This lays down the groundwork of offering a new and safer treatment option that could be further explored to be made into one having actual clinical outreach.

KEYWORDS: *Cyclea peltata*, leukemia, cell line studies, DPPH assay, antioxidant, LCMS.

INTRODUCTION:

Cancer is the second frequent cause of death globally and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer[1]. Various types of cancer can afflict human beings. One such is leukemia. It is responsible for 3.8% of total cancer deaths around the world[2]. It is a malignant condition characterized by atypical proliferation of blood cells in the bone marrow and blood-forming organs. It can be further classified depending on the blood cell afflicted into myeloid leukemia (which affects myeloid cells, granulocytes like neutrophils, basophils, and eosinophils, and monocytes) and lymphocytic leukemia which involves T and B lymphocytes[3]. Current therapy includes the use of potent drugs mostly in combination and at regular time intervals with the intention to annihilate or irreparably damage the cancerous cells. Current treatment options are Gemtuzumabozogamicin (Mylotarg™), Midostaurin (Rydapt®), Daunorubicin and cytarabine (Vyxeos™), Venetoclax (Venclexta®), Glasdegib (DaurismoTM), and Ivosidenib (Tibsovo®). It is common knowledge that this chemotherapy by itself is the reason for a lot of side effects and the cause of suffering in most patients. Though all patients react differently to the treatment and hence the side effects are

Original Article

Formulation And Development Of Nanosuspension For Solubility Enhancement Of Gefitinib

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Abstract

Gefitinib (GFT) is a BCS class II tyrosine kinase inhibitor with limited solubility and bioavailability. In the present investigation, nanosuspensions (NSPs) were formulated to overcome these pitfalls. The GFT-NSPs nine batches were prepared by nanoprecipitation method using Poloxamer-188 (Polo-188) and Tween-80. The developed formulations were subjected to determine percent drug content, percent drug entrapment, particle size, polydispersity index, zeta potential, x-ray diffraction pattern, formulation morphology, solubility and *in vitro* drug release. Following the percent drug content and entrapment, NSP-6 was selected as an optimized batch. In the study's outcomes, it was observed that NSP-6 showed 96.71 percent drug content and 96.61 percent drug entrapment. In particle size analysis, NSP-6 explored 357.6.4 nm dimensions, 0.325 polydispersity index and -26.5 zeta potential. X-ray diffractogram of NSP-6 indicated characteristics peak of both GFT and Polo-188. Morphological photomicrographs of NSP-6 explored small spherical structures. In the solubility study, it was observed that NSP-6 showed higher solubility enhancement than pure GFT in purified water, methanol and pH 7.4 phosphate buffer. *In vitro* dissolution study of pure GFT and NSP-6 exhibited 97.23% and 99.14% drug dissolution. NSP showed a maximum drug dissolution rate; therefore, NSP was considered a suitable approach for the solubility enhancement of GFT. The developed NSP significantly increased the water solubility and bioavailability of GFT, suggesting its potential as a nanocarrier in the delivery of GFT for future clinical application.

Keywords: Gefitinib, Nanosuspension, Solubility, Tuberculosis, Tyrosine kinase inhibitors

1. INTRODUCTION

Low aqueous solubility is one of the significant challenges during the formulation of new chemical entities and generics. In drug discovery, most new candidates share this undesirable physicochemical property[1]. Due to the slow dissolution of these compounds, absorption and bioavailability are limited when administered orally. Some of the most common technologies applied to enhance biopharmaceutical properties of drugs are micronization, nanosizing, crystal engineering, application of solid dispersions, molecular or lipid encapsulations, and other colloidal drug delivery systems such as formulation of microemulsions and self-emulsifying drug delivery systems[2]. The biopharmaceutics classification system is a scientific classification designed for actives based on their aqueous solubility and *in vivo* bioavailability. BCS takes two fundamental factors: solubility and intestinal permeability, into account, predicting oral drug absorption of solid dosage forms[3]. GFT is BCS class II drug demonstrating poor water solubility and high permeability. GFT is a type of drug called a tyrosine kinase inhibitor (TKI). Kinases are proteins in the body that regulate how the cells grow and divide. GFT restricts mycobacterium tuberculosis growth through increased lysosomal biogenesis and modulation of cytokine signalling [4]. The GFT inhibit target protein (EGFR) is a family of receptors which includes Her 1 (erb-B1), Her 2 (erb-B2), and Her 3(erb-B3).GFT is absorbed slowly after oral administration with a mean bioavailability of 60%[5]. It is metabolised by CYP 3A4, primarily eliminated by the liver, and faces 48 hours elimination half-life. As aforesaid, GFT is a poorly water-soluble drug; hence various technologies have been developed to enhance its solubilities, such as solid dispersion, crystal engineering, salt formation, and complexation. All methods are utilized to attack universal applicability to all drugs[2]. Nanotechnology is one of the emerging fields in pharmaceutical development to enhance the solubility of poorly soluble drugs. In nanotechnology nanoemulsion, nanoparticles and NSPs are the most commonly used methods [6]. Regarding NSPs, submicron colloidal dispersions of nanosized drug particles stabilized by surfactants and poorly water-soluble drugs are without any matrix material suspended in dispersion. NSPs help in enhance solubility as well as the bioavailability of drugs. Precipitation, high-pressure homogenization, and solvent evaporation techniques using stabilizers and co-stabilizer are the most common methods for NSP development[7]. As previously mentioned, GFT is a

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ARIPIPRAZOLE NANOSPONGE: NASAL IN-SITU GEL FORMULATION FOR NOSE TO BRAIN DELIVERY

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ABSTRACT

Aripiprazole offers treatment for schizophrenia but the drug undergoes significant degradation in GI tract leading to poor bioavailablity. The aim of present study is to formulate *in-situ* nasal gel for nose to brain delivery of Aripiprazole loaded nanosponge (ARP-NS) to achieve better treatment outcomes. **Method:** Nanosponges (NS) offer the advantage of enhanced dissolution, permeation and drug stability. NS were prepared using β-CD and diphenyl carbonate; parallel reaction synthesizer at temperature 85°C, 1000 rpm. The formulation was optimized for Carbopol 940 and HPMC K100 concentration using 3^2 factorial designs. The ARP-NS was characterized by FTIR, DSC, XRPD, zeta size and SEM. The formulations were evaluated for parameters such as pH, drug content, viscosity, drug release, mucoadhesion, *ex-vivo* permeation and stability studies. **Results:** The PyMOL Molecular Graphics software was used to model β –CD NS and entrapment of Aripiprazole in the cavity, which along with other characterization techniques confirmed drug entrapment. Drug release from formulation and plain drug was found to be 93.85 ± 0.43% and 41.92 ± 0.36% respectively in 6 h. Treatment outcome was better from *in-situ* gel formulation compared to oral ARP solution on performing locomotor studies on psychosis induced rats. Pharmacokinetic evaluation was performed on Sprauge dawley male rats. Cmax, Tmax & AUC of ARP-NS (in brain) was found to be 4929 ± 21.56 ng/mL, 3 h and 930.35 ± 24.5 ng.h/mL. **Conclusion:** This study showed that Aripiprazole could be delivered effectively to the brain using nanosponge incorporated in *in-situ* gel which produced sustained drug release.

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Research article

Design, molecular modeling, synthesis and biological evaluation of novel pyrazole based schiff Bases as fungal biofilm inhibitors

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ABSTRACT

We designed series of pyrazole based Schiff bases on the basis of Bioisosteric replacement principle and validated for drug likeness using Absorption, Distribution, Metabolism, and Excretion (ADMET) criteria. The designed Schiff bases who have excellent pharmacokinetics properties, Low toxicity when *In-silico* analyzed for inhibition potential using molecular docking study. The top hit of molecular docking having free energy of binding in between -6.95to -4.28 kcal/mol was synthesized and biologically evaluated for fungal biofilm inhibition and minimum inhibitory concentration. The *invitro* biological assay of synthesized Schiff bases suggesting antibiofilm activity of Schiff base MPY10 inhibitory concentration (IC50=41.7µM) and MPY1 (IC50=44.7µM) very much equivalent to standard drug Fluconazole. The inhibition potential of MPY10 (MIC=42.6µg), MPY1 (MIC=54.4µg), MPY2 (MIC=58.1µg), MPY6 (MIC=61.8µg) and MPY4 (MIC=64.2µg) reproduces the molecular docking results shown against *c. albicans* biofilm drug target secreted aspartic proteinases (Sap5) signifying antifungal activity as that of standard.

Keywords: Schiff bases, Secreted aspartic proteases (Saps), Biofilm, Pharmacokinetics properties, Molecular docking, Antifungal assay.

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INTRODUCTION

Fungi are one of the most silent killers in infectious diseases to humankind. There is very high biodiversity of fungal species and around 3.8 million of fungal species has been identified from the around 300 are pathogenic to humans. The recent study has shown that the symptoms caused by fungal infection and COVID-19 are very much similar. More than 150 million the serious cases of fungal infection reported every year which results in death of 1.7 million of people each year. Almost billions of the people every year infected with avoidable topical fungal diseases whereas millions of the people have serious mucosal candidiasis fungal infection [1–2]. The fungal species such as Aspergillus, Candida, Cryptococcus species, P. jiroveci and H. capsulatumare the most virulent among the all the fungal species. The person with weak immunity or concurrent diseases where immunity is compromised in diseases such as Cancer, AIDS, COVID-19, organ transplant, asthma and concurrent therapy of corticosteroids may lead to serious life threatening condition in fungal infection [3].The clinical observation of patient who is admitted in intensive care unit and those on ventilators are having a great possibility to have serious fungal infections. The antifungal agents such as antifungal antibiotics, azoles, triazole, tetrazoles, allyamine etc are formulated in various formulations which either kill or suppress the fungal growth in order to treat topical or systemic infection. Similar to antibacterial agent's fungal species also develops the resistance towards antifungal agents [4]. The resistance to antifungal agent can be serious complication if it is invasive fungal infection. The drug target for antifungal agents is generally cell wall synthesis, plasma membrane synthesis or synthesis of fungal nucleic acid or proteins. The drug resistance for antifungal agents is mostly due to mutation in the target gene or protein or increase in efflux of the drugs or by formation of biofilm by resistance strain of fungi[5].To break this mash of drug resistance it is important to have agents who are selective and they should not inhibit or interfere with host metabolic or any other cellular functions. Identification and establishment of new drug target will be the key stone in design or development of novel lead molecules to counter the fungal infection [6]. As the concurring of drug resistance is a vital aspect in current

Original Article

Alleviation of Hepatotoxicity by Natural Chelators in Lead-induced Poisoning in Rats

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Abstract

Aims: The study intends to monitor the consequences of lead on the body, its reversal by natural chelators (chitosan and chitosamine), and comparison of monotherapy with the combination using the synthetic ones. **Materials and Methods:** A total of 42 albino Wistar male rats (200–250 g) were divided into seven groups (n = 6). Except for the first group which received sodium acetate 1 g/L (drinking water, vehicle control), all groups received lead acetate 0.4 mg/kg body weight peroral (p.o.). Group II (toxic) received merely lead acetate, whereas the third and fourth groups received 0.2 g/kg (p.o.) of chitosan and chitosamine, respectively. Groups V–VII received ethylenediaminetetraacetic acid (EDTA) 495 mg/kg (p.o.). In addition, the sixth and seventh groups received chitosan and chitosamine (0.2 g/kg) (p.o.), respectively. The hematological, biochemical, oxidative stress parameters, number of porphobilinogen molecules formed/h/mL, and histopathology were assessed. The data obtained were compared using analysis of variance following Tukey's test. **Results:** The results revealed a statistically significant reduction in the hemogram parameters, antioxidant enzymes, porphobilinogen molecules and an increase in oxidative stress, liver biomarkers along with malondialdehyde in the toxic group in comparison with control and treatment groups. The histopathological findings revealed a significant improvement in the chitosan and chitosamine treatment groups when compared with the toxic group, whereas the results obtained from combination therapy with respect to its monotherapy were most significant than the monotherapy alone. **Conclusion:** Chitosan and chitosamine are found to improve hemato- and hepatotoxicity by chelation and can be used as potent detoxifiers in heavy metal toxicities.

Keywords: *Chelation, chitosamine, chitosan, lead toxicity, oxidative stress*

Introduction

Heavy metals possess toxic effects on the human body, out of which the two most common widely studied metal ions are lead and mercury possessing the highest toxicity to the developing central nervous system. According to the World Health Organization, lead ion present in the earth is a highly toxic element present in nature's ecosystem. Its extensive use results in environmental pollution causing significant public health issues owing to human exposure in various corners of the world. Sources of lead are polluted water, air, dust, various food items, or other consumer products. The major treatment involves the removal of lead by chelation therapy.[1] There is indeed a low safety margin between existing occupational blood lead suspension limits and subclinical effects owing to which the parameters for the lead users were set at a low level as per the voluntary Code of Practice observed in some national legislation, specifically Control of Lead at Work Act 2002. Lead being non-biodegradable has devastating effects on the body causing rapid accumulation in the liver, kidney, and other human organs following intestinal absorption.[2] There is not a single organ system in the human frame not influenced by lead poisoning. Unlike the developed countries such as the USA and Canada where the lead is being used meticulously, it is still used intensely in the developing countries.[3] Lead exposure causes various ill effects on the hematopoietic, renal, reproductive, and central nervous system, primarily due to oxidative insults. Blood lead levels exceeding 70 µg/dL are rare, resulting in encephalopathy, coma, and death.[4] These variations play a noticeable role in disease diagnosis and their manifestations.[5] Chelation therapy is suggested in children

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Original Article

Amelioration of Hepato-renal Impairment by Natural Chelators in Lead-induced Poisoning in Rats

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ABSTRACT

Background: Hepato-Renal impairment refers to renal dysfunction in a liver compromised state concerning lead metal exposure. Natural chelators (marine source) have potent chelating properties claiming to ameliorate hepato-renal dysfunction in heavy metal toxicity **Material and Methods:** A total of 42 male albino Wistar rats weighing between 200 to 250 g were categorised into seven groups ($n=6$). Except for the first group (control), which received sodium-acetate (1,000 mg/L in drinking water), all of the groups received lead acetate 0.4 mg/kg body weight per oral (p.o). Second-group is the negative control group (toxic), the third and fourth received Chitosan and Chitosamine 0.2 g/kg (p.o) respectively. Ethylene diaminetetra acetic acid (EDTA) 495 mg/kg (p.o) was given to the fifth, sixth, and seventh groups, whereas Chitosan and Chitosamine [0.2 g/kg (p.o)] were given to the sixth and seventh groups, respectively. **Results:** There is statistical significant increase in atherogenic indices, serum lipid profile, renal tissue oxidative-stress, renal function biomarkers, kidney weights, and decrease in body weights of experimental animals in the toxic as compared to control whereas these values ameliorated in treatment groups as compared to toxic group. Histopathology of toxic group kidneys revealed histologic and pathological changes in nephrons along with dyslipidemia which healed to normal architecture and analytical values in treatment groups. Thus, the study confirms the nephro protective effect and improvement of dyslipidemia as a consequence of hepato-renal impairment by natural chelators. **Conclusion:** The natural chelators have hepatic and nephro protective effect in lead metal induced poisoning.

Keywords: Lead Toxicity, Nephrotoxicity, Chitosan, Chitosamine, Chelation, Atherogenic indices, Oxidative Stress.

INTRODUCTION

Plumbism, or lead (Pb) toxicity, was recognized as early as 370 BCE when Hippocrates coined the term "lead colic".[1] Human well-being is known to be affected predominantly by lead and its compounds as these are widely distributed in nature and rapidly accumulate in the liver, kidney, and other human organs after intestinal absorption.[2] Lead has an impact on three major organ systems that are the central and peripheral nervous systems, the heme biosynthetic pathway; and the renal system. It is one of the poisonous metals in the environment having a deleterious impact on most organs of the human body viz. physiological, biochemical, neurological, behavioural, impairment of renal system functions and reproductive systems.[3] Lead can translocate through the food chain and cause harmful effects on humans and other living organisms.[4] Lead targets the body mainly through three main routes viz. digestive, respiratory tracts and skin which further causes deleterious effects on several organ systems, but those in the kidney are the most steadily. Acute lead nephropathy is characterized by proximal tubular dysfunction with the distinct syndrome known as Fanconi-type alongside alterations in mitochondrial structure, and the advancement in inclusion bodies (cytosolic and nuclear). Metallothionein, a specific

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ARIPIPRAZOLE NANOSPONGE: NASAL IN-SITU GEL FORMULATION FOR NOSE TO BRAIN DELIVERY

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ABSTRACT

Aripiprazole offers treatment for schizophrenia but the drug undergoes significant degradation in GI tract leading to poor bioavailablity. The aim of present study is to formulate *in-situ* nasal gel for nose to brain delivery of Aripiprazole loaded nanosponge (ARP-NS) to achieve better treatment outcomes. **Method:** Nanosponges (NS) offer the advantage of enhanced dissolution, permeation and drug stability. NS were prepared using β-CD and diphenyl carbonate; parallel reaction synthesizer at temperature 85°C, 1000 rpm. The formulation was optimized for Carbopol 940 and HPMC K100 concentration using 3^2 factorial designs. The ARP-NS was characterized by FTIR, DSC, XRPD, zeta size and SEM. The formulations were evaluated for parameters such as pH, drug content, viscosity, drug release, mucoadhesion, *ex-vivo* permeation and stability studies. **Results:** The PyMOL Molecular Graphics software was used to model β –CD NS and entrapment of Aripiprazole in the cavity, which along with other characterization techniques confirmed drug entrapment. Drug release from formulation and plain drug was found to be 93.85 ± 0.43% and 41.92 ± 0.36% respectively in 6 h. Treatment outcome was better from *in-situ* gel formulation compared to oral ARP solution on performing locomotor studies on psychosis induced rats. Pharmacokinetic evaluation was performed on Sprauge dawley male rats. Cmax, Tmax & AUC of ARP-NS (in brain) was found to be 4929 ± 21.56 ng/mL, 3 h and 930.35 ± 24.5 ng.h/mL. **Conclusion:** This study showed that Aripiprazole could be delivered effectively to the brain using nanosponge incorporated in *in-situ* gel which produced sustained drug release.

life

Review

An Overview of Diabetic Foot Ulcers and Associated Problems with Special Emphasis on Treatments with Antimicrobials

Mirza Shahed Baig [1], Ahmadi Banu [2], Mehrukh Zehravi [3], Ritesh Rana [4], Sushil S. Burle [5], Sharuk L. Khan [6,*], Fahadul Islam [7], Falak A. Siddiqui [6], Ehab El Sayed Massoud [8,9,10], Md. Habibur Rahman [11,*] and Simona Cavalu [12,*]

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Abstract: One of the most significant challenges of diabetes health care is diabetic foot ulcers (DFU). DFUs are more challenging to cure, and this is particularly true for people who already have a compromised immune system. Pathogenic bacteria and fungi are becoming more resistant to antibiotics, so they may be unable to fight microbial infections at the wound site with the antibiotics we have now. This article discusses the dressings, topical antibacterial treatment, medications and debridement techniques used for DFU and provides a deep discussion of DFU and its associated problems. English-language publications on DFU were gathered from many different databases, such as Scopus, Web of Science, Science Direct, Springer Nature, and Google Scholar. For the treatment of DFU, a multidisciplinary approach involving the use of diagnostic equipment, skills, and experience is required. Preventing amputations starts with patient education and the implementation of new categorization systems. The microbiota involved in DFU can be better understood using novel diagnostic techniques, such as the 16S-ribosomal DNA sequence in bacteria. This could be achieved by using new biological and molecular treatments that have been shown to help prevent infections, to control local inflammation, and to improve the healing process.

Keywords: diabetic foot ulcers; diabetes mellitus; Wagner grade; diabetic neuropathy; antimicrobials; biofilms

1. Introduction

More than 415 million people throughout the world are diagnosed with diabetes, and that number is expected to climb to 640 million (1 in 10) by the year 2040, according to the

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DUAL TARGETING OF VEGFR-2 AND C-MET KINASES VIA THE DESIGN AND SYNTHESIS OF SUBSTITUTED BENZYLIDENE-6-(5-CHLOROPYRIMIDIN-2-YL)-9H-PURINE-2,6-DIAMINE DERIVATIVES AS ANGIOGENESIS INHIBITORS

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ABSTRACT

We have designed and synthesized a unique library of benzylidene-6-(5-chloropyrimidin-2-yl)-9H-purine-2,6-diamine derivatives as angiogenesis inhibitors. The designed scaffolds were subjected to docking and ADME prediction studies so as to guage the particular interaction. Further anti-proliferative activity was allotted by employing the SRB method as a target for colorectal cancer on HT-29 and COLO-205 cell lines. The SM-6 derivative showed good anticancer activity and was subjected to in-vitro enzyme inhibition activity using a flow cytometer to test the enzyme inhibition potential. It also induced apoptosis and cell cycle arrest at the G0/G1 phase on HT-29 cells supported by DAPI staining and propidium iodide (PI) staining followed by flow cytometry analyses. These compounds exhibited slight inhibitory effects against VEGFR and c-Met kinases, so their active skeletons warrant further study and will have a positive effect on the event of small anticancer inhibitors of dual-target VEGFR/c-Met kinase.

Keywords: Synthesis, Anti-Proliferative Activity, Cell Cycle Analysis, Apoptosis Assay, VEGFR-2 Inhibitory Assay, Molecular Docking, In-silico ADME Study, MM/GBSA.

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INTRODUCTION

Tumors can be a multi-stage, complex process with life-threatening consequences for people's health and lives.[1] For tumor spread, growth, and survival (RTK) a variety of signal transduction pathways including receptor tyrosine kinases are required for cell differentiation, proliferation, angiogenesis, and apoptosis.[2] In response to ligands, RTK primarily activates transcription factors that mediate target organic phenomenon. RTK signaling pathways are complicated including a wide range of metabolic events and molecular mediators in complex signaling networks.[3] Vascular endothelial protein receptor-2 (VEGFR-2) is taken into account because of the main effector of VEGF/ VEGFR signal transduction in promoting tumor angiogenesis.[4,5] The phosphorylation of VEGFR-2 activates the Raf-1/MAPK/ERK signaling pathway, which results in angiogenesis and improves vascular permeability and tumor migration.[6] Therefore, inhibition of the VEGFR-2 signaling pathway is taken into account in the concert of the foremost important pathway within the development of tumor chemotherapy.[7,8] Mesenchymal epithelial transfer factor tyrosine kinase (c-MET) may be a crucial member of the receptor tyrosine kinases (RTK) family.[9] c-MET is activated by extracellular binding of its ligand, hepatocyte growth factor/ scatter factor (HGF/SF).[10] The aberrant expression of c-MET/ HGF signaling arises from c-MET mutations or overexpression or genomic amplification, which may promote proliferation, migration, invasion, and tumor angiogenesis.[11] The role of c-MET and VEGFR-2 have a synergistic role within the angiogenesis of human cancer. The utilization of dual targets i.e., c-MET and VEGFR-2 inhibitor may act as a necessary element within the development of targeted therapy.[12,13] c-MET is up-regulated in response to VEGFR pathway inhibition and so plays a vital role in tumor angiogenesis and progression.[14] However, the matter of drug resistance frequently arises within the research of single-target drugs and combination drugs. It is found that multi-target drugs may

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Systematic Review on Cholangiocarcinoma: A Rare Desmoplastic Cancer of Biliary Tree

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Abstract

Cholangiocarcinoma (CCA) a malignancy of biliary epithelium can arise anywhere within the biliary system from the intrahepatic ducts to the hepatopancreatic ampulla whose molecular pathogenesis remains largely un-deciphered, understanding biliary anatomy and breadth of its variation find particular importance in the treatment of CCA. Their incidence increasing globally accounting for 15 % of all primary level cancers and 3% of gastrointestinal malignancy. The salient presentation of these tumors combine with their highly aggressive nature and refractoriness to chemotherapy contribute to their alarming mortality representing 2% of all cancer related deaths worldwide yearly. We aim to provide valuable information on classification, pathological features, risk factors, geographical variation, biomarkers, tumor microenvironment, animal models and potential treatment for inhibition of CCA and its heterogeneity.

Key words: CCA: Cholangiocarcinoma, ICCA Intrahepatic Cholangiocarcinoma, DCCA Distal Cholangiocarcinoma

Introduction

Cholangiocarcinoma is a very malignant tumor and epithelial cell cancer which arises from the bile duct which has cholangiocyte differentiation (1). Cholangiocarcinoma occurs anywhere between the biliary tree and is classified based on the anatomical position of the tumor (2).They are very rare type of tumors constituting to about 3% of the total gastrointestinal cancers and occurs to every 2 per 100,000 people (3). It is classified into 2 subtypes mainly intra-hepatic and extra hepatic-extra hepatic is further subdivided into perihilar cholangiocarcinoma and distal cholangiocarcinoma .Cholangiocarcinoma has a notoriously poor prognosis and is very difficult to diagnose and detect and the detection is based on the noninvasive techniques.
Most patients present with painless jaundice and at this stage the life expectancy is below 1 year because they are ineligible for a surgical resection to remove the tumor, and if in some cases the cholangiocarcinoma is resected, the survival rate in the next five years after surgery is very disappointingly low which is less than 30%. Cholangiocarcinoma can form anywhere in the biliary tree but PCCA (perihilar cholangiocarcinoma) is very common and accounts for 50% of the total cases. And even after resection or transplant of the liver there are more than 50% chances that the CCA will soon recur within 1 year of the resection.

Classification of Cholangiocarcinoma;

1. ***Intrahepatic Cholangiocarcinoma***;

ICCA is mostly arising from intrahepatic biliary tract patients are observed with intrahepatic mass lesions ICCA can be further subdivided into 4 subtypes

- Mass forming
- Periductal – infiltrating
- Intraductal

Mass forming ICCA is the most common and spreads via venous and lymphatic vessels, ICCA are usually adenocarcinoma which has poor differentiation.

2. Perihilar Cholangiocarcinoma

They develop between the second orders biliary ducts at the site of the cystic duct origin. They are the most common accounting for 50% of the total cholangiocarcinoma cases
They have the following patterns

- Mass forming (xerophytic)
- Intraductal growth patterns

Intraductal PCCA can be nodular or periductal infiltrating.

antibiotics

MDPI

Article

The Design, Synthesis, and Evaluation of Diaminopimelic Acid Derivatives as Potential *dap*F Inhibitors Preventing Lysine Biosynthesis for Antibacterial Activity

Mohd Sayeed Shaikh [1,*], Mayura A. Kale [2], V. Muralidharan [3], T. Venkatachalam [4], Syed Sarfaraz Ali [5], Fahadul Islam [6], Sharuk L. Khan [7], Falak A. Siddiqui [7], Humaira Urmee [8], Ganesh G. Tapadiya [9], Sachin A. Dhawale [9], Long Chiau Ming [10], Ibrahim Abdel Aziz Ibrahim [11], Abdullah R. Alzahrani [11], Md. Moklesur Rahman Sarker [12,13,*] and Mohd Fahami Nur Azlina [14,*]

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Abstract: We created thiazole and oxazole analogues of diaminopimelic acid (DAP) by replacing its carboxyl groups and substituting sulphur for the central carbon atom. Toxicity, ADME, molecular docking, and in vitro antimicrobial studies of the synthesized compounds were carried out. These compounds displayed significant antibacterial efficacy, with MICs of 70–80 µg/mL against all tested bacteria. Comparative values of the MIC, MBC, and ZOI of the synthesized compound were noticed when compared with ciprofloxacin. At 200 µg/mL, thio-DAP (1) had a ZOI of 22.67 ± 0.58, while ciprofloxacin had a ZOI of 23.67 ± 0.58. To synthesize thio-DAP (1) and oxa-DAP (2), l-cysteine was used as a precursor for the L-stereocenter (l-cysteine), which is recognized by the *dap*F enzyme's active site and selectively binds to the ligand's L-stereocenter. Docking studies of these compounds were carried out using the programme version 11.5 Schrodinger to reveal the hydrophobic and hydrophilic properties of these complexes. The docking scores of compounds one and two were −9.823 and −10.098 kcal/mol, respectively, as compared with LL-DAP (−9.426 kcal/mol.). This suggests that compounds one and two interact more precisely with *dap*F than LL-DAP. Chemicals one and two were synthesized via the SBDD (structure-based drug design) approach and these act as inhibitors of the *dap*F in the lysine pathway of bacterial cell wall synthesis.

Keywords: diaminopimelic acid; *dap*F inhibitors; structure-based drug design; heterocyclic; antibacterial; enzyme

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EXPLORING ANTICANDIDAL AND ANTIBIOFILM POTENTIALS OF SYNTHESIZED *N-(SUBSTITUTEDBENZYLIDENE)-4,6-DIMETHOXYPYRIMIDIN-2-AMINE* ANALOGUES

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The emergence of resistance in the immunocompromised patients against existing anticandidal agents makes them ineffective causing high incidence and accompanying mortality due to the fungal infections. The generation of biofilms by various species of candida is the most frequent underlying mechanism in the emergence of resistance. Biofilms are defined as encapsulated complex microbial colonies in extracellular polymeric substances (EPS) matrix. The development of newer anticandidal with lower resistance remains a challenging task for researchers. We herein report, a series of N-(substituted benzylidene)-4,6-dimethoxypyrimidin-2-amine analogs along with their antibiofilm and anticandidal potential in-vitro. Compounds ***3a, 3b, 3i, 3k, and 3l*** *have shown better inhibition against C. albicans than Fluconazole (standard anticandidal agent). Compounds* ***3a, 3b, and 3i*** *also exhibited good antibiofilm activity suggesting their antibiofilm as well as anticandidal potential. The results show that the new compounds could serve as an important lead in the discovery of effective anticandidal agents to overcome the resistance problem associated with the existing anticandidal agents.*

Keywords: *Pyrimidine Schiff bases; Anticandidal activity; Antifungal; Antibiofilm*

INTRODUCTION

Candidiasis is a pathological condition that is mainly found in immunocompromised patients. Candidiasis is mainly caused by *Candida albicans*.[1-3] Morphologically, is a versatile microbe that exists in three forms i.e. yeasts, pseudohyphae, and hyphae. The lifestyle of *C. albicans* has two forms, i.e. planktonic and biofilm form which is a dormant condition that helps in the survival of microbe in adverse environmental conditions.[4-12] The key virulent characteristic of *C. albicans* is morphogenetic [Yeast-to-Hypha (Y-H)] transitions that facilitate host tissue invasion by the microbe.[6-10] Besides this Y-H transition, the other contributing factor in *Candida* infections is the formation of biofilms on host tissues or abiotic devices.[8-10] Biofilms are defined as encapsulated complex microbial colonies in extracellular polymeric substances (EPS) matrix. An organism developing into a biofilm displays changes in morphology, cellular composition, polymeric substance secretion, and EPS synthesis.[11] The EPS contains extracellular nucleic acid and extracellular polymers that uphold the biofilm structure.[11] EPS possess nucleic acid which is mainly responsible for structural and protective properties in *C. albicans* biofilms. The other core of EPS is β 1,3-glucans, which play important role in the protection of biofilm by preventing contact of anticandidal with target cells.[11] The matrix of biofilm plays a dual role in biofilm; it contributes to biofilm structure by providing physical support as well as it is essential for increased tolerance to anticandidal drugs. Biofilms formed by *Candida* turn them more resistant to anticandidal agents than planktonic cells.[13] The traditional treatment for *Candida* infections includes azoles (fluconazole, itraconazole, and voriconazole),

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ORIGINAL ARTICLE

Phytochemical, Histochemical and *In Vitro* Antimicrobial Study of Various Solvent Extracts of *Costus speciosus* (J. Koenig) Sm. and *Costus pictus* D. Don

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ABSTRACT

Objectives: Costaceae family comprises many ornamental and medicinal plants used for different diseases. This investigation includes the phytochemical, histochemical, and *in vitro* antimicrobial study of *Costus speciosus* (J. Koenig) Sm. and *C. pictus* D. Don.

Materials and Methods: Solvents such as methanol, ethyl acetate, and hexane were used to extract the leaves and rhizomes of both plants. The antibacterial study was executed using the agar well diffusion technique.

Results: Phytochemical study confirmed that alkaloids, flavonoids, quinones, and saponins were present in solvent extracts of both plants. The macromorphological studies including size, shape, texture, surface characters, and color, were analyzed. *Salmonella typhi, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus* were used for the antibacterial study. Agar well diffusion and agar disk diffusion methods were performed to determine the susceptibility of bacterial strains to various extracts of these plants.

Conclusion: Histochemical analysis revealed alkaloids, proteins, and phenols in the vascular bundles, the cortex, and epidermis of stem, root, and leaves of the plants. Inhibition zones caused by the methanol and hexane extracts showed better antibacterial activity compared to those of other extracts. Future work on the isolation, purification, and characterization of the active constituents and the elucidation of possible mechanisms can be executed.

Key words: Costaceae, *Costus pictus, Costus speciosus,* histochemical, antibacterial activity

INTRODUCTION

Plants have been used as medicine since the start of the human race.[1] These medicines were initially used as poultices, tinctures, teas, powders, *etc*.[2] Medicinal plants are familiar sources of medicine. Substantial evidence can be cited favoring herbs being used to treat diseases and restoring and fortifying body systems in the ancient systems of medicines such as Ayurvedic, Unani, and Chinese traditional medicine.[3] Antimicrobial activity is one of the most eyed usefulness in the field of herbal medicines. A measurement of determination of antibacterial activity is zone of inhibition. There is a proportionate relationship between the zone of inhibition and antibacterial activity.[4] Many plants have shown a profound antimicrobial activity. The family of Zingiberaceae comprises about 1.300 species and 52 genera spread all over Asia, tropical Africa, and the Americas.[5] In a country like India, the plant propagates in the sub-Himalayan region, central India, Maharashtra, Karnataka, and Kerala.[6] The *Costus* spp. from the family Costaceae are commonly grown as medicinal and ornamental plants.[7,8] The *Costus* spp. additionally used as a dietary supplement to manage many diseases throughout the world.[9] *Costus speciosus* (CS), commonly known as crepe ginger,[10] is an essential plant grown in India.[11] The name CS was changed recently to *Hellenia speciosa* (J. Koenig ex Smith) S. Dutta.[12,13] The pharmacological activities reported for CS are antioxidant, antibacterial, analgesic, anti-cholinergic activity, antidiabetic, anti-inflammatory, antidiuretic, antifungal, larvicidal, estrogenic activities, and anti-stress.[14,15] *Costus pictus* (CP) is another ornamental plant from the family of Costaceae. CP is also known as fiery *Costus,* insulin plant, spiral flag, and step ladder.[16,17] The rhizome and leaves show antidiuretic,

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DIURETIC EFFECT OF NOVEL STRUCTURAL ANALOGUES OF ETHACRYNIC ACID

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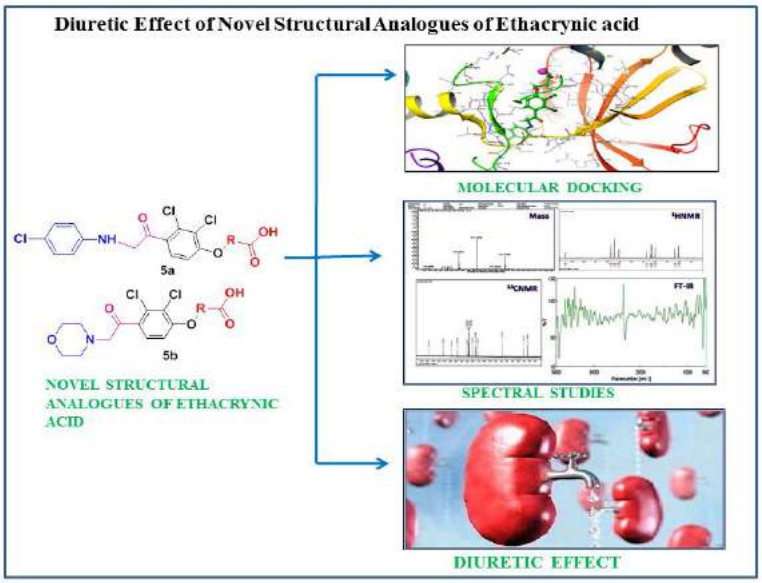
ABSTRACT
Ethacrynic acid is a highly effective clinically used loop diuretic. Literature reveals that it can produce diuresis in patients with chronic renal failure. The present research study aims to develop novel structural analogues of ethacrynic acid having greater diuretic effect. Designed compounds were docked against NKCC2 (PDB: 5DBX) using Ethacrynic acid as standard. After evaluation of docking results compounds were slected for synthesis. Synthesis was completed in three steps with the Convenient synthetic route as shown in the scheme. The Structures of novel synthesized molecules were confirmed by spectral characterization such as FTIR, ^{1}HNMR, ^{13}CNMR and Mass spectrometry. Toxicological and ADME studies were done to ensure safety and drug like properties of the novel compounds.Ten structural analogues of ethacrynic acid were synthesized and evaluated for diuretic effect in albino wistar rats. The diuretic effect was measured by calculating different parameters such as urine volume, urinary electrolyte levels (Na, K, Cl ions mmol/lit), urine pH, and conductivity. Diuretic index was calculated to correlate the diuretic potential of novel synthesized compounds. Compounds **C1, C3, C4, C5, C6** have maximum docking score as well as found with higher diuretic index/ diuretic action.We have succeeded in developing structural analogues of ethacrynic acid. All the Compounds were found with diuretic activity. Compound **C3, C5, C6,** were found with higher diuretic effect where as compound **C4** was found with the excellent diuretic activity. The research studies presented here was found to be helpful in development of new therapeutic agents with high diuretic potential.

KEYWORDS: Structural analogues, Ethacrynic acid, Diuretic potential, Molecular docking, Spectroscopy, Diuretic Index.

GRAPHICAL ABSTRACT



Diuretic Response of Novel Structural Analogues of Ethacrynic Acid

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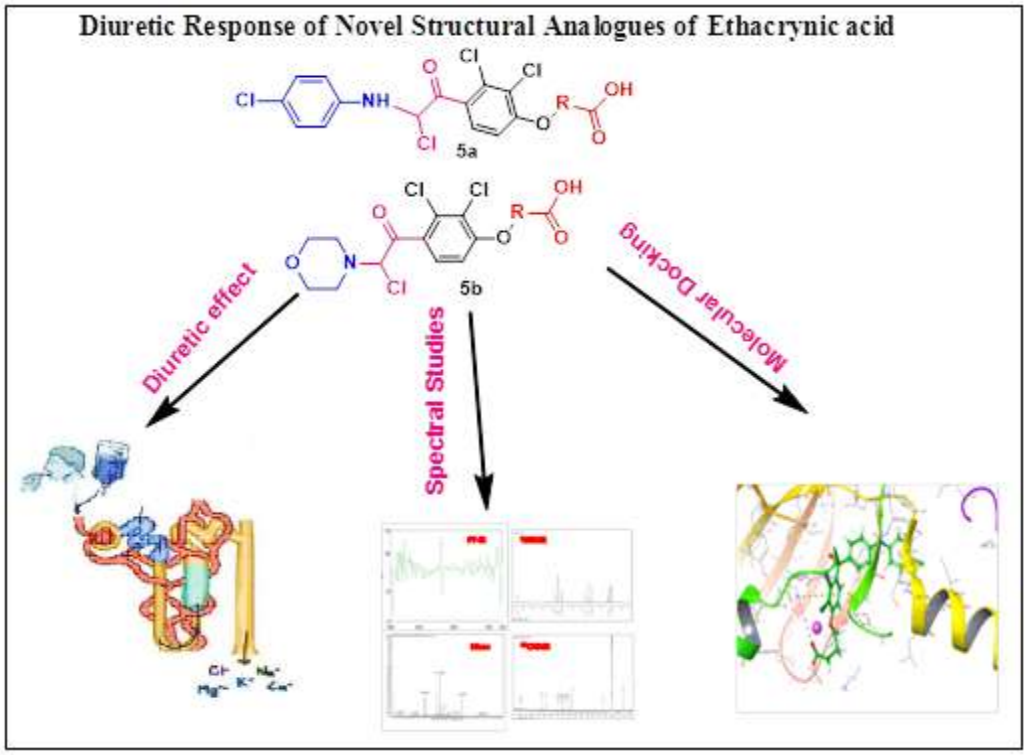
ABSTRACT
Ethacrynic acid is a strongly effective loop diuretic agent. The present study aims to develop novel structural analogues of ethacrynic acid having greater diuretic response. Designed and synthesized compounds were screened for diuretic effect in albino wistar rats using ethacrynic acid as standard drug. Molecular docking was done to determine favorable accommodation of novel molecules in binding pocket of the receptor. Structures of novel synthesized molecules were confirmed by spectral characterization such as IR, 1HNMR, 13CNMR. Toxicological and pharmacokinetic studies were done to ensure safety of the compound. Results of biological evaluation studies showed that all compounds having diuretic activity. Compound B1,B2 possesses good diuretic activity where as compound B6 was found with the excellent diuretic activity. The research studies were found to be adventitious for further development of new agents with high eficasy of diuretic effect.

Keywords: Synthesis, Ethacrynic acid, Diuretic activity, Molecular docking, Spectroscopy

Graphical Abstract



INTRODUCTION:

Ethacrynic acid is strongly effective diuretic agent[1]. It induces diuresis by inhibiting Na+, K+, Cl- symporter or co-transporter (NKCC2). Symporter or co-transporter (NKCC2) In the thick ascending loop is responsible for reabsorption of sodium and chloride in blood. Due to inhibition of symporter in thick ascending limb reabsorption of electrolytes in blood decreases and loss in urine increases with large volume of urine contributes to diuretic effect of ethacrynic acid[2,3].

The thick ascending limb has a high reabsorptive capacity and is responsible for reabsorbing 25% of the filterd load of sodium. As ethacrynic acid blocks Na+K-Cl- co-transporter (symporter). Ethacrynic acid-induced diuresis is characterized by increased sodium (up to 25% of the filtered load), potassium, chloride, calcium, magnesium, and water excretion resulting in higher diuretic effect of ethacrynic acid[4]. The active form of the drug is not ethacrynic acid it is converted to the complex ethacrynic-cystein complex in tubular lumen which is

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Key words: Costaceae, *Costus pictus, Costus speciosus,* histochemical, antibacterial activity

INTRODUCTION

Plants have been used as medicine since the start of the human race.[1] These medicines were initially used as poultices, tinctures, teas, powders, *etc*.[2] Medicinal plants are familiar sources of medicine. Substantial evidence can be cited favoring herbs being used to treat diseases and restoring and fortifying body systems in the ancient systems of medicines such as Ayurvedic, Unani, and Chinese traditional medicine.[3] Antimicrobial activity is one of the most eyed usefulness in the field of herbal medicines. A measurement of determination of antibacterial activity is zone of inhibition. There is a proportionate relationship between the zone of inhibition and antibacterial activity.[4] Many plants have shown a profound antimicrobial activity. The family of Zingiberaceae comprises about 1.300 species and 52 genera spread all over Asia, tropical Africa, and the Americas.[5] In a country like India, the plant propagates in the sub-Himalayan region, central India, Maharashtra, Karnataka, and Kerala.[6] The *Costus* spp. from the family Costaceae are commonly grown as medicinal and ornamental plants.[7,8] The *Costus* spp. additionally used as a dietary supplement to manage many diseases throughout the world.[9] *Costus speciosus* (CS), commonly known as crepe ginger,[10] is an essential plant grown in India.[11] The name CS was changed recently to *Hellenia speciosa* (J. Koenig ex Smith) S. Dutta.[12,13] The pharmacological activities reported for CS are antioxidant, antibacterial, analgesic, anti-cholinergic activity, antidiabetic, anti-inflammatory, antidiuretic, antifungal, larvicidal, estrogenic activities, and anti-stress.[14,15] *Costus pictus* (CP) is another ornamental plant from the family of Costaceae. CP is also known as fiery *Costus,* insulin plant, spiral flag, and step ladder.[16,17] The rhizome and leaves show antidiuretic,

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Evaluation of *in vitro* anticancer, antimicrobial and antioxidant activities of new Cu(II) complexes derived from 4(3*H*)-quinazolinone: Synthesis, crystal structure and molecular docking studies

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ABSTRACT

Present study describes synthesis of a series of Cu(II) metal complexes (C_1 - C_3) of bidentate Schiff base ligands (L_1 - L_3) derived from the condensation reaction of 3-amino-2-methyl-4(3H)quinazolinone with 2-chlorobenzaldehyde, 4-bromobenzaldehyde and 2-nitrobenzaldehyde. The structural characterization of synthesized compounds has been analyzed on the basis of FT-IR, UV-Visible, ^{1}H NMR and mass spectroscopy. The orthorhombic structure of the L_3 is determined by X-ray crystallographic analysis. *In silico* analysis of all compounds against various protein targets prove to have better interaction parameters in case of c-MET and VEGFR, thus in accordance with the docking score, the colon cell line (HT-29) was selected for further *in vitro* analysis and the results revealed that L_3, C_1, C_2 and C_3 exhibit important anticancer activity when compared with the standard drug Adriamycin. Further, synthesized compounds have shown excellent activity against Gram-positive (*Staphylococcus aureus*) and Gram-negative pathogens (*Escherichia coli*) but exhibited poor activity against fungal strain. Antioxidant activity of the all compounds revealed that the complexes displayed a higher scavenging activity than the corresponding ligands. These studies reveal that the coordination of Cu(II) ion with mixed ligands play a vital role in the enhancement of the biological potential of the complexes.

1. Introduction

A Schiff base ligand containing pyrazole-1-thiocarboxylate nucleus is one of the most encountered heterocycles often leads to an extensive applications in the biological field [1]. In addition, many substituted quinazoline derivatives and their metal complexes have recently earned great interest in various fields like medicinal chemistry. These kinds of compounds have been studied also for their luminescent properties, catalyst as well as chemosensors [2–5]. Cu(II) complexes have been widely explored for the versatility of their spectroscopic properties, coordination geometries, exquisite colors, and their applications. Metal based drugs, *i.e.*, cisplatin and its derivatives, have been used for the treatment of cancers for more than 50 years. Unfortunately, many side effects are associated with these drugs including neurotoxicity and renal impairment [6,7]. Therefore, the medicinal chemistry has gained demand in obtaining novel drug-like molecules and evaluation of the same for their anticancer property [8]. The use of an organic moiety with a Schiff base scaffold with a schetile biochemical functionality is meaningful and its novel model metal complexes exhibit potent biological activities like antioxidant, anti-inflammatory, antimicrobial property, etc. [9]. The human body, as a result of its metabolism, produces reactive oxygen species (ROS), including singlet oxygen, superoxide radicals, hydrogen peroxide,

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A Review on Current Scenario in Drug-Loaded Nanocapsules in Cancer Treatment

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ABSTRACT

Various types of carriers presently available in care of cancer for targeted medicine delivery, each with its own combination of advantages and disadvantages.Polymeric nanocarrier like, micelles, dendrimers, magnetic and gold nanoparticles,liposomes, quantum dots, silica nanoparticles, polyethylene glycol, and carbon nanotubes were given special consideration.To achieve controlled drug release and effective delivery of drug, nanocapsule of dispersed polymercan be used as a drug transporter that is nanoscale in size.The main determinants, stability of dispersion are the surfactant structure and the outer coating shape.The structure and configuration of capsule walls have a major impact on release and deterioration characteristics of the capsules.The nanocapsule size range is between 1 to 100 nm.There are major methods for producing nanocapsules arepolymerization, interfacial polymerization, arc discharge,emulsion polymerization andencapsulation of nanocapsule method.Measurement of capsule surface, Capsule radius distribution, thermal or chemical decomposition, capsule membrane thickness and permeability are the most significant capsule parameters.

Keywords: Nanocapsules; Cancer treatment;Drug-Loaded Nanocapsules; nanoencapsulation.

Introduction

Cancer is a word that refers to a group of diseases in which malignant cells develop abnormally and spread to other areas of the body[1,2]which results to cause death, hencecancer is one of the deadly illnesses on the planet.

Nanomedicine is the recent nanotechnology in medicinewhich is composed of Nanomaterials, whose sizes vary from around one nanometer to many hundred nanometers[3,4].

Various considerations can affect the use of Cancer-fighting nanomaterials detection and medicine distribution in cancer treatment.

- The nanomaterial's size.
- The nanosystem's biocompatibility.
- The nanosystem'scapacity to degrade.
- The drug's desired release profile.
- The encapsulated drug's toxicity and antigenicity.
- The entrapped medicine's properties in the nanomaterial
  Ex. medicationsolubility or stability in water and other solvents.

Nanocapsules are a type of nanoparticle that consists of a protective matrix known as shell and one or more active materials known as corein which the therapeutic substance can be enclosed. The protective coating on the nano-capsules,this is usually pyrophoric and rapidly oxidizes [5].

The use of nanoparticles as drug carriers has been widely studied, with majority of their applications in cancer care and detection. Chemotherapeutic agents that have beenconjugated with or incorporated into nanocarriers are known as nanomedicines.Sustained release, increased medication selectivity as well as potency, enhanced drug bioavailability and reduced toxicity of drugs are the significant features.When nanocapsules injected through the IV route, which are submicron in size, hit the target and release the encapsulated compound.

Nanocapsules are polymeric nanoparticles with a polymeric wall which is made up of macromolecule,surfactants that are non-ionicoil baseandphospholipids[6-9]. Interfacial nano-deposition and interfacial polymerization are the most popular methods for manufacturing of nanocapsules and they are used to deliver medicines in a controlled manner while also protecting proteins, enzymes and foreign cells.

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Alysicarpus vaginalis Bio-Actives as ESR Signaling Pathway Inhibitor for Breast Cancer Treatment: A Network Pharmacology Approach

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ABSTRACT

In our previous study *Alysicarpus vaginalis* (AV) has appeared as a promising target for breast cancer hence we have screened potential targets by *in silico*, In Vitro and In Vivo methods. A network pharmacology (NP) approach involves prediction and validating of targets via molecular modeling, western blotting and In Vivo MNU-induced mammary cancer. The PPI network showed the 573 edges between 214 nodes (targets) that are involved in breast cancer and important one are ESR-1, ESR-2, AR, EGFR, NOS3, MAPK, KDR, SRC and MET. Compound-target-pathway network involves 04 compounds and 221 interactive protein targets associated with breast cancer. GO and KEGG enrichment analysis predicted the ERR, c-MET, PDGFR-α/β, EGFR, and VEGF as a key targets in the breast cancer treatment which are validated via molecular modeling. Expression of ER-α, AR and EGFR were significantly down regulated by AV in MCF-7 cell line. In addition, the immunoreactivity of ER-α was reduced significantly in MNU-induced mammary carcinoma, which is a key target in ER+breast cancer. Overall, this study scientifically light ups the pharmacological mechanism of AV in the treatment of breast cancer, strongly associated with the regulation of ESR signaling pathway.

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Introduction

Network pharmacology (NP) is a novel concept supported on the hypothesis of systems biology and network analysis of biological systems to propose the new multi-target drugs. It scientifically scrutinizes the influence and intervention of drugs on the disease network, and reveals the mystery of multi-target drugs synergistically targeting disorder or disease (1). Conventionally, the new drugs discovery is based on identifying and/or designing a pharmacologically active agent that explicitly interacts with a single target (2). NP is more useful for creating a network of "compound-protein/gene-disease" and illuminating the regulation principle of small molecule in a high throughput mode (3). NP has come out as a potential way to elucidate the systems level mechanisms of natural components. It recognizes complex diseases, like cancer, as a perturbation of interrelated complex biological networks and recognizes the drug mechanism in terms of the network topology (4,5). This preferably leads to therapies that are not as much of susceptible to drug resistance and less significant side effects by means of targeting the disease network at the systems level through synergistic and lethal interactions. Nature is a precious pool of novel compounds. According to an approximation, concerning 50% of the medications validated from 1981 to 2010 have natural origins (i.e., 28% semi-synthetic, 17% mimics of natural compounds and 5% natural entities). Natural components are identified to exert their therapeutic effects by acting on multiple targets of multiple compounds, and the mechanism of action is well suited to the theory of NP. As a result, researchers have engaged in NP methods to find out the potent anticancer targets and pathways of component from natural products (6–8).

Alysicarpus vaginalis (AV) is a medicinal plant that has been used for the treatment of cough, dysentery, colics, sword wounds, bone fractures and antiviral activity in folk medicine. Extracts have been shown to berich in a variety of phenolic compounds (9,10). Our previous laboratory findings have been revealed that the favorable effects of ethyl acetate fraction of AV can be recognized to their anti-breast cancer

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Research Article

Pyridine/Pyrimidine Substituted Imidazol-5-one Analogs as HIV-1 RT Inhibitors: Design, Synthesis, Docking and Molecular Dynamic Simulation Studies

Author(s): Santosh Mokale, Deepak Lokwani* and Abdul Mujaheed

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Abstract

Background: This paper reports the synthesis, Non-nucleoside reverse transcriptase inhibitory (NNRTIs) activity and computational studies of 2-((4-chloro-2-subtitutedphenoxy) methyl)-4-(furan-2-ylmethylene)-1-substituted Pyridine/-pyrimidine-1H-imidazol-5(4H)-ones.

Methods: The imidazol-5-one analogs were synthesized by conventional method and characterized by FT-IR, NMR and mass spectral data. All compounds were evaluated for in-vitro NNRTI activity by using reverse transcriptase (RT) assay kit (Roche). The in-silico docking studies were conducted on RT enzyme to investigate binding site interactions of synthesized compounds. The MMGBSA method was also used to calculate the binding free energy between the inhibitors and RT enzyme. The MD simulation was further performed for the apo form of the RT enzyme and docked complex of compound A6-RT enzyme to better understand the stability of the protein-ligand complex.

Results: The bioactivity analysis revealed that most of the synthesized compounds showed significant inhibitory activity against RT enzyme and the IC50 value was found to be in the range of 1.76-3.88 μM. The computational studies suggest that the docked compounds form the H-bonding with amino acid residue Lys101 and hydrophobic interactions with amino acid residues Tyr188, Tyr181, Trp229, and Tyr318, which act as the primary driving forces for protein-ligand interaction.

Conclusion: The reported imidazol-5-one analogs can act as lead for further development of prospective RT inhibitors.

Keywords: NNRTIs, imidazol-5-one, HIV-1, docking, MMGBA, MD simulation.

« Previous Next »

Graphical Abstract

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Theoretical and experimental verification of molecular properties of novel benzamide derivatives using computational platforms and in vitro antibacterial activity

Poonam M. Wanjari[1] · Santosh N. Mokale[2] · Avinash V. Bharati[1] · Vishwas N. Ingle[3]

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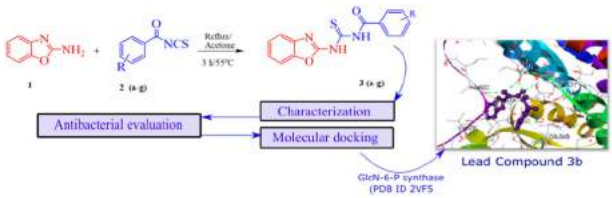
Abstract

A series of N-(benzo[*d*]oxazol-2-ylcarbamothioyl)-2/4-substituted benzamides were synthesized by the reaction of 2-aminobenzoxazole with apposite benzoyl isothiocyanate. The structure of the newly synthesized compounds was confirmed by chemical tests, elemental (C, H, N, and S), and spectral (IR, ^{1}H NMR, ^{13}C NMR, and mass) analysis. All the synthesized compounds were evaluated experimentally for their antibacterial activity against Gram-positive and Gram-negative bacteria. The test results show moderate to potent antibacterial activity compared to the standard drug. The binding interactions of newly synthesized ligand and protein were correlated using a molecular docking study using a binding pocket of GlcN-6-P synthase.

Graphical Abstract



Keywords 2-Aminobenzoxazole · Benzamide · Benzoyl isothiocyanate · Molecular docking

Introduction

The discovery of antibiotics brought almost a paradigm shift in the field of medicines. Earlier, till the end of the last century, most of the deaths were caused by insufficient/improper treatment for infections. In the current situation, almost all microbial infections are treated by antibiotics in many medical procedures practiced across the globe. This revolution is remarkable in medicinal chemistry. From the current point of view, it is found that antibiotic research went through a dry spell with a lack of new class of antibiotics discovery [1]. Hence, we need focussed research to identify new targets and drugs to treat infectious diseases. So it is needful to discover and develop novel antibacterial compounds with simple structure and high efficiency.

Many benz-fused hetero, bicyclic ring systems such as benzimidazole [2], benzoxazole [3], and benzothiazole [4]

Supplementary information The online version of this article (https://doi.org/10.1007/s00044-020-02671-9) contains supplementary material, which is available to authorized users.

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Design and Synthesis of N-4-(substituted benzylidene)-N-2-(4-chloropyrimidin-2-yl)-6, 7-dimethoxyquinazoline-2, 4-diamines as Anticancer Agents

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A novel series of N-4-(substituted benzylidene)-N-2-(4-chloropyrimidine-2-yl)-6,7-dimethoxyquinazoline-2,4-diamine compounds were designed, synthesized and evaluated for their anti-cancer properties. The structures of the target derivatives were elucidated using spectral techniques like ^{1}H NMR, ^{13}C NMR and mass spectroscopy. All the designed compounds were tested for their probable anti-cancer activity on human colon-rectal cell lines (HT-29 and COLO-205), followed by cell-cycle analysis, apoptosis assays, and enzyme inhibitory assays. VEGFR-2 kinase inhibitory assays and cell cycle analyses were performed to validate the target selectivity of the designed compounds. Among the synthesized derivatives, **SM-8 (GI_{50}= 10.64 µM)** showed good inhibition activity against HT-29 cell lines. Cellular mechanism studies confirmed that compound SM-8 could induce apoptosis in HT-29 cells in G1 phase, which was concentration-dependent. In order to evaluate the specific interaction with tyrosine kinase, designed scaffolds were subjected to docking, *in-silico* physicochemical properties and ADME prediction studies. MM/GBSA was performed to calculate the ligand binding free energies.

Key words: Quinazoline; *in-vitro* activity; molecular Docking; *in-silico* ADME study

Received: April 2022; Accepted: September 2022

Receptor Tyrosine Kinases (RTKs) play a vital role in various cellular processes and signal transduction pathways. In the current era RTKs have been found to have divergent roles in different chemo-therapeutic medications. RTKs play an important role in phosphorylating the tyrosine amino acid in several proteins with the help of ATP (ɣ-phosphoryl group donor). Phosphorylation ultimately leads to activation of a signalling pathway at the cellular level which includes crucial processes for differentiation, proliferation, migration, and antiapoptotic pathways. The c-mesenchymal epithelial transition factor (c-MET) is a widely over-expressed RTK in human tumours and a receptor for hepatocyte growth factor (HGF). HGF binding to c-Met causes phosphorylation of tyrosine residues on c-Met, which activates the downstream signalling pathway involved in cell proliferation, invasion, metastasis, and angiogenesis in a variety of cancers. c-Met activation has been linked to poor clinical outcomes in a variety of human solid tumours and haematological cancers [1,2]. Additionally, c-Met overactivation leads to therapeutic resistance. As a result of resistance, inhibiting c-Met activity could be a promising treatment option for malignancies. Small molecule inhibitors of c-Met can be divided into several types based on their binding mechanisms. Multikinase inhibitors, for example, are a common form of c-Met inhibitor that also inhibits VEGFR and other Homologous kinases. Endothelial cells contain a tyrosine kinase receptor known as vascular endothelial growth factor receptor 2 (VEGFR-2, also known as KDR). When VEGF binds to VEGFR, it causes a conformational shift in the receptor, which is followed by dimerization and phosphorylation of tyrosine residues [3]. VEGFR-2-mediated VEGF signalling has been found to play a key role in tumour angio-genesis regulation. VEGF expression is increased in a variety of human cancers, and high levels of VEGF are linked to a poor prognosis and clinical stage in patients with solid tumours. As a result, VEGF/VEGFR-2 signalling represents a promising therapeutic target in cancer treatment. The synergistic collaboration of c-Met and VEGFR-2 has been shown to promote angiogenesis in the development and progression of several human malignancies [4, 5, 11]. As a result, compounds that inhibit both c Met and VEGFR-2 at the same time may be preferable to c Met- or VEGFR-2-specific inhibitors because they can disrupt numerous signalling pathways involved in tumour proliferation, metastasis, and angiogenesis. Several kinase inhibitors, such as cabozantinib and foretinib, have been shown to suppress both c-Met and VEGFR-2 kinases at the same time. Consequently, we began developing dual c-Met and VEGFR-2 TKIs with substantial anti-tumour effectiveness using the quinazoline nucleus, which is widely used in drug development, particularly in RTK inhibitors [6].

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Formulation and Optimization of Novel Bilayer Mucoadhesive Polymeric Films: Defolding and Gastroretention

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ABSTRACT
The aim of the present study was to develop a novel gastrorentative dosage form (GRDF), as drug loaded polymeric film folded in hard gelatin capsule. The proposed mechanism for gastroretention was expansion (unfolding as well as swelling) and bioadhesion to gastric mucosa. Furosemide was selected as model drug. The dosage form was developed as bilayer film having combination of immediate (IR) and controlled release (CR) layer. The optimum formulation of GRDF was obtained on the basis of folding patterns, in-vitro drug release profile, in-vitro bioadhesion, swelling and mechanical performance. The developed formulation was studied via Scanning Electron Microscopy (SEM), X-Ray Diffractometry (XRD), and Differential Scanning Calorimetry (DSC). The obtained data presented that the developed formulation exhibited favorable gastrorentative properties.

KEYWORDS: *Gastroretention, Unfolding, Swelling, Bioadhesion, Bilayer film*

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I. INTRODUCTION

Oral controlled release (CR) dosage forms (DFs) have developed from last 3 decades due to their considerable therapeutic advantages. The drugs having narrow absorption window have gain importance in development of controlled release dosage forms. However, a problem frequently encountered with such a developed dosage forms is the inability to increase residence time in the stomach and proximal portion of the small intestine. To achieve more residence time of dosage forms in this region, many strategies have been developed based on the following approaches (1): (a) low density form of the DF that floats on gastric fluid (2); (b) high density DF that is retained in the bottom of the stomach; (c) bioadhesion to the mucosa (3); (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs and excipients; (e) expansion by swelling or unfolding to a large size which limits the emptying of the DF through the pyloric sphincter.

Above approaches have their own merits and demerits. Hence we developed such formulation which combines basic principles of bioadhesion and physical property such as expansion by unfolding as well as swelling of dosage form. The said formulation has been designed in such a way that it contains a drug loaded polymeric film which is to be folded in hard gelatin capsule. After ingestion the drug loaded polymeric film get defolded in the stomach and swells to a large size which limits its emptying through pyloric sphincter. The swelled film also has bioadhesion so that it adheres to the stomach mucosa.

Furosemide (4-chloro-2-furfurylamino-5-sulphamoyl benzoic acid) is a widely used “high ceiling” loop diuretic which acts on the ascending limb of the loop of Henle (4). Apart from a strong, rapid and short diuretic action it has a haemodynamic effect on the heart. The onset of diuresis by oral dosing commence within 20 minutes and lasts for 4-5 hours (5). The drug has extensive application in oedema of pulmonary, cardiac or hepatic origin as well as in the treatment of hypertension and in the chronic treatment of cardiac infarction. Furosemide is BCS class IV drug having poor aqueous solubility and poor permeability. Furosemide is acidic in nature with pKa value of 3.9, due to which the major absorption site is upper gastrointestinal tract. Furosemide has short half life of less than 2 hours. It has pH dependent solubility. It is practically insoluble in acidic pH and solubility increases with increase in pH (6).

The conventional dosage form of Furosemide shows erratic absorption which results in poor bioavailability i.e. 30-60% and is needed to administer 3-4 times a day which presents the issue of non-compliance (5). These dosage forms are also associated with peak diuresis effect. The peak diuresis causes weakness and fatigue symptoms particularly in elderly patients.

Hence there is a strong need to develop a controlled release formulation for drug like furosemide. Controlled release formulation of furosemide with reduced side effects will be more efficient than presently available conventional dosage forms. Generally these formulations are comprises with loading dose which

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REVIEW ARTICLE

Application of Carbon Nanotubes In Drug Delivery of Non-cancerous Diseases: A Review

Shahebaaz Khan[1], Puja Jawlikar[1], Swaroop Lahoti[1], Omprakash Bhusnure[2], Sohan Chitlange[3] and Jaiprakash Sangshetti[1,*]

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Abstract: Carbon Nanotubes (CNT) are the allotropes of carbon in nanosize dimension and are popular in medicinal field. These nano-based technologies are gaining high interest in the recent years for the treatment of diseases that are previously considered to be impossible to cure. CNTs have gained significance in the treatment of the majority of disorders such as Malaria, Alzheimer's disease, Infectious disease, and Asthma. Moreover, patient's responsiveness also increased in cardiovascular and pulmonary diseases. To date, a number of reviews are available in the literature covering applications of CNT in cancer. However, the purpose of this review is to focus on the use of CNTs in drug delivery of non-cancerous diseases. The novelty of this review is that it is focused on the applicability of CNT in the various non-cancerous diseases. Detailed information was collected from the literature which will guide and encourage researchers to explore the applicability of CNT in various non-cancerous diseases in the future.

Keywords: Carbon nanotubes, drug delivery, targeted therapy, non-cancerous diseases.

1. INTRODUCTION

Sumio Iijima and co-workers (Nippon realistic company) in the year 1991 discovered Carbon Nanotubes (CNT) by using a high--resolution electron microscope. The initially discovered CNT was a multiwall carbon nanotube (MWCNT) and later in 1993 the single-walled carbon nanotube (SWCNT) was discovered. Before the discovery of Iijima, the CNTs were accidentally discovered by Oberlin, Endo, and Koyama by using the vapor growth technique [1]. Radushkevich and Lukyanovich in the soviet journal of physical chemistry published 50-nanometer diameter tubes made from carbon in 1952 [2b]. Hollow tubes rolled graphite synthesis from chemical vapor growth technique was observed by the scientist Morinober Endo of CNRS in the year 1976 at 14th Biennial conference of carbon at Pennsylvania state university. John Abrahamson offered proof of CNT in 1979. TEM images and XRD patterns were utilized for the structural characterization of CNT produced by thermo catalytical disproportion of carbon monoxide and were published by a soviet scientist in 1981. Howard G. Tennet of hyperion issued a US patent for cylindrical discrete carbon fibril production with a constant diameter of 3.7-70 nm length that is 10^2 times the diameter in 1987. Finally, arch burned graphite rod MWCNT was discovered by scientist Iijima in 1991 [2a, b]. Fig. (**1**) contains a summarized representation of the discovery of CNT.

1.1. CNTs and their Structure

In general, the size of CNT is up to 100 nm. The administration of CNT into the body is convenient owing to its small size. However, the size of CNT should be optimized because too small size may lead to leaking of CNT from the blood capillaries and too large size makes it engulfed by reticuloendothelial cells present in the blood circulation [3]. CNT's are made up of graphene. Graphene is the allotrope of carbon which has hexagonal lattice geometry made up of a single layer of the carbon atom. The CNTs are organized in sp2 bonded carbon atom. CNTs have a hexagonal structure and their structural arrangement is sp2 hybridized [4]. SWCNT is obtained from a pair of integers (n, m). Depending upon wrapping SWCNT is divided into three types armchair (n=m) zigzag (m=0) chiral (any other nm). The electrical properties of CNT's are affected by the wrapping of CNTs [5]. The surface of the CNTs should be hydrophilic, and this can be achieved by treating polymers on the surface of CNTs. These CNTs have wide-ranging medical applications because it consists of thermal, mechanical, electrical, and biological property [6]. CNTs can be administered into the human body by various methods oral, IV, transdermal, subcutaneous, intraperitoneal, inhalation, like the structure of CNT, which makes it more reliable for penetration in the cell [7]. The cellular internalization needs various factors such as surface characterization, chemical concentration, roughness, functionalization, shape, periodicity, hydrophilicity, and hydrophobicity [3, 7].

1.2. Types of CNTs

Depending upon the number of walls present in its structure; CNT's are divided into three types: Single-walled CNTs (SWCNT), double-wall carbon nanotube (DWCNT), and multiple-walled CNTs (MWCNT) [5].

1.2.1. SWCNT

SWCNT consists of a monolayered cylindrically rolled graphitic carbon sheet, using single-walled CNTs for delivering a drug through various routes. The diameter of SWCNT varies from 0.4-2 nm [8]. Li wie *et al.* reported the aggregation of carbon nanotube under different circumstances. It is a major problem in the application of CNTs by using the PL sideband tool. For this experiment SWCNT with the different chiral structures was used for investigation. The suspension containing the SWCNT bundle was observed by ultracentrifugation. The result showed that photoluminescence sideband depends on the aggregation of nanotubes [9]. The fundamental behavior of hydroxylated SWCNT was observed shortly after introducing iodine 131 as dressing material into the animal body for 2-60 minutes. The injection mode influenced the biodistribution and pharmacokinetic parameters for studies, however within

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RP-HPLC Method Development and Validation for the Estimation of Lansoprazole in Presence of Related Substances by QbD Approach

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

A rapid specific RP-HPLC method has been developed for the determination of Lansoprazole impurities in the drug substance. The control of pharmaceutical impurities is currently a critical issue in the pharmaceutical industry. The International Council for Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. The objective of the recent study was to develop and validate a HPLC method for the quantitative determination of process-related impurities of Lansoprazole in pharmaceutical drug substance. Lansoprazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]-sulfinyl]- 1H-benzimidazole is an proton pump inhibitor used in the management of gastric ulcers. Chromatographic identification of the impurities was carried out by response surface methodology, applying a three-level Box Behnken design with three center points. Three factors selected were a mobile phase, flow rate, column temperature. Evaluation of the main factor, their interaction, and the quadric effect on peak resolution were done on Waters Symmetry C_8, 250 x 4.6mm, 5µm column is used for the development of the method.

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Bioanalytical Method Development and Validation for the Determination of Favipiravir in Spiked Human Plasma by using RP-HPLC

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This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

A precise, simple and reproducible reverse phase liquid chromatography (RP-HPLC) method was developed and validated for determination of Favipiravir by using Carbamazepine as internal standard in spiked human plasma. A chromatographic separation was accomplished with Cromasil C18 (250mm x 4.6ID, Particle size: 5 micron) column using mobile phase consists of methanol: water in the ratio (35:65, %v/v), at pH 3.0 with binary gradient system-maintained flow rate at 0.8ml/min. The detection wavelength of drug sample was at 225 nm. Extraction was done by using ethyl acetate as extracting solvent. The retention time of Favipiravir was found to be 6.62 min. The method was found to be linear in the concentration range of 0.2-3.2 µg/ml. Limit of quantitation (LOQ) value was found to be 0.72. The intra- and inter day precision and accuracy lies within the specified range. The recovery studies were found to be in the range of 97.6 to 100.2%. %Relative standard deviation (RSD) was found to be in the range of 0.07-2.80%. All parameters were found to be validated from spiked human plasma. The proposed RP-HPLC method is highly accurate and rapid for the determination of favipiravir in human plasma and can be applied for pharmacokinetic studies and Therapeutic drug monitoring.

Keywords: Favipiravir; RP-HPLC; human plasma; validation; bioanalytical; method development.

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Research Article

FORMULATION AND EVALUATION OF SIMVASTATIN LOADED MICROEMULSION BASED GEL: IN VITRO CHARACTERIZATION

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ABSTRACT

The Simvastatin loaded microemulsion based gel was formulated and in-vitro evaluation was done for the treatment of diabetic wound healing. Simvastatin is BCS class II drug which promotes wound healing by increasing the production of vascular endothelial growth factor (VEGF). Microemulsions (MEs) are oil and water colloidal system stabilized by the mixture of surfactant and co-surfactant offering enhance skin permeability for both hydrophobic and hydrophilic drugs. At first, microemulsion (ME) was prepared by water titration method and the existence of ME region was determined using pseudo-ternary phase diagram. Formulations were prepared using oil (oleic acid), Tween 80 and PEG 400 as surfactant and co-surfactant. Optimization of formulation was done using 3^2 factorial designs. Carbopol 940 was used as gelling agent for preparing microemulsion gel. The formulations were evaluated for physical appearance globule size, polydispersity index, zeta potential, percent transmittance, thermodynamic stability, dilution test, drug content, and in vitro drug release. The optimized formulation of ME showed average globule size of 151 nm and the optimized ME gel had a homogeneous texture, showed good spreadability and in vitro drug release. The present study indicates the simvastatin loaded microemulsion gel could act as promising vehicle for topical drug delivery of drug for diabetic wound healing.

KEYWORDS: Diabetic wound; 3^3 factorial design; gel; Microemulsion; Simvastatin; topical drug delivery.

INTRODUCTION

Diabetic wound is most common complication for diabetic patient during their life time[1]. Diabetic wound is classified under the class of chronic type of open wound. Wound is a loss or breaking of cellular and functional continuity in the epithelial integrity of the living tissues. Healing is very complex process start immediately after occurrence of injury. There are four stages involved in wound healing namely haemorrhage, inflammatory and proliferation phase and maturation phase[2]. Wound healing impairment in diabetic patient is due to both the impaired glucose metabolism and neurovascular complication[3].

Literature suggests that beside lipid lowering effect statin shows wound healing action in diabetic mice[4]. Besides having lipid lowering effect simvastatin promotes vascular endothelial growth factor (VEGF) production thus stimulating angiogenesis, reduce oxidative stress, improve micro vascular function and improve endothelial function, thus improving efficiency of wound healing[5,6]. It can enhance epithelialization and restore the normal skin epidermal barrier via reducing isoprenylation downstream targets of mevalonate and farnesyl pyrophosphate (FPP), decreasing FPP level can promote keratinocyte migration in vitro and epithelialization and wound closure in an ex vivo human culture wound healing model[7].

ME is thermodynamically more stable as compared to emulsion and nanoemulsion. It is isotropically clear dispersion of oil and water, stabilized by surfactant and co-surfactant. ME has emerged as potential drug delivery system for topical delivery because of its unique solubilisation capacity of both hydrophilic and lipophilic drug[8]. Due to presence of both hydrophilic and lipophilic domain penetration of drug through skin is better with ME[9]. ME based gel is less greasy and easily spreadable as compared to cream and ointment and offer solubilisation of lipophilic drug and increases its topical availability [10,11].

Simvastatin is a drug with low solubility, high permeability and classified as BCS class II drug[12] to optimize ME based gel and to study the effect of concentration of excipients such as oil and Smix on globule size and drug release. The aim of the study was to prepare and evaluate ME based gel of simvastatin to increase its solubility and availability at the site of diabetic wound.

MATERIALS AND METHODS

Simvastatin was purchased from Swapnroop Pharmaceutical Pvt. Ltd. India. Carbopol 940 was a gift sample from Wockhardt Pvt. Ltd. Oleic acid, Tween 80, PEG 400, Triethanolamine were procured from Loba chemicals Pvt. Ltd. Mumbai, India. All other ingredients used were of analytical grade.

Preparation of Simvastatin microemulsion

Selection of oil, surfactant and co-surfactant

The solubility study of simvastatin in various oil, surfactant and co-surfactant was done to screen suitable combination. Different

Formulation and In-vitro Evaluation of Ethosomal Gel of Repaglinide for Transdermal Delivery

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ABSTRACT

The present research aimed at developing and evaluating a vesicular drug carrier system for topical delivery of Repaglinide to provide sustained drug delivery. Repaglinide ethosomes were formulated using the method of thin film hydration by soya lecithin and evaluated for percent entrapment efficiency, vesicle size, percent drug content, surface morphology, and in-vitro drug release. The ethosomes were prepared by varying the variables such as concentrations of soya lecithin and ethanol, while entrapment efficiency and drug release were the chosen responses. Ethosomal formulation was optimized using the 3^2 factorial design. The vesicle size of optimized batch was found to be 198.92 nm with zeta potential of -13.42 mV. The % entrapment efficiency was found to be 92.40 % and percent drug release of ethosomal gel was found to be 73.24%. Optical microscopic and scanning electron microscopic observations showed formation of spherically shaped vesicles. The in-vitro drug release of the formulation increases with increase in ethanol concentration and decrease in lipid concentration.

Key Words: *Repaglinide, Ethosomes, Factorial design, Film hydration*

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INTRODUCTION

The most extensive and easily accessible organ of the human body is skin. Skin as a means of medicine delivery may provide different benefits more than old drug delivery systems, such as lesser alterations in plasma medicine contents, prevention of gastrointestinal disorders and hepatic metabolism of the medicines, and high patient agreement [1]. It provides a superb obstacle to molecular transport, since stratum corneum is the most difficult obstacle to the passage of many medicines, except for low molecular weight and lipophilic medicines. For more efficiency of transdermal medicine delivery system, the medicine should be capable of penetrating the skin obstacle and reach the target region [2, 3].

Ethosomes are the ethanolic phospholipid vesicular carriers which are soft, shapable vesicles utilized for medicines delivery to reach the deep skin layers or the systemic circulation. Ethosomes commonly use transdermal route for medicines delivery. Medicine can be entrapped in ethosomes that have different physicochemical properties such as amphiphilic, lipophilic, or hydrophilic. The ethosomal system comprises of phospholipid, high concentration of water and alcohol. The high content of ethanol makes ethosome unique. Ethanol results in disorder of skin fat bi-layer organization and so when incorporates into a vesicle membrane, it enhance the vesicle capability to penetrate the stratum corneum [4].

Repaglinide is of meglitinide class used to lower blood glucose level in type 2 diabetes mellitus. It decreases blood glucose level by stimulation of insulin release from the pancreas. Dosing frequency of repaglinide is 0.5-4 mg, 3- 4 times daily. It indicates quick start of action but for shorter period of action, as it is quickly eliminated from the blood stream with a half-life of nearly one hour. The mean definite bioavailability is approximately 56% due to its first pass metabolism [5].

Repaglinide is a drug having high first pass metabolism and very short half-life, so there is requirement of frequent dosing for maintaining plasma concentration in body. Literature studies have shown the applications of

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Organic & Supramolecular Chemistry

Benzopyranyl Phosphonate and β-Phosphono Malonates Derivatives: An Exciting Breakthrough in Chemistry

Satish U. Deshmukh,[a, c] Jaiprakash N. Sangshetti,[b] Sidhanath V. Bhosale,[c] and Rajendra P. Pawar*[a]

In this review, we paid attention to the reported methods and recent advances in the development of 2-amino-3-cyano-4*H*-chromen-4-yl-phosphonates and functionalized β-phosphonomalonates heterocyclic compound. Small-molecular architectures are considered with the highlighting on their structural design and synthesis approach. The scope of the 2-amino-3-cyano-4*H*-chromen-4-yl-phosphonates and functionalized β-phosphonomalonates heterocyclic compound *via* reactions like Knoevenagel, Pinner-cyclisation and advanced phospha-Michael addition reactions using different catalyst for synthesis is listed up to 2020.

1. Introduction

Multicomponent Reactions (MCR) are the reactions containing three or more constituents that come together and result in a final product that includes all elements used as initial material in their scaffold. In recent years, a multicomponent reaction is the centre of researcher's attention due to their variety and represents a powerful tool in chemistry and efficient drug discovery processes.[1] This remarkable attention of MCR is striking when quickly increasing the molecular complexity. MCR plays a vital role for synthetic chemistry mostly in the construction of heterocyclic compounds. These heterocyclic compounds engage in chemistry as MCR symbolic for their flexibility.[2]

Convergent nature of multicomponent reactions is the general waste reduction process. Taking to in consideration the advantages in research work, a synthetic pathway of MCR is constantly utilized. It includes resources in an efficient action in the synthesis, but also staged on shortening of the complete synthetic pathway with the positive eco-friendly consequences.

Phosphorus chemistry is essential and acts as a basic and fundamental position in human life. Phosphates in biological molecules appear as fundamental units of the cell. Phosphorus compounds are also found in the minerals of our various body parts. This significance of the element makes it an ideal constituent. Phosphorus is also the main element for plants and fertilizer which help for their development. Synthesis of 2-Amino-4*H*-1-benzopyran-4-yl phosphonates plays an important role in medicinal chemistry. These well-known phosphorus analogues of amino acid compounds have received much more noticeable applications in the discipline of pharmaceuticals. These nuclei play a key role in antibody generation.[3] Phosphorus containing naturally or synthesized heterocyclic compounds having tremendous potential for applications in medicinal chemistry.[4] These significant building blocks were also used in various biological activities such as peptide mimetics,[5] Renin inhibitors.[6,7] 2-amino-3-cyano-4*H*-chromen-4-yl-phosphonates showed potential anticancer activity,[8,9] antiviral activity.[10] 2-amino-3-cyano-4*H*-chromen-4-yl-phosphonates are those that bear with the distinguish of pioneer reaction Knoevenagel, Pinner-cyclisation and advanced phospha-Michael addition reactions.

In this review, we focused on synthetic methods and recent advances of the 2-amino-3-cyano-4*H*-chromen-4-yl-phosphonates compound. These synthesized molecules are considered with the importance on their design approach. The scope of the 2-amino-3-cyano-4*H*-chromen-4-yl-phosphonates heterocyclic compounds using these reactions in a different catalyst for this synthesis of the nucleus is listed in Figure 1.

Synthesis of 2-amino-3-cyano-4*H*-chromen-4-yl-phosphonates compound propose the plausible mechanism of reaction described in Figure 2.

1.1. Base Catalyzed Reaction

*1.1.1. Synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl) phosphonate compounds using inorganic and organic base-catalyzed reaction*

Shen *et al.* reported the synthesis of 2-amino-3-cyano-4*H*-chromene-4-yl phosphonate derivatives from salicylaldehydes **1**, malononitrile **2** and diethyl phosphite or triphenylphosphite **3** using lithium hydroxide (LiOH) as a catalyst. This synthetic protocol has more encouraging key points such as low-cost of catalyst, easy work-up and mild reaction condition which offers

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From the journal:
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A copper-catalyzed synthesis of aryloxy-tethered symmetrical 1,2,3-triazoles as potential antifungal agents targeting 14 α-demethylase†

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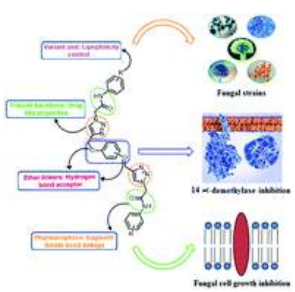
Abstract

The search for potent therapeutic agents has prompted the design and synthesis of a library of twenty-six aryloxy-tethered and amide-linked symmetrical 1,2,3-triazoles (**8a–z**) using a copper(I)-catalyzed click chemistry approach. All the synthesized compounds have been screened for their *in vitro* antifungal activity against four different fungal strains as well as the enzymatic study for the inhibition of 14 α-demethylase enzyme. The bioactivity results show that most of the synthesized compounds were found to be better antifungal agents as compared to Miconazole. Among them, compound **8a** showed the most promising antifungal activity against all the tested fungal strains. Furthermore, the enzymatic study reveals that compounds **8i** and **8o** are the most promising inhibitors of the 14 α-demethylase enzyme. In support of these results, the molecular docking study of the synthesized molecules against the sterol 14 α-demethylase (CYP51) could provide the structural basis for the antifungal activity. These compounds have also been analyzed for the ADME properties.



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Article

New 1,2,3-Triazole-Appended Bis-pyrazoles: Synthesis, Bioevaluation, and Molecular Docking

Ashruba B. Danne, Mukund V. Deshpande, Jaiprakash N. Sangshetti, Vijay M. Khedkar, and Bapurao B. Shingate*

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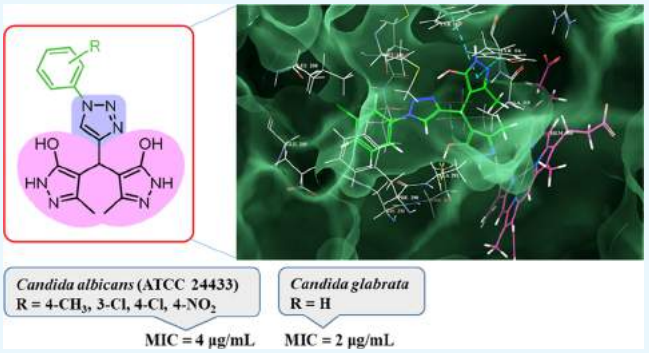
ABSTRACT: The present work describes design of a small library of new 1,2,3-triazole-appended bis-pyrazoles by using a molecular hybridization approach, and the synthesized hybrids were evaluated for their antifungal activity against different fungal strains, namely, *Candida albicans*, *Cryptococcus neoformans*, *Candida glabrata*, *Candida tropicalis*, *Aspergillus niger*, and *Aspergillus fumigatus*. All the compounds exhibited broad-spectrum activity against the tested fungal strains with excellent minimum inhibitory concentration values. The molecular docking study against sterol 14α-demethylase (CYP51) could provide valuable insights into the binding modes and affinity of these compounds. Furthermore, these compounds were also evaluated for their antioxidant activity, which also resulted in promising data.



1. INTRODUCTION

Candidiasis is normally a harmless fungal infection affecting the skin and mucous membranes of the mouth or intestines.[1] Invasive fungal infections are life-threatening and mostly caused by opportunistic fungal pathogens such as *Candida* species, *Aspergillus fumigatus*, and *Cryptococcus neoformans*.[2] *Candida albicans* and other nonalbicans species are the infectious agents in immunocompromised patients, and they cause morbidity and mortality.[3] Fluconazole is preferred as first-line antifungal therapy.[3] The dependence on existing antifungal drugs such as azoles (fluconazole, voriconazole, itraconazole, and posaconazole), polyenes (amphotericin B), allylamines (terbinafine and naftifine), and echinocandins (caspofungin and micafungin), has resulted in the development of drug-resistant fungal strains.[4] The current status of fungal infections and the drawbacks of existing drugs demand for the development of more effective and safe antifungal agents with novel targets.

Pyrazole is an important pharmacophore scaffold[5] and found in various drugs, *viz.*, betazole (histamine H_2 receptor agonist), rimonabant (anorectic antiobesity), CDPPB (antipsychotic), lonazolac, difenamizole, celecoxib (anti-inflammatory), and fezolamine, which is an antidepressant drug. Pyrazole exhibits a wide range of pharmacological activities such as antioxidant,[6] antifungal,[7] antitubercular,[8] antimalarial,[9] antiproliferative,[10] anticancer,[11] anti-inflammatory,[12] and antimicrobial[13] activities. In addition to this, heterocyclic hybrids of pyrazole derivatives have been reported[14−16] as they display an antifungal activity profile.

Several researchers have paid attention toward the synthesis of bis-pyrazole molecules[17] because of their diverse biological activities; the representative structures of the molecules **1**−**7** are shown in Figure 1. Sujatha and co-workers reported[18] the facile synthesis of bis-pyrazoles **1** and evaluated their *in vitro* antiviral activity. The pyrazole-based molecules **2** were synthesized and evaluated for their antimicrobial activity.[19] Farag *et al.* reported[20] *N*-phenylpyrazoles **3** and exhibited antitumor activity. The coumarin-appended bis-formylpyrazoles **4** show antimicrobial and antioxidant activities.[21] Dai *et al.* reported[22] bis-pyrazole molecules **5** as antitumor agents. Pyrazole-5-carboxamides **6** were reported for their anti-tobacco mosaic virus activity.[23] The dipyrazolo-pyranylquinolones **7** were synthesized and evaluated for their antitubercular and antimicrobial activity.[24] This gave a great impetus for the search of potential pharmacologically active drugs carrying a pyrazole unit in their molecular structure.

1,2,3-Triazole is a well-recognized pharmacophore unit derived from the copper-catalyzed 1,3-dipolar cycloaddition reaction of azides and alkynes.[25] The increasing impact of click chemistry in the field of medicinal chemistry and drug discovery is due to the high affinity of the triazole scaffold

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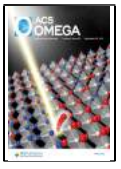

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One pot synthesis, in silico study and evaluation of some novel flavonoids as potent topoisomerase II inhibitors

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ABSTRACT

A library of novel flavonoid derivatives with diverse heterocyclic groups was designed and efficiently synthesized. Structures of the newly synthesized compounds **4a-i** and **8a-l** have been characterized by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. Anticancer activities were evaluated against MCF-7, A549, HepG2 and MCF-10A by MTT based assay. Compared with the positive control Adriamycin, compounds **4a**, **4b**, **4c**, **4d**, **8d**, **8e** and **8j** were found to be most active anti-proliferative compounds against human cancer cell line. We found that compounds **4a** and **4c** exhibited inhibition of enzyme topoisomerase II with IC_{50} values 10.28 and 12.38 μM, respectively. *In silico* docking study of synthesized compounds showed that compounds **4a** and **4c** have good binding affinity toward topoisomerase IIα enzyme and have placed in between DNA base pair at active site of enzyme. *In silico* ADME prediction results that flavonoid coumarin analogues **4a-i** could be exploited as an oral drug candidate.

Cancer is a significant worldwide health problem generally due to the lack of comprehensive early detection methods, associated poor prognosis of patients diagnosed in later stages of the disease and its increasing incidence on a global scale. Indeed, struggle to combat cancer is one of the greatest challenges of mankind. In industrialized countries, lung carcinoma is the leading cause of cancer death in men while breast carcinoma which is the most frequent cause of cancer death.[1–4] To date, available treatment regimens are not able to achieve a cure, nor improve survival substantially, except in rare cases. Thus, new targets for prevention and new agents for therapy need to be identified. Among the variety of molecular targets for cancer therapy, DNA topoisomerases (TOPO) are well-characterized targets owing to their essential roles in triggering, controlling, and modifying a wealth of topological DNA problems during cell proliferation, differentiation, and survival.[5] On the basis of their mechanisms, topoisomerases can be classified into two major classes: type I and type II DNA topoisomerases. TOPO-II is mostly expressed in ovarian and breast carcinomas. Hence, recent studies have concentrated on the exploitation of drugs or agents targeting TOPO-II.[6]

As widely occurring natural products, flavonoids are an important source for drug discovery due to their structural diversity and broad-spectrum biological activity. Most interestingly, compelling data have indicated that flavonoids have important chemo preventive and chemotherapeutic effects on cancer. Attention has been focused on their potential anticancer effect for decades.[7–10] For example, coumarin

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Development of novel, biocompatible, polyester amines for microglia-targeting gene delivery†

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Recent progress in personalized medicine and gene delivery has created exciting opportunities in therapeutics for central nervous system (CNS) disorders. Despite the interest in gene-based therapies, successful delivery of nucleic acids for treatment of CNS disorders faces major challenges. Here we report the facile synthesis of a novel, biodegradable, microglia-targeting polyester amine (PEA) carrier based on hydrophilic triethylene glycol dimethacrylate (TG) and low-molecular weight polyethylenimine (LMW-PEI). This nanocarrier, TG-branched PEI (TGP), successfully condensed double-stranded DNA into a size smaller than 200 nm. TGP nanoplexes were nontoxic in primary mixed glial cells and showed elevated transfection efficiency compared with PEI-25K and lipofector-EZ. After intrathecal and intracranial administration, PEA nanoplexes delivered genes specifically to microglia in the spinal cord and brain, respectively, proposing TGP as a novel microglia-specific gene delivery nanocarrier. The microglia-specific targeting of the TGP nanocarrier offers a new therapeutic strategy to modulate CNS disorders involving aberrant microglia activation while minimizing off-target side effects.

Introduction

Microglia are innate immune cells of the central nervous system (CNS) and play pivotal roles in CNS physiology and pathophysiology.[1] During neurodegeneration and natural brain aging, microglia lose their homeostatic cellular properties, show aberrant activation such as increased production of pro-inflammatory cytokines and reactive oxygen species (ROS), and develop dysfunctional lysosomal deposits showing impaired phagocytosis.[2] Moreover, microglia are involved in the regulation of CNS homeostasis while pruning unnecessary synapses and managing cell debris.[3] Microglia play a significant role in the clearance of amyloid plaques and aggregated α-synuclein in Alzheimer's disease (AD)[4] and Parkinson's disease (PD),[5] respectively. Increased cell-to-cell propagation of α-synuclein in grafted dopaminergic neurons and PD was observed due to pharmacological ablation of microglia using PLX5622.[6] In contrast, uncontrolled over-activation of microglia and subsequent neurotoxic mediators are suggested to contribute to these neurodegenerative diseases.[7] In neuropathic pain animal models, microglial activation and subsequent pro-inflammatory gene expression in the spinal cord elicit central pain sensitization to induce chronic pain.[8–10] All these studies point to the critical role of microglia in CNS disease and propose microglia as a prime therapeutic target for these CNS disorders.

Given such a role of microglia, efforts have been made to specifically deliver drugs to microglia in the CNS using nanoparticle-mediated delivery. In neuropathic pain studies, specific targeting of microglia using the CD11b antibody-conjugated nanozyme significantly reduced microglial reactive oxygen species production and thereby alleviated neuropathic pain.[11] In addition, poly-ε-caprolactone-based nanoparticles[12] and polyamidoamine dendrimers[13] were utilized to deliver drugs specifically to microglia in a neuropathic pain animal model. Although these nanoparticles have successfully delivered drug molecules to microglia and show a certain level of therapeutic efficacy, the development of microglia-targeting nanocarriers that efficiently deliver nucleic acids for gene therapy is lacking.

Despite recent technical advances in gene delivery systems, several issues such as cytotoxicity, low transfection efficiency, and cell specificity have remained the main challenges for researchers. For the past few decades, different vectors have been tested as gene carriers. Though gene therapy using viral vectors has shown clinical progress, restrictions associated with use, such as adverse immune reactions, smaller cargo size, and repeated administration, persist.[14,15] Non-viral vectors have

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Article

QbD-Based Development and Validation of an Efficient RP-HPLC Method for Estimation of Abiraterone Acetate in Bulk, Tablet, and In-House-Developed Nano-Formulation

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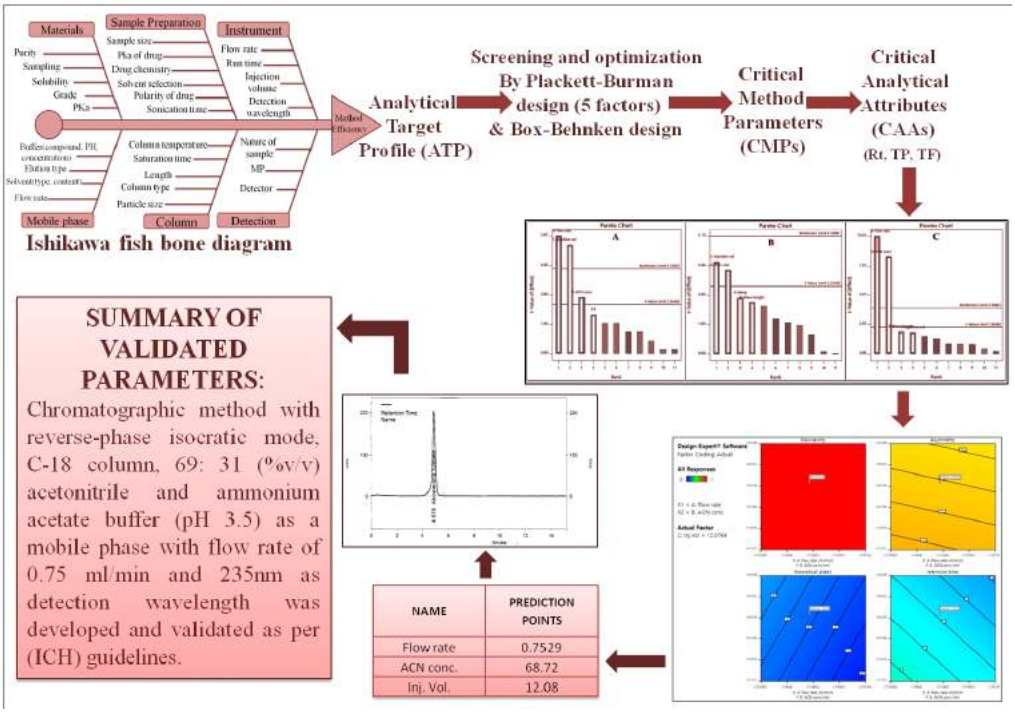

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RP-HPLC Method Development and Validation for the Estimation of Lansoprazole in Presence of Related Substances by QbD Approach

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

A rapid specific RP-HPLC method has been developed for the determination of Lansoprazole impurities in the drug substance. The control of pharmaceutical impurities is currently a critical issue in the pharmaceutical industry. The International Council for Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. The objective of the recent study was to develop and validate a HPLC method for the quantitative determination of process-related impurities of Lansoprazole in pharmaceutical drug substance. Lansoprazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]-sulfinyl]- 1H-benzimidazole is an proton pump inhibitor used in the management of gastric ulcers. Chromatographic identification of the impurities was carried out by response surface methodology, applying a three-level Box Behnken design with three center points. Three factors selected were a mobile phase, flow rate, column temperature. Evaluation of the main factor, their interaction, and the quadric effect on peak resolution were done on Waters Symmetry C_8, 250 x 4.6mm, 5µm column is used for the development of the method.

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Rectification of Pulmonary Toxicity by Natural Chelators in Lead-Induced Poisoning in Rats

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ABSTRACT

Chitosan and Chitosamine are natural polysaccharides from a marine source having potent chelation properties as confirmed by in-vitro studies. Our study investigated the same potency to be reflected in in-vivo studies on the respiratory system by inducing lead- acetatetoxicity in rats. **Material and Method**: Forty-two male albino Wistar rats (200-250g) were divided into seven groups (n=6). All the groups received lead acetate 0.4 mg/kg body wt. peroral (p.o) except the first-group (control) which receives sodium-acetate 1,000 mg/L in drinking water. Second-group is the toxic group, the third and fourth received Chitosan and Chitosamine 0.2 g/kg (p.o) respectively. Fifth, sixth & seventh group received ethylenediaminetetraacetic acid (EDTA) 495 mg/kg (p.o) whereas, sixth and seventh group received Chitosan and Chitosamine [0.2 g/kg (p.o)] respectively in addition.**Results:**The findings revealed a statistically significant increase in lungs weight, Malondialdehyde (MDA) levels, inflammation markers [rat C-Reactive Protein (rCRP), Erythrocyte sedimentation rate(ESR), and plasma viscosity (PV)]in the toxic group as compared to control one whereas, antioxidant enzymes viz. superoxide dismutase, catalase, and tissue glutathione levels were found to be decreased in the same as compared to toxic group. These levels were significantly rectified in treatment groups as compared to the toxic control indicating potent chelation property of natural chelators. These findings were further confirmed by histopathological examinations of the lungs section of rats resembling the control group, again confirming the chelation of heavy metals.**Conclusion**: The study entreaties to include natural chelators in daily diet as a nutraceutical agent and a prophylactic measure in rectifying heavy metals blood burdens in the body.

KEYWORDS: Pulmonary toxicity, Chelation, Chitosan, Chitosamine, Lead Toxicity.

INTRODUCTION: A large number of heavy metals dwell in the earth's crust mostly with no biological significances rather have deleterious effect on coming in contact with the body. Heavy metals such as Arsenic, bismuth, cadmium, lead, mercury, etc. are found enormously in ecological system having potential to imbalance homeostasis and co-ordination of various bio systems on earth (Luckey et.al.,1975).These heavy metals from various sources of environment enter the food chain through soil and upgrade its concentration at each step of food pyramids being non-biodegradable in nature (Babalola et al. 2005).Lead has topped the list amongst the most dangerous and serious environmental contaminants amongst the toxic harmful heavy metals throughout the world. Our study investigated the ill effects of lead as a heavy metal exposure via additives from gasoline, lead-based paints,food cans,ceramic glazes, cosmetics drinking water pipes , containers system, and industries of plastic recycling plant ,etc. (Dioka et al., 2004) The alimentary

Liposomes chemistry, manufacturing and control: Regulatory perspective

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Abstract

The US Food and Drug Administration (FDA) issued the final Guidance for Industry: *Liposome Drug Products, Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* in April 2018. This review articles focuses on chemistry, manufacturing and control (CMC) – characterization requirements for liposome drug product as per recommendation by FDA.

Key issues in manufacturing of liposome drug product are variability between and within batches. Hence, to have batch to batch consistency in liposome manufacturing, FDA guidance document provides recommendation on range of categories for which an applicant should provide characterization data which include composition, physicochemical properties (for example morphology, particle size distribution, zeta potential etc.), lipid component, control on manufacturing process variability and identification and control of critical quality attributes which may changes during manufacturing and storage.

Key Words: Liposomes Chemistry Manufacturing Control Regulatory

Introduction

Bangham first discovered liposomes in 1965 and the first liposomal pharmaceutical product, Doxil®, (Ben Venue Laboratories, Inc Bedford, OH) received US Food and Drug Administration (FDA) approval in 1995 for the treatment of chemotherapy refractory acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma.

The federal agency of the United States Department of Health and Human Services FDA has defined liposome drug products as follows: Liposomes are micro-vesicles composed of one or more bilayers of amphipathic lipid molecules enclosing one or more aqueous compartment, and Liposome drug products are those drug products that contain drug substances encapsulated or intercalated in the liposomes.

Chemistry, Manufacturing and Controls / Pharmaceutical Quality

This review article discussion addresses major critical aspect of chemistry, manufacturing and controls (CMC)/ Pharmaceutical qualityrequirements of the liposome drug product as per FDA guidance: *Liposome Drug Products, Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* (FDA guidance April 2018).

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Gastro-protective effect of Natural Chelators in Lead induced gastrointestinal toxicity in rats.

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ABSTRACT: Chronic lead exposure poses serious complications causing deterioration in anatomy and physiology in the body. In a view to observe the deleterious effect of lead poisoning on the gastrointestinal system and assess the amelioration by natural chelators, the parameters concerning gastric pH, the concentration of mucosal content, mucosal nitric oxide, and gastric ulcer index alongside histopathology of gastric mucosa were estimated. The main aim of the study is to determine the chelating effect of natural chelators on long-term exposure (24 weeks) of lead acetate concerning gastro-protective activity and to relate the chelating potency of natural and synthetic forms to include the one in day to day diet as a nutraceutical agent. Forty-two male albino Wistar rats (200-250g) were divided into seven groups (n=6). All the groups received lead acetate 0.4 mg/kg body wt. peroral (p.o) except the first-group (control) which receives sodium-acetate 1,000 mg/L in drinking water. Second-group is the toxic group, the third and fourth received Chitosan and Chitosamine 0.2 g/kg (p.o) respectively. Fifth, sixth & seventh group received ethylenediaminetetraacetic acid (EDTA) 495 mg/kg (p.o) whereas, sixth and seventh group received Chitosan and Chitosamine [0.2 g/kg (p.o)] respectively in addition. The findings revealed a decrease in stomach and body weights of animals alongside gastric pH, Mucin content, mucosal nitrite content, and increased oxidative stress by a reduction in SOD, CAT, GSH, and increase in MDA levels in the toxic group concerning the control group. These results were found to be ameliorated with a statistically significant increase in groups treated with chelators concerning the toxic group. Histopathological findings revealed congested blood vessels with cellular swelling in gastric mucosa along with cell infiltration in a toxic group with negligible change in gastric mucosal architecture in the control group. The reports of treatment groups of chelators showed normal gastric mucosal glands tubular architecture and related findings compared with the control group. Thus, it can be concluded that natural chelators have a gastro-protective role in lead-induced poisoning and are equipotent as synthetic ones to be used as a prophylactic heavy metal detoxifier nutraceutical agent.

KEYWORDS: Chitosan, Chitosamine, Lead Poisoning, Chelation, Gastro-Protective Effect.

I. INTRODUCTION

Saturnism is a common term used for lead toxicity. In spite being the number of heavy metals to have existed in the earth's crust, lead has proved to be a nuisance metal in disturbing the ecological balance. The unique physical and chemical property of lead ion has caused to increase its use and enhance its concentration making it a harmful environmental pollutant. [1] There is not a single system in the physiology of the body that is not being deteriorated by lead. Several previous studies revealed the distribution of lead ions in the blood, lung, liver, heart, brain, and kidney. The continuous use of lead made it accumulate in nature being non-biodegradable. Moreover, its lipophilic nature made it accumulate in adipose tissues, bones, and cartilages which are the least clearance region in the body. [2] The toxic consequences of lead are distinct not only in adults but also have major developmental side effects in children[3]. The lead is found to disrupt the proteins, enzymes, electron transport system as well as interferes in ATP formation. The major mode of the entrance of lead in the body is mainly inhalation and ingestion, where ingestion directly targets the gastrointestinal system.[4] The findings from previous studies revealed that lead toxicity decreases erythrocytic concentration leading to cellular ischemia.[5] It has also reported that lead ions enhances the pro-oxidant ability of ferrous ion and potentiates generation of reactive oxygen species (ROS), which might be one of the reasons of incidence of gastric ulcers[6].

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Activity of mushrooms against diabetic and inflammation: A review

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Abstract

Since ancient people, mushroom have been used as a source of food and in therapeutic remedies. Many recent studies confirm different biological activities of mushrooms which include antioxidant, antimicrobial, anticancer, antidiabetic and anti-inflammatory activities.

Many mushroom species have been evaluated for their antidiabetic and anti-inflammatory activities. This study highlights the effectiveness of mushrooms as antidiabetic and anti-inflammatory agents.

Keywords: Inflammation; Diabetic; Mushrooms; Active compounds; Anti-inflammation; Antidiabetic

1. Introduction

1.1. Diabetes

Diabetes mellitus its a group of metabolic diseases characterized by hyperglycemia, in which level of blood sugar elevated either because body cells do not respond properly to the insulin produced (insulin dysfunction) or the pancreas do not produce enough insulin (lack of insulin). Its a common health problem around the world and it have been estimated that by 2045 the number of diabetic patients could reach 629 million [1, 2].

1.2. Diabetes mellitus classification

Diabetes mellitus is classified as: type I diabetes, type II diabetes, gestational and other specific types of diabetes mellitus [3].

In type I diabetes mellitus, there is an absolute deficiency of insulin secretion due to the autoimmune destruction of beta pancreatic cells that lead to metabolic disturbances, especially affecting glucose homeostasis [4]. In type II diabetes mellitus, some mechanisms get damaged which regulate the cell sensitivity to insulin that ultimately leads to insufficient insulin secretion by the pancreatic beta cells, insulin dysfunction, and delayed insulin secretion through insulin resistance [5, 6]. In gestational diabetes mellitus, diabetes mellitus arises during second or third trimester of pregnancy.

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NUTRITIONAL VALUES, ETHNO-MEDICINAL USES AND ANTIOXIDANT ACTIVITY OF MUSHROOMS: A REVIEW

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ABSTRACT
Consume of mushrooms by human are maily due to their nutritional value and flavors. Traditional use of mushrooms in different countries has been reported by many researcher. During years, Many of mushrooms were reported to possess antioxidant activity due to the prescence of many active compounds like polysaccharides, lipids, proteins, phenolic compounds and flavonoids. The following review will summarize the nutritional values, Ethno-medicinal uses and antioxidant activity of mushroom.

KEYWORDS: Mushrooms, Ethno-medicinal, Free radicals, Active compounds, Antioxidant.

INTRODUCTION
Mushrooms are macrofungi and commonly belonging to Basidiomycotina and rarely to Ascomycotina. Mushrooms can be either hypogeous or epigeous and large enough to be seen with naked eye and to be picked by hand.[1] They obtain their nutrition through being symbiotic, saprotrophs and parasites as mycorrhiza. Mushrooms have a vegetative phase (mycelia) and reproductive phase (fruiting bodies).[2] Numerous mushrooms are considered not only as nutritionally rich food but also have medicinal properties. Present study reviews nutritional values, ethno-medicinal and traditional uses of mushroom, medicinal properties of mushroom as antioxidant and antimicrobial.

MUSHROOMS AND THEIR NUTRITIONAL VALUES
Mushrooms are filamentous fungi with both sexual and asexual reproduction cycle. The characteristic of basidiomycetes is a spore-producing structure or fruiting body (cap) called basidium. The morphological unit of the basidium is the hyphae, and a mass of hyphae is called mycelium. The spores produced inside the basidium are called basidiospore and are responsible for its reproduction and its dissemination. Sexual reproduction begins when the basidiospore germinates and grown as a haploid mycelium in optimal environmental conditions.[3,4] Mushrooms are well-known as edible and nonedible macro-fungi. The edible and non-edible mushroom can differentiate based on morphological characteristics like color, appearance, and shape of the cap.[5]

Mushrooms are considered as a functional food and can be used for medicinal purposes for humans. Mushrooms nutritionally contain carbohydrate, protein, several vitamins (B, C, D, K), essential oil, fibers, unsaturated fatty acid, enzymes, minerals (potassium, phosphorus) and trace elements (selenium).[6-8] Mushrooms in general contain 90% water and 10% dry matter and due to their high water content, they have low caloric value.[9] Carbohydrates constitute about one-half of mushroom dry matter (DM) and have a significant role in medicinal properties of mushrooms through their immune-stimulating glucans, along with other polysaccharides.[10] Protein content in dry mushrooms was 228 and 249 g/kg DM.[11] Mushrooms crude fat are low, ranging from 20 to 30 g/kg DM. Also, ascorbic acid content is 150–300 mg/kg DM, vitamin D_2 content was 16.88 µg/g, vitamin B_2 content was 12.68 µg/g but certain species contain detectable amount of vitamin D when exposed to UV light. Also, B-group vitamin contents of riboflavin (2.6–

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QbD-Based Development and Validation of an Efficient RP-HPLC Method for Estimation of Abiraterone Acetate in Bulk, Tablet, and In-House-Developed Nano-Formulation

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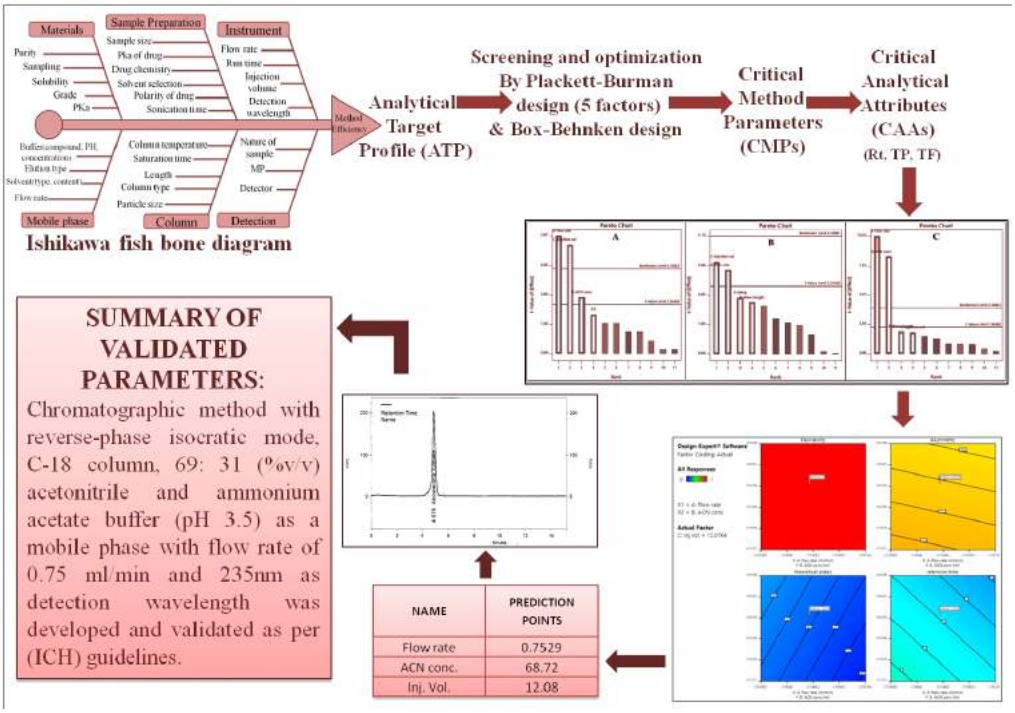

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Alysicarpus vaginalis Bio-Actives as ESR Signaling Pathway Inhibitor for Breast Cancer Treatment: A Network Pharmacology Approach

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ABSTRACT

In our previous study *Alysicarpus vaginalis* (AV) has appeared as a promising target for breast cancer hence we have screened potential targets by *in silico*, In Vitro and In Vivo methods. A network pharmacology (NP) approach involves prediction and validating of targets via molecular modeling, western blotting and In Vivo MNU-induced mammary cancer. The PPI network showed the 573 edges between 214 nodes (targets) that are involved in breast cancer and important one are ESR-1, ESR-2, AR, EGFR, NOS3, MAPK, KDR, SRC and MET. Compound-target-pathway network involves 04 compounds and 221 interactive protein targets associated with breast cancer. GO and KEGG enrichment analysis predicted the ERR, c-MET, PDGFR-α/β, EGFR, and VEGF as a key targets in the breast cancer treatment which are validated via molecular modeling. Expression of ER-α, AR and EGFR were significantly down regulated by AV in MCF-7 cell line. In addition, the immunoreactivity of ER-α was reduced significantly in MNU-induced mammary carcinoma, which is a key target in ER+breast cancer. Overall, this study scientifically light ups the pharmacological mechanism of AV in the treatment of breast cancer, strongly associated with the regulation of ESR signaling pathway.

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Introduction

Network pharmacology (NP) is a novel concept supported on the hypothesis of systems biology and network analysis of biological systems to propose the new multi-target drugs. It scientifically scrutinizes the influence and intervention of drugs on the disease network, and reveals the mystery of multi-target drugs synergistically targeting disorder or disease (1). Conventionally, the new drugs discovery is based on identifying and/or designing a pharmacologically active agent that explicitly interacts with a single target (2). NP is more useful for creating a network of "compound-protein/gene-disease" and illuminating the regulation principle of small molecule in a high throughput mode (3). NP has come out as a potential way to elucidate the systems level mechanisms of natural components. It recognizes complex diseases, like cancer, as a perturbation of interrelated complex biological networks and recognizes the drug mechanism in terms of the network topology (4,5). This preferably leads to therapies that are not as much of susceptible to drug resistance and less significant side effects by means of targeting the disease network at the systems level through synergistic and lethal interactions. Nature is a precious pool of novel compounds. According to an approximation, concerning 50% of the medications validated from 1981 to 2010 have natural origins (i.e., 28% semi-synthetic, 17% mimics of natural compounds and 5% natural entities). Natural components are identified to exert their therapeutic effects by acting on multiple targets of multiple compounds, and the mechanism of action is well suited to the theory of NP. As a result, researchers have engaged in NP methods to find out the potent anticancer targets and pathways of component from natural products (6–8).

Alysicarpus vaginalis (AV) is a medicinal plant that has been used for the treatment of cough, dysentery, colics, sword wounds, bone fractures and antiviral activity in folk medicine. Extracts have been shown to berich in a variety of phenolic compounds (9,10). Our previous laboratory findings have been revealed that the favorable effects of ethyl acetate fraction of AV can be recognized to their anti-breast cancer

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Investigating optical, electrical, and mechanical traits of thiourea admixtured KDP single crystals to explore NLO device applications

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ABSTRACT

The 0.5 and 1 mol% thiourea "mixed" potassium dihydrogen phosphate (KDP) crystals have been developed by conventional slow solution evaporation method. The crystallographic parameters of grown crystals have been determined by employing single crystal X-ray diffraction technique. The functional groups of grown crystals were successfully identified by means of FTIR spectral analysis. The optical transmittance is 79%, 84%, and 89% for KDP, 0.5 mol thiourea mixed KDP, and 1 mol thiourea mixed KDP crystal. The energy band gap (E_g) of KDP, 0.5 mol thiourea mixed KDP, and 1 mol thiourea mixed KDP crystal is 3.71 eV, 3.61 eV, and 3.75 eV, respectively. The Kurtz–Perry test has been employed to determine the SHG efficiency and SHG efficiency of 0.5 and 1 mol thiourea mixed KDP crystal is 2.09 and 2.22 times superior to KDP crystal. Effect of thiourea mixing on hardness properties of KDP crystal have been scrutinized using the Vickers microhardness studies. The frequency dependent dielectric behavior of grown crystals has been analyzed at room temperature.

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RESEARCH ARTICLE

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Benzimidazole-1,2,3-triazole hybrid molecules: synthesis and study of their interaction with G-quadruplex DNA†

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A series of new benzimidazole-1,2,3-triazole hybrid derivatives have been synthesized *via* 'click' reaction and evaluated for their *in vitro* cytotoxicity as well as DNA binding affinity. MTT assay showed that all the six compounds are cytotoxic to PC3 and B16-F10 cancer cell lines. Though all the compounds showed moderate interaction with G4, c-Myc promoter DNA and dsDNA, **4f** exhibited selective interaction with G-quadruplex DNA over duplex DNA as demonstrated by spectroscopic experiments like UV-vis spectroscopy, fluorescence spectroscopy, CD spectroscopy, thermal melting and fluorescence lifetime experiments. They also confirm the G-quadruplex DNA stabilizing potential of **4f**. Viscosity measurements also confirm that **4f** exhibits high G-quadruplex DNA selectivity over duplex DNA. Docking studies supported the spectroscopic observations. Cell cycle analysis showed that **4f** induces G_2/M phase arrest and induces apoptosis. Hence, from these experimental results it is evident that compound **4f** may be a G-quadruplex DNA groove binding molecule with anticancer activity.

Introduction

Cancer is one of the leading causes of death worldwide. It is a heterogeneous group of diseases characterized by abnormal cell division beyond the Hayflick limit.[1] Tumor formation is a multistep process and attaining replicative immortality is one of the hallmarks of cancer.[2] In normal cells the chromosomal ends contain a hexanucleotide "TTA GGG" repeat which becomes shortened after each division and finally, after reaching critical length, the cells become senescent.[3] Tumor cells compensate for the loss of telomeres by overexpressing the telomerase enzyme that adds telomeric repeats to the end of the chromosomes. This process helps cancer cells to continue DNA replication and cell division indefinitely. As telomerase is detected in cancer cells and untraceable in most of the normal somatic cells, cancer cells can be effectively targeted by telomerase inhibitors without affecting the normal cells.

The formation of G-quadruplex by the telomeric region inhibits the interaction of telomerase with DNA, resulting in DNA damage and cell death. G4 motifs have been found in the promoter regions of oncogenes like c-Myc, c-kit, Bcl-2, and KRAS.[4] Hence, ligands that stabilize G-quadruplexes may act as excellent anticancer agents by limiting telomeric length and by inhibiting the expression of oncogenes. Small molecules that stabilize G-quadruplex through loop binding, groove binding and intercalation are of immense value in anticancer research. The design of ligands which can specifically stabilize the G-quadruplex DNA structure and thereby inhibit the telomerase binding to DNA has become a promising strategy in anticancer drug discovery.[5] In DNA-targeted anticancer therapy, ligands with poor discriminating ability between duplex and G-quadruplex DNA may cause undesirable side effects. Hence, the development of G-quadruplex-selective molecules is the need of the hour.

Recently, several synthetic molecules and natural small molecules were shown to exhibit potential anticancer activity by stabilizing G-quadruplex DNA and inducing apoptosis.[4–7]

It was reported earlier that benzimidazole pharmacophore, a good bioisostere of biological nucleotides, exhibits a wide range of biological activities[9–12] (Fig. 1).

Hoechst, which is widely used to stain DNA molecules, is a benzimidazole-based molecule. Benzimidazole derivatives

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Pellets containing quercetin amino acid co-amorphous mixture for the treatment of pain: Formulation, optimization, in-vitro and in-vivo study

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A B S T R A C T

Quercetin (QCT) shows many therapeutic applications but is constrained to its oral use due to its low bioavailability. In this study, co-amorphous mixture QCT with different amino acids (Arginine, Glutamic acid, Aspartic acid, Tryptophan, and Glycin) of different molar ratios was prepared using ball milling method. The solubility and physicochemical study of the mixtures was done using FTIR and XRD study. The co-amorphous mixtures QCT: ARG (1:2) was formulated in pellets using extrusion spheronization method. *In-vitro* dissolution study F1 formulation showed ($95.74 \pm 4.58\%$) significant increase ($P < 0.005$) compared to the pure drug ($21.85 \pm 3.42\%$) and other formulations. The *in-vivo* study F1 showed a significant ($p < 0.05$) increases in percent inhibition (67.00%) compared to pure drug (31%). The F1 formulation was stable when subjected to stability study. Therefore, the prepared co-amorphous mixture loaded pellets enhance the solubility, bioavailability, and stability of quercetin.

1. Introduction

Quercetin (QCT) is a bio-flavonoid, generally found in onions, apples and various fruit juices shows the antioxidant, cardiovascular disease, anti-inflammatory and anti-tumor activity with many therapeutic applications reported in various studies [1–5]. The therapeutic use have been restricted due to its poor solubility, low bioavailability and rapid first-pass metabolism [6]. Various studies were done to increase the bioavailability of quercetin using nanofabrication, complexation, and solid dispersion [7], nanocrystals [8] nanosuspension [9] self emulsifying delivery [10] micelles [11]. Co-amorphous mixture is the new technique to increase solubility, bioavailability, and stability of poorly soluble drug using grinding or milling [12]. From the improvement point of view, ball milling is a green technology and is better than solvent approaches [13]. Various studies reported that the use of small molecules like saccharine, amino acids, citric acid, and sugars can stabilized the amorphous drugs in a co-amorphous mixture [14–16]. Amino acids are used as a excellent co-former for the preparation of co-amorphous formulation for various poorly soluble drugs such as valsartan [17], carbamazepine and indomethacin [18]. Many literature reported the increase in dissolution rate of a co-amorphous mixtures of various drugs such as indomethacin and naproxen [19,20], simvastatin [21], carbamazepine, lurasidone [22] and curcumin [23]. QCT showed the outstanding glass forming ability due to its relatively high Tg value [24]. Therefore QCT is an ideal candidate for preparation of co-amorphous mixture. Mechanistic understanding of previously mentioned problems of Quercetin has motivated us to enhance the solubility and dissolution using amino acid. Hence, the present research was focused to prepare co-amorphous mixtures of QCT by using different amino acid (arginine, glutamic acid, aspartic acid, tryptophan, and glycin) of different molar ratios using the ball milling method. Further, a mixture with the highest solubility was formulated in pellets by extrusion spheronization technique which would become a potential approach for pain management.

2. Materials and methods

2.1. Materials

Quercetin (M 302.236 g/mol) was purchased from Yarrow Chem Products, Mumbai, India. Arginine (ARG) (M = 174.20 g/mol), Glutamic acid (GLA), Aspartic acid (APA), Tryptophan (TTP) (M = 204.23 g/mol), Glycin (GLY), Microcrystalline cellulose 101, Xantham gum, and Lactose were obtained from Molychem, Mumbai, India. All other chemicals and solvent used in the study were of analytical reagent grade.

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Article

Quality by Design Approach in the Formulation of Glibenclamide Mucoadhesive Buccal Films

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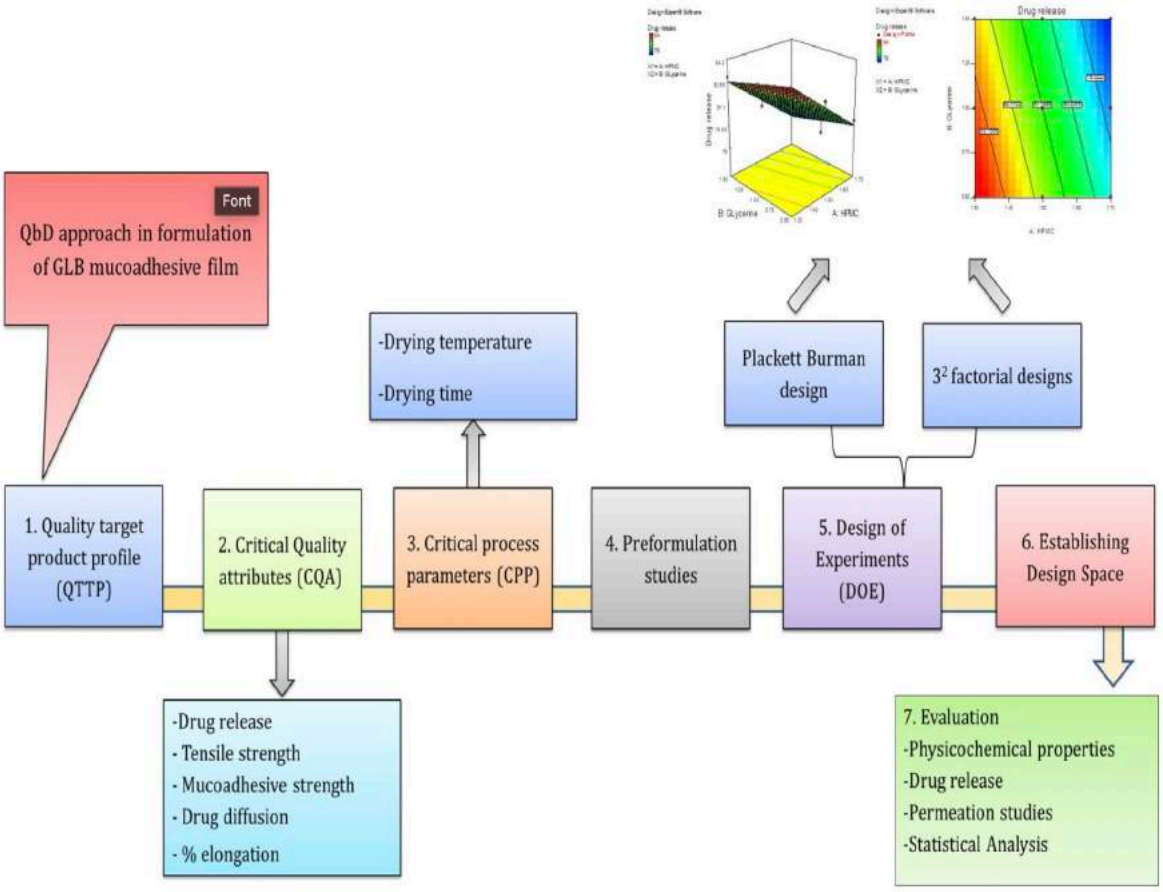
Graphical abstract



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Article

QbD-Based Development and Validation of an Efficient RP-HPLC Method for Estimation of Abiraterone Acetate in Bulk, Tablet, and In-House-Developed Nano-Formulation

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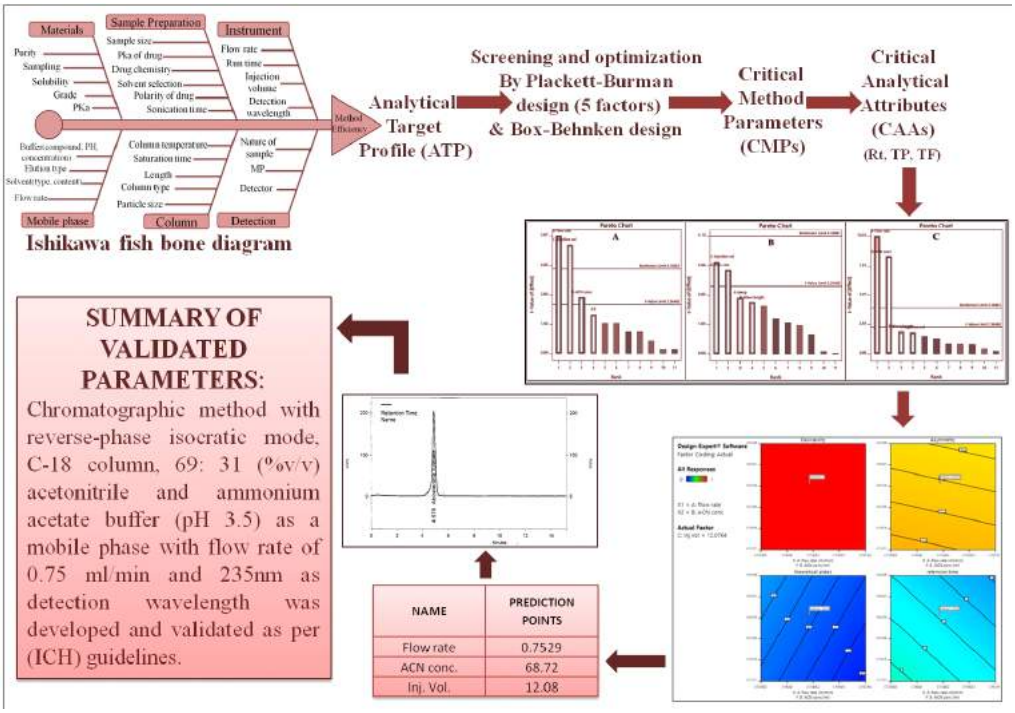

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Current Pharmaceutical Design, 2021, *27*, 1-14

REVIEW ARTICLE

Application of Carbon Nanotubes In Drug Delivery of Non-cancerous Diseases: A Review

Shahebaaz Khan[1], Puja Jawlikar[1], Swaroop Lahoti[1], Omprakash Bhusnure[2], Sohan Chitlange[3] and Jaiprakash Sangshetti[1,*]

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Abstract: Carbon Nanotubes (CNT) are the allotropes of carbon in nanosize dimension and are popular in medicinal field. These nano-based technologies are gaining high interest in the recent years for the treatment of diseases that are previously considered to be impossible to cure. CNTs have gained significance in the treatment of the majority of disorders such as Malaria, Alzheimer's disease, Infectious disease, and Asthma. Moreover, patient's responsiveness also increased in cardiovascular and pulmonary diseases. To date, a number of reviews are available in the literature covering applications of CNT in cancer. However, the purpose of this review is to focus on the use of CNTs in drug delivery of non-cancerous diseases. The novelty of this review is that it is focused on the applicability of CNT in the various non-cancerous diseases. Detailed information was collected from the literature which will guide and encourage researchers to explore the applicability of CNT in various non-cancerous diseases in the future.

Keywords: Carbon nanotubes, drug delivery, targeted therapy, non-cancerous diseases.

1. INTRODUCTION

Sumio Iijima and co-workers (Nippon realistic company) in the year 1991 discovered Carbon Nanotubes (CNT) by using a high--resolution electron microscope. The initially discovered CNT was a multiwall carbon nanotube (MWCNT) and later in 1993 the single-walled carbon nanotube (SWCNT) was discovered. Before the discovery of Iijima, the CNTs were accidentally discovered by Oberlin, Endo, and Koyama by using the vapor growth technique [1]. Radushkevich and Lukyanovich in the soviet journal of physical chemistry published 50-nanometer diameter tubes made from carbon in 1952 [2b]. Hollow tubes rolled graphite synthesis from chemical vapor growth technique was observed by the scientist Morinober Endo of CNRS in the year 1976 at 14th Biennial conference of carbon at Pennsylvania state university. John Abrahamson offered proof of CNT in 1979. TEM images and XRD patterns were utilized for the structural characterization of CNT produced by thermo catalytical disproportion of carbon monoxide and were published by a soviet scientist in 1981. Howard G. Tennet of hyperion issued a US patent for cylindrical discrete carbon fibril production with a constant diameter of 3.7-70 nm length that is 10^2 times the diameter in 1987. Finally, arch burned graphite rod MWCNT was discovered by scientist Iijima in 1991 [2a, b]. Fig. (**1**) contains a summarized representation of the discovery of CNT.

1.1. CNTs and their Structure

In general, the size of CNT is up to 100 nm. The administration of CNT into the body is convenient owing to its small size. However, the size of CNT should be optimized because too small size may lead to leaking of CNT from the blood capillaries and too large size makes it engulfed by reticuloendothelial cells present in the blood circulation [3]. CNT's are made up of graphene. Graphene is the allotrope of carbon which has hexagonal lattice geometry made up of a single layer of the carbon atom. The CNTs are organized in sp2 bonded carbon atom. CNTs have a hexagonal structure and their structural arrangement is sp2 hybridized [4]. SWCNT is obtained from a pair of integers (n, m). Depending upon wrapping SWCNT is divided into three types armchair (n=m) zigzag (m=0) chiral (any other nm). The electrical properties of CNT's are affected by the wrapping of CNTs [5]. The surface of the CNTs should be hydrophilic, and this can be achieved by treating polymers on the surface of CNTs. These CNTs have wide-ranging medical applications because it consists of thermal, mechanical, electrical, and biological property [6]. CNTs can be administered into the human body by various methods oral, IV, transdermal, subcutaneous, intraperitoneal, inhalation, like the structure of CNT, which makes it more reliable for penetration in the cell [7]. The cellular internalization needs various factors such as surface characterization, chemical concentration, roughness, functionalization, shape, periodicity, hydrophilicity, and hydrophobicity [3, 7].

1.2. Types of CNTs

Depending upon the number of walls present in its structure; CNT's are divided into three types: Single-walled CNTs (SWCNT), double-wall carbon nanotube (DWCNT), and multiple-walled CNTs (MWCNT) [5].

1.2.1. SWCNT

SWCNT consists of a monolayered cylindrically rolled graphitic carbon sheet, using single-walled CNTs for delivering a drug through various routes. The diameter of SWCNT varies from 0.4-2 nm [8]. Li wie *et al.* reported the aggregation of carbon nanotube under different circumstances. It is a major problem in the application of CNTs by using the PL sideband tool. For this experiment SWCNT with the different chiral structures was used for investigation. The suspension containing the SWCNT bundle was observed by ultracentrifugation. The result showed that photoluminescence sideband depends on the aggregation of nanotubes [9]. The fundamental behavior of hydroxylated SWCNT was observed shortly after introducing iodine 131 as dressing material into the animal body for 2-60 minutes. The injection mode influenced the biodistribution and pharmacokinetic parameters for studies, however within

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REVIEW ARTICLE

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ORIGINAL ARTICLE

Caesalpinia pulcherrima Arrests Cell Cycle and Triggers Reactive Oxygen Species-Induced Mitochondrial-Mediated apoptosis and Necroptosis via Modulating Estrogen and Estrogen Receptors

Nikhil S. Sakle, Deepak Lokwani[1], Santosh Namdeo Mokale

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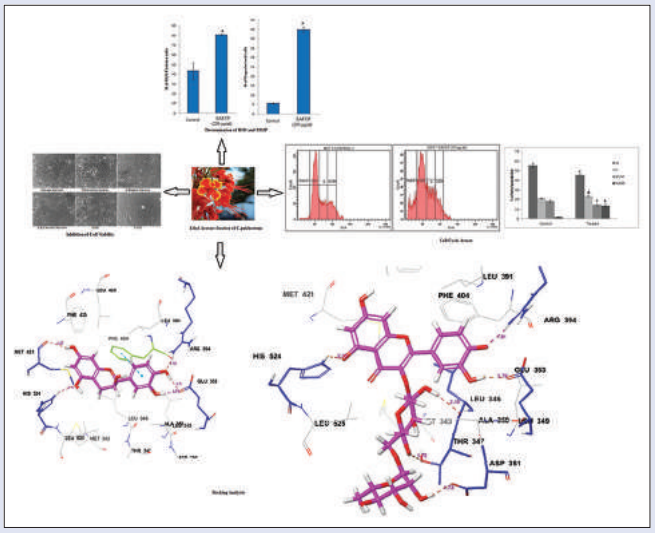
ABSTRACT

Background: *Caesalpinia pulcherrima* belonging to the family *Fabaceae* is used in India as a traditional medicine for a variety of ailments. Globally, traditional medicines are presently being used for the treatment of cancer. **Objective:** The present study was aimed at investigating the chemomodulatory potential of *C. pulcherrima* flowers in breast cancer and explaining its possible mechanism. **Materials and Methods:** The cytotoxic potential of ethyl acetate fraction of *C. pulcherrima* (EAFCP) flower was tested in MCF-12A (normal breast), MCF-7 (estrogen receptor [ER] positive), and MDA-MB-453 (human epidermal growth factor receptor 2 positive) human breast cancer cells by sulforhodamine B assay. Chemomodulatory potential was evaluated *in vivo* against N-methyl-N-nitrosourea (MNU)-induced mammary carcinoma in female Sprague Dawley® rats. The mechanism for anticancer potential was screened by *in vitro* studies involving Annexin V-FITC assay (apoptosis), cell cycle patterns, intracellular reactive oxygen species, and mitochondrial membrane potential measurement (FACS based) followed by docking study on estrogen receptor-alpha (ER-α). **Results:** The fractions showed perceptible cell growth inhibition potency (IC_{50} <50 μg/ml) in MCF-7 breast cancer cells. In MNU-treated animals, antioxidant enzymes and histological examination showed statistically significant ($P < 0.001$) changes. Treatment of MCF-7 cells with EAFCP reduced cell growth rate by a mechanism associated with both apoptotic and necrotic cell death. Molecular docking study further showed that rutin and catechin have a comparable binding affinity for the ER-α. **Conclusion:** In this study, we confirmed that EAFCP was most effective in reducing cell viability, scavenging physiological oxidant species, and causing mitochondria-mediated apoptosis and necroptosis in MCF-7 cell by selectively modulating the functions of ER-α.

Key words: Antioxidant, breast cancer, estrogen receptor modulator, high-performance liquid chromatography, histopathology

SUMMARY

- Ethyl acetate fraction of Caesalpinia pulcherrima (EAFCP) flower showed cytotoxic potential against breast cancer cells by sulforhodamine B assay. The anticancer and antioxidant potential of EAFCP flower was evaluated against N-methyl-N-nitrosourea-induced mammary cancer in female Sprague Dawley rats. The in vitro results of the present study showed that EAFCP can induce mitochondrial-mediated apoptosis and necroptosis through reactive oxygen species generation with loss of mitochondrial membrane potential in MCF-7 via modulating the functions of estrogen receptor-alpha *in silico*.



Abbreviations used: EAFCP: Ethyl acetate fraction of *Caesalpinia pulcherrima*; MNU: N-methyl-N-nitrosourea; ROS: Reactive oxygen species; ER-α: Estrogen receptor-α; HPLC: High-performance liquid chromatography; TBARS: Thiobarbituric acid-reactive substances; HP: Hydroperoxides; LPO: Lipid peroxidation; CAT: Catalase; SOD: Superoxide dismutase; NBT: p-nitro blue tetrazolium chloride; GP_X: Glutathione peroxidase; GST: Glutathione-S-transferase; CDNB: 1-Chloro-2,4-dinitrobenzene; GR: Glutathione reductase; GSH: Reduced glutathione; MMP: Mitochondrial membrane potential; H and E: Hematoxylin and eosin; TB: Toluidine blue; LBD: Ligand-binding domain; TAM: Tamoxifen; ADR: Adriamycin; ANOVA: Analysis of variance.

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INTRODUCTION

Breast cancer is one of the most common malignancies in the world and a major cause of cancer-related deaths in women. It has been observed that estrogen level is an important factor in the initiation and development of breast cancer. Estrogen receptor-alpha (ER-α) is a well-characterized mediator in breast cancer for the proliferation of cells.[1] On the other hand, estrogens and estrogenic compounds are a subject of

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ORIGINAL ARTICLE

Caesalpinia pulcherrima Arrests Cell Cycle and Triggers Reactive Oxygen Species-Induced Mitochondrial-Mediated apoptosis and Necroptosis via Modulating Estrogen and Estrogen Receptors

Nikhil S. Sakle, Deepak Lokwani[1], Santosh Namdeo Mokale

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Submitted: 06-03-2019 Revised: 16-04-2019 Published: 26-08-2019

ABSTRACT

Background: *Caesalpinia pulcherrima* belonging to the family *Fabaceae* is used in India as a traditional medicine for a variety of ailments. Globally, traditional medicines are presently being used for the treatment of cancer. **Objective:** The present study was aimed at investigating the chemomodulatory potential of *C. pulcherrima* flowers in breast cancer and explaining its possible mechanism. **Materials and Methods:** The cytotoxic potential of ethyl acetate fraction of *C. pulcherrima* (EAFCP) flower was tested in MCF-12A (normal breast), MCF-7 (estrogen receptor [ER] positive), and MDA-MB-453 (human epidermal growth factor receptor 2 positive) human breast cancer cells by sulforhodamine B assay. Chemomodulatory potential was evaluated *in vivo* against N-methyl-N-nitrosourea (MNU)-induced mammary carcinoma in female Sprague Dawley® rats. The mechanism for anticancer potential was screened by *in vitro* studies involving Annexin V-FITC assay (apoptosis), cell cycle patterns, intracellular reactive oxygen species, and mitochondrial membrane potential measurement (FACS based) followed by docking study on estrogen receptor-alpha (ER-α). **Results:** The fractions showed perceptible cell growth inhibition potency (IC_{50} <50 μg/ml) in MCF-7 breast cancer cells. In MNU-treated animals, antioxidant enzymes and histological examination showed statistically significant ($P < 0.001$) changes. Treatment of MCF-7 cells with EAFCP reduced cell growth rate by a mechanism associated with both apoptotic and necrotic cell death. Molecular docking study further showed that rutin and catechin have a comparable binding affinity for the ER-α. **Conclusion:** In this study, we confirmed that EAFCP was most effective in reducing cell viability, scavenging physiological oxidant species, and causing mitochondria-mediated apoptosis and necroptosis in MCF-7 cell by selectively modulating the functions of ER-α.

Key words: Antioxidant, breast cancer, estrogen receptor modulator, high-performance liquid chromatography, histopathology

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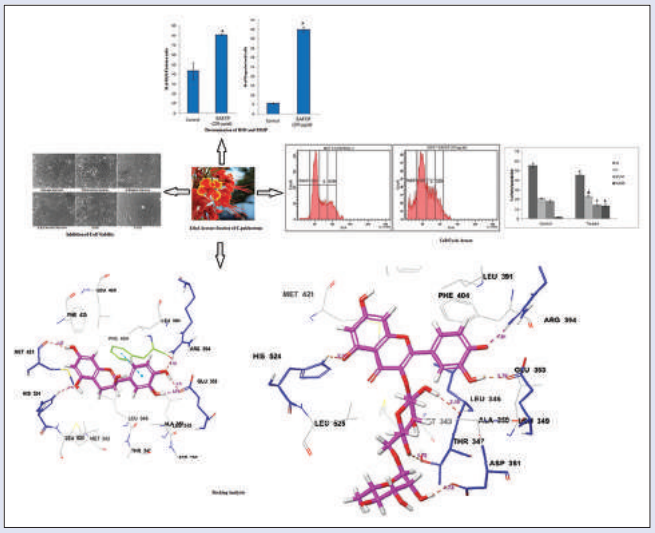
- Ethyl acetate fraction of Caesalpinia pulcherrima (EAFCP) flower showed cytotoxic potential against breast cancer cells by sulforhodamine B assay. The anticancer and antioxidant potential of EAFCP flower was evaluated against N-methyl-N-nitrosourea-induced mammary cancer in female Sprague Dawley rats. The in vitro results of the present study showed that EAFCP can induce mitochondrial-mediated apoptosis and necroptosis through reactive oxygen species generation with loss of mitochondrial membrane potential in MCF-7 via modulating the functions of estrogen receptor-alpha *in silico*.



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Breast cancer is one of the most common malignancies in the world and a major cause of cancer-related deaths in women. It has been observed that estrogen level is an important factor in the initiation and development of breast cancer. Estrogen receptor-alpha (ER-α) is a well-characterized mediator in breast cancer for the proliferation of cells.[1] On the other hand, estrogens and estrogenic compounds are a subject of

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REVIEW ARTICLE

Application of Carbon Nanotubes In Drug Delivery of Non-cancerous Diseases: A Review

Shahebaaz Khan[1], Puja Jawlikar[1], Swaroop Lahoti[1], Omprakash Bhusnure[2], Sohan Chitlange[3] and Jaiprakash Sangshetti[1,*]

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ARTICLE HISTORY

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Abstract: Carbon Nanotubes (CNT) are the allotropes of carbon in nanosize dimension and are popular in medicinal field. These nano-based technologies are gaining high interest in the recent years for the treatment of diseases that are previously considered to be impossible to cure. CNTs have gained significance in the treatment of the majority of disorders such as Malaria, Alzheimer's disease, Infectious disease, and Asthma. Moreover, patient's responsiveness also increased in cardiovascular and pulmonary diseases. To date, a number of reviews are available in the literature covering applications of CNT in cancer. However, the purpose of this review is to focus on the use of CNTs in drug delivery of non-cancerous diseases. The novelty of this review is that it is focused on the applicability of CNT in the various non-cancerous diseases. Detailed information was collected from the literature which will guide and encourage researchers to explore the applicability of CNT in various non-cancerous diseases in the future.

Keywords: Carbon nanotubes, drug delivery, targeted therapy, non-cancerous diseases.

1. INTRODUCTION

Sumio Iijima and co-workers (Nippon realistic company) in the year 1991 discovered Carbon Nanotubes (CNT) by using a high--resolution electron microscope. The initially discovered CNT was a multiwall carbon nanotube (MWCNT) and later in 1993 the single-walled carbon nanotube (SWCNT) was discovered. Before the discovery of Iijima, the CNTs were accidentally discovered by Oberlin, Endo, and Koyama by using the vapor growth technique [1]. Radushkevich and Lukyanovich in the soviet journal of physical chemistry published 50-nanometer diameter tubes made from carbon in 1952 [2b]. Hollow tubes rolled graphite synthesis from chemical vapor growth technique was observed by the scientist Morinober Endo of CNRS in the year 1976 at 14th Biennial conference of carbon at Pennsylvania state university. John Abrahamson offered proof of CNT in 1979. TEM images and XRD patterns were utilized for the structural characterization of CNT produced by thermo catalytical disproportion of carbon monoxide and were published by a soviet scientist in 1981. Howard G. Tennet of hyperion issued a US patent for cylindrical discrete carbon fibril production with a constant diameter of 3.7-70 nm length that is 10^2 times the diameter in 1987. Finally, arch burned graphite rod MWCNT was discovered by scientist Iijima in 1991 [2a, b]. Fig. (**1**) contains a summarized representation of the discovery of CNT.

1.1. CNTs and their Structure

In general, the size of CNT is up to 100 nm. The administration of CNT into the body is convenient owing to its small size. However, the size of CNT should be optimized because too small size may lead to leaking of CNT from the blood capillaries and too large size makes it engulfed by reticuloendothelial cells present in the blood circulation [3]. CNT's are made up of graphene. Graphene is the allotrope of carbon which has hexagonal lattice geometry made up of a single layer of the carbon atom. The CNTs are organized in sp2 bonded carbon atom. CNTs have a hexagonal structure and their structural arrangement is sp2 hybridized [4]. SWCNT is obtained from a pair of integers (n, m). Depending upon wrapping SWCNT is divided into three types armchair (n=m) zigzag (m=0) chiral (any other nm). The electrical properties of CNT's are affected by the wrapping of CNTs [5]. The surface of the CNTs should be hydrophilic, and this can be achieved by treating polymers on the surface of CNTs. These CNTs have wide-ranging medical applications because it consists of thermal, mechanical, electrical, and biological property [6]. CNTs can be administered into the human body by various methods oral, IV, transdermal, subcutaneous, intraperitoneal, inhalation, like the structure of CNT, which makes it more reliable for penetration in the cell [7]. The cellular internalization needs various factors such as surface characterization, chemical concentration, roughness, functionalization, shape, periodicity, hydrophilicity, and hydrophobicity [3, 7].

1.2. Types of CNTs

Depending upon the number of walls present in its structure; CNT's are divided into three types: Single-walled CNTs (SWCNT), double-wall carbon nanotube (DWCNT), and multiple-walled CNTs (MWCNT) [5].

1.2.1. SWCNT

SWCNT consists of a monolayered cylindrically rolled graphitic carbon sheet, using single-walled CNTs for delivering a drug through various routes. The diameter of SWCNT varies from 0.4-2 nm [8]. Li wie *et al.* reported the aggregation of carbon nanotube under different circumstances. It is a major problem in the application of CNTs by using the PL sideband tool. For this experiment SWCNT with the different chiral structures was used for investigation. The suspension containing the SWCNT bundle was observed by ultracentrifugation. The result showed that photoluminescence sideband depends on the aggregation of nanotubes [9]. The fundamental behavior of hydroxylated SWCNT was observed shortly after introducing iodine 131 as dressing material into the animal body for 2-60 minutes. The injection mode influenced the biodistribution and pharmacokinetic parameters for studies, however within

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ORGINAL ARTICLE

Pharmacokinetic Drug Food Interaction Study of Nateglinide and Pomegranate Fruit Juice

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Abstract

Objective: Pomegranate juice is inhibitor of CYP450 enzyme system such as CYP2C9 and CYP3A4. The objective of the present study was to determine the consequence of pomegranate fruit juice on the pharmacokinetics of oral hypoglycemic drug nateglinide in rats.

Materials and Methods: This is a laboratory study to investigate drug-food interaction effects of Punica granatum fruit juice (3 ml) and nateglinide (in doses 10 and 20 mg/kg body weight, p.o.) in live animals where the effects of food drug interaction on pharmacokinetics parameters such as Cmax and AUC in vehicle and nateglinide and pomegranate juice and nateglinide treated rats was undertaken. Four groups of Wistar albino rats comprising of (n=5) animals in each group were taken and treated with vehicle and nateglinide (in doses 10 and 20 mg/kg body weight, p.o.) pomegranate juice (3ml, p.o.) and nateglinide (in doses 10 and 20 mg/kg body weight, p.o.).

Results: The rats which were administered with pomegranate juice + nateglinide (in doses 10 and 20 mg/kg body weight, p.o.) showed raised C_{max} to 2.85 fold and 2.21-fold respectively and an increase in AUC was found to be 1.34 fold and 1.47 fold respectively, when vehicle + nateglinide 10mg/kg and vehicle + 20mg/kg drug treated groups were compared. The results were compared at *P*-value< 0.01.

Conclusion: A significant drug interaction was observed when nateglinide and pomegranate juice was administered indicating caution must be exercised when such food and drug is co-administered as the chance of more hypoglycemia may occur due to this potential drug-food interaction.

Keywords: Food–Drug interaction, Pomegranate, Nateglinide

Introduction

Food-drug interactions are defined as modification of drug disposition or action of a drug or dietary component or a deficiency in dietary status as a result of the adding of a drug (1). A study has detailed that when grapefruit juice and felodipine or nifedipine, which are calcium channel antagonists were co-administered has resulted

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Research Article

Quality by Design Based Approach for the Estimation of Telmisartan in Presence of Related Substances by RP-HPLC Method

SACHIN GHOLVE[1]*, MOHAMMAD IMRAN ANEES[1], MARIA SAIFEE[1], JAIPRAKASH SANGSHETTI[1], OMPRAKASH BHUSNURE[2], ABUBAKAR SALAM BAWAZIR[1]
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ABSTRACT:
A rapid specific RP-HPLC method has been developed for the determination of telmisartan in presence of impurity in the pharmaceutical drug substances. The control of pharmaceutical impurities is currently a critical issue in the pharmaceutical industry. The International Council for Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. The objective of the recent study was to develop and validate a HPLC method for the quantitative determination of process-related impurities of telmisartan in pharmaceutical drug substances. Telmisartan is an angiotensin II receptor antagonist used in the management of hypertension. Chromatographic identification of the impurities was carried out on Eclipse XDB Phenyl (250×4.6 mm) column is used for the development of the method. The mobile phase consists of buffer and acetonitrile. The flow rate of the mobile phase was 1.0 mL/min with gradient elution. The column temperature is 30°C ± 2°C and the detection wavelength is 296 nm. The injection volume is 10 µL. The method was validated for linearity in the range of 2-12 µg/ml concentration and the LOD &LOQ values obtained were 0.00005123 and 0.0001341 µg/ml respectively which specifies the method's sensitivity. The proposed method was successfully used to estimate the telmisartan in presence of related substances.

Keywords: Telmisartan, RP-HPLC, Impurities, linearity, validation, ICH Guidelines.

INTRODUCTION

Telmisartan,4′-[(1,4′-dimethyl-2′-propyl[2,6′-bi-1H-benzimidazol]-1′-yl)methyl][-1,1′-biphenyl]-2-carboxylic acid is an angiotensin II receptor antagonist used in the management of hypertension. Generally, angiotensin II receptor blockers such as Telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure[1]. Several analytical methods have been reported in the literature for the determination of Telmisartan and its impurities. Pharmaceutical impurities are the unwanted chemicals that co-exist with the active pharmaceutical ingredient (API) or they may develop during formulation, or upon aging of both API and formulated APIs to medicines. The presence of these impurities even in minor amounts can influence the efficacy and safety of drugs[2,3]. There are various types of sources of impurities that are affected by products. That is i) synthesis related impurity, ii) organic impurity and, iii) inorganic impurity[4]. There is an ever-increasing interest in impurities present in API[5]. The International Council for Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use ICH has also published guidelines for validation of methods for analyzing impurities in new drug substances, products, residual solvents, and microbiological impurities[6]. In the overwhelming majority of the pharmacopoeial monographs, impurities in the active pharmaceutical ingredient are determined by selective (usually high-performance liquid chromatography (HPLC)) or non-selective (usually titrimetric or ultraviolet (UV) spectrophotometry) methods[7]. HPLC is the most accurate method widely used for the qualitative and quantitative analysis of drug products[8]. Analytical method development and validation play important roles in drug discovery, drug development, and the manufacture of pharmaceuticals. It involves the detection of the

Title

Design of Experiment Approach in Development of Hydrophilic Matrix Tablet of Venlafaxine HCl: In vitro and In vivo studies.

Authors

SAIFEE, MARIA; RAO, V. U.; BARHATE, S. D.

Abstract

The objective of the study was to develop hydrophilic matrix drug delivery system of venlafaxine HCl (Ven HCl) for once a day administration. The formulation was optimized using Design of Experiment, 33 full factorial designs were used to optimize independent variables i.e. concentrations of hydroxypropyl methylcellulose (HPMC) K 4M, K15M, and K100M. Formulations were statistically analysed using design Expert software and design of space was determined using contour and surface response plot. The optimized formulation was prepared within the design space and evaluated for various in vitro and in vivo parameters. The in vivo studies of optimized formulation was done against the pure solution of Ven HCl in rabbits and parameters like Cmax, Tmax and AUC was compared. Optimized formulation showed lower Cmax (p<0.0001) and the time (Tmax 6 h) required to reach peak plasma concentration (Cmax) was also longer as compared to the immediate oral solution.

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Research Article

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Nano-embedded microparticles based dry powder inhaler for lung cancer treatment

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[2] Department of Pharmaceutics, Faculty of Y.B. Chavan College of Pharmacy, Aurangabad (MS) 431001, India.
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ABSTRACT: Lower efficacy of chemotherapeutic agents through the systemic route for treatment of lung cancer is attributed to its lower concentration in the lungs. Conversely, higher concentrations of drug in the lungs can be achieved by pulmonary administration *via* the inhalation route. For effective deposition of the formulation at the target region (small airways and alveoli) of the lung, the aerodynamic diameter has to be controlled (1-5 µm) and its retention is of key importance. The present study attempted to design a dry powder inhalation formulation with combined benefits of micron- and nano-sized particles [nano-embedded microparticles (NEMs)], which upon redispersion, results in nanoparticles (NPs) exhibiting good retention in the lungs. The present attempt is the foremost one to utilize NEMs administered by pulmonary route for the treatment of lung cancer. Docetaxel (DTX) NPs was formulated using sonication solvent evaporation technique and characterized. Thereafter, DTX-NPs were embedded into microparticles using the spray drying technique. The NEMs exhibited the desired flow properties with Carr's index 10.18±2.79 and Hausner ratio 1.11±0.034. The mass median aerodynamic diameter was 3.74±0.11 µm and the fine particle fraction 42.96±1.66%. Redispersed NP fraction was 47.78±4.65% with NPs retaining the desired properties. NPs demonstrated a sustained release of upto 144 h. The particle size and PDI of the redispersed NPs were unaffected. NEMs displayed stability upon charging under accelerated conditions for upto 3 months. Comparison of the cytotoxicity of DTX and DTX-NEMs revealed that the DTX-NEMs had more cytoxicity owing to the increased uptake of liberated NPs by cells. The prepared formulation could successfully entrap NPs (with mucus barrier-evading properties) in lactose microparticles, which can be deposited in the lungs and eventually, disintegrate to give back NPs under simulated lung conditions. The results suggest that the developed NEMs can be used in inhaled chemotherapy for the treatment of non-small cell lung cancer.

KEYWORDS: Nano-embedded microparticles; docetaxel; dry powder inhaler; lung cancer; aerodynamic properties.

1. INTRODUCTION

The pulmonary drug delivery route has proven to be a prospective route for the local and systemic therapies following inhalation [1-5]. The delivery of nanoparticles *via* the inhalation route for therapeutic benefits has gained much attention in the recent years, driven by the advantages such as enhanced bioavailability, reduced frequency of dosing, allayed side effects and the capability of effectively evading the phagocytic and mucociliary clearance mechanisms of the lung after deposition in the desired region [1,5,6,7–9]. Utilization of nanoparticles in chemotherapy has improved the therapeutic efficacy in lung cancer to a considerable extent [10–13]. Successful delivery of particles to the anticipated region in the lungs *via* pulmonary route demands control of the theoretical aerodynamic diameter (dAt) at 1-5 µm. Particles of dAt<1 µm were breathed out because of low inertia, while those >5 µm were mainly deposited in the mouth and throat regions because of the potential impact. Effective delivery of the nanoparticles to the desired pulmonary area while retaining the benefits of nanoparticles is the key for desired effectiveness; this is highly dependent on the particle size of the nanoparticles [14–16]. This could be realised either with the use of NP aqueous suspensions delivered by nebulizers, formulation of micron-sized dry powders composed of NP, or the Nano-embedded Microparticles (NEMs), also called as the Trojan particles, prepared by various techniques such as spray drying (SD), spray freeze drying (SFD) and electrostatic assembly [17].

The literature reports the use of sugars such as lactose, trehalose, or mannitol, as inert micron-sized carriers of NPs for use in the deposition of NPs in the lung (NEMs) [18,19–23]. The microparticles dissolve

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ORIGINAL ARTICLE

Mapping the Impact of a Polar Aprotic Solvent on the Microstructure and Dynamic Phase Transition in Glycerol Monooleate/Oleic Acid Systems

Gliserol Monooleat/Oleik Asit Sistemlerinde Polar Aprotik Çözücünün Mikroyapı ve Dinamik Faz Geçişine Etkisinin Haritalanması

Marzuka Shoeb KAZI*, Mohammed Hassan DEHGHAN

Y.B. Chavan College of Pharmacy, Department of Pharmaceutics, Dr. Rafiq Zakaria Campus, Aurangabad, India

ABSTRACT

Objectives: The impact of incorporating a polar aprotic solvent, dimethyl sulfoxide (DMSO), in glycerol monooleate/oleic acid systems was evaluated briefly to map its influence on the gel microstructure and dynamic phase transition in controlling the performance of a polyene antifungal drug delivery system.

Materials and Methods: An *in situ* gelling fluid precursor system (IGFPS) exhibiting inverse lyotropic liquid crystalline phases was developed by simple solution add-mixture method. Polarized light microscopy, small angle X-ray scattering (SAXS), differential scanning calorimetry (DSC), and oscillatory rheological assessments were performed to ascertain microstructural modulations. The developed system was examined for minimum gelling volume, gelling time, swelling behavior, mucoadhesion, *in vitro* antifungal activity, and *in vitro* drug release.

Results: The SAXS study identifies the coexistence of Im3m cubic phase with HCP P63/mmc hexagonal structures. The SAXS and DSC data highlight DMSO's unique ability to work both as a kosmotropic or chaotropic solvent and to be a function of its concentration. The *in vitro* antifungal test results indicate the concentration of DMSO to be a controlling factor in drug release and diffusion. The *in vitro* drug release kinetic studies reveal that most of the gel samples follow the matrix model and anomalous type release as implied by Peppas model.

Conclusion: Finally, the antifungal IGFPS formulated was found to have the required low viscosity, responsive sol-gel phase transition, appreciative mechanical properties, and desirable antifungal effect with sustained drug release performance.

Key words: Dimethyl sulfoxide, glycerol monooleate, microstructure, oleic acid, small angle X-ray scattering

ÖZ

Amaç: Bir polien antifungal ilaç taşıyıcı sistem performansını kontrol etmek için polar aprotik çözücü olan dimetil sülfoksit'in (DMSO), gliserol monooleat/oleik asit sistemlerine dahil edilmesinin, jel mikroyapısı ve dinamik faz geçişi üzerindeki etkisi araştırılmıştır.

Gereç ve Yöntemler: İnvers liyotropik sıvı kristalin (LLC) fazları sergileyen in situ jelleşen öncü sıvı sistemi (IGFPS), basit çözelti ilave etme yöntemi ile geliştirilmiştir. Polarize ışık mikroskopisi (PLM), küçük açılı X-ışını saçılması (SAXS), diferansiyel tarama kalorimetrisi (DSC) ve reolojik osilatör ölçümleri mikroyapısal modifikasyonları belirlemek için yapılmıştır. Geliştirilen sistem, minimum jelleşme hacmi, jelleşme süresi, şişme davranışı, mukoyapışkanlık, *in vitro* antifungal aktivite ve *in vitro* ilaç salımı açısından incelenmiştir.

Bulgular: SAXS çalışması, Im3m kübik fazın HCP P63/mmc altıgen yapılarla bir arada varlığını tanımlamıştır. SAXS ve DSC verileri, DMSO'nun hem bir kozmotropik hem de kaotropik çözücü olarak görev yaptığını ve işlevini konsantrasyon bağımlığı olarak gerçekleştirdiğini gösterdiğinden DMSO'nun eşsiz yeteneğini vurgulamıştır. *İn vitro* antifungal test sonuçları, DMSO konsantrasyonunun ilaç salımı ve difüzyonunda kontrol edici bir faktör olduğunu göstermiştir. *İn vitro* ilaç salım kinetik çalışmaları, jel örneklerinin çoğunun matris modeli ve Peppas modelinin belirttiği gibi anormal tip salım kinetiğini takip ettiğini ortaya koymuştur.

Sonuç: Sonuç olarak, formüle edilen antifungal IGFPS'nin, gerekli düşük viskoziteye, duyarlı sol-jel faz geçişine, istenen mekanik özelliklere ve sürekli ilaç salım performansı ile arzu edilen antifungal etkiye sahip olduğu bulunmuştur.

Anahtar kelimeler: Dimetil sülfoksit, gliserol monooleat, mikroyapı, oleik asit, küçük açılı X-ışını saçılması

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Journal of Research in Pharmacy

Research Article

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Ocular delivery of natamycin based on monoolein/span 80/poloxamer 407 nanocarriers for the effectual treatment of fungal keratitis

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ABSTRACT: A 3^2 factorial design was used to develop Natamycin cubosome nanoparticles with enhanced corneal permeation, so as to effectively treat ocular fungal keratitis. Probe sonication technique was deployed to disperse the dry lipidic film to obtain colloidal dispersion. The colloidal dispersion was characterized for critical quality attributes such as particle size, poly dispersibility index (PDI), zeta potential and entrapment efficiency. The optimized batch exhibited a particle size of 158.2 nm, zeta potential -40 mV, PDI 0.328 in addition, entrapment efficiency of 99.85%. The *in vitro* drug release of natamycin from optimized cubosome demonstrated a cumulative %drug release of 84.29% at the end of 8 hours. The optimized cubosomal dispersion exhibited enhanced *in vitro* antifungal activity against *Candida albicans* and *Aspergillus fumigatus* as compared to a pure drug suspension. The optimized formulation was further analyzed for polarized light microscopy (PLM), transmission electron microscopy (TEM) and small angle X-ray scattering (SAXS) to state the morphology of formed cubosome nanoparticles and was noted to be Im3m bicontinous cubic mesophasic structure. X-ray diffraction (XRD) studies affirmed the complete encapsulation of natamycin into cubosome vesicles. *Ex vivo* corneal permeation studies of optimized formulation revealed enhanced corneal permeation in comparison to a pure drug suspension. The ocular irritation studies performed on rabbits indicated the cubosome to be non-irritant. Finally, the developed natamycin cubosome nanoparticles demonstrated sustained drug release and increased corneal penetration. Thus, these cubosome nanocarriers present a propitious delivery system for effective management of ocular fungal keratitis.

KEYWORDS: Natamycin; cubosome; ocular fungal keratitis; nanoparticles; factorial design.

1. INTRODUCTION

Fungal keratitis is a severe ocular infection characterized by decreased vision, photophobia, feathery-edged infiltrates and satellite lesions across the cornea that leads to cataclysmic visual fallouts [1]. The causative agent is a species of fungi such as yeasts (*Candida*), filamentous with septae (*Aspergillus*, *Fusarium*, *Cladosporium*, *Curvularia*) and filamentous with non-septated (*Rhizopus*) [2]. Natamycin is BCS class II drug and due to its high molecular weight, corneal permeation is low. The conventional therapy for natamycin surfaces some notable drawbacks such as high dosing frequency, longer time period treatment cycles (4–6 weeks) and due to fast removal by nasopharyngeal drainage residence time at the ocular mucosa is short [3]. Extensive efforts have been directed towards the enhancement of ophthalmic drug bioavailability by exploring novel drug delivery strategies [3]. The delivery alternatives aim at improving both the precorneal residence time and in boosting the trans-corneal permeation of the drug [4, 5]. Thus, the challenge faced in designing a successful delivery can only be overcomed by circumventing the shielding barriers of the eye without enduring any tissue injury.

Nanocarriers or nanoparticulate systems proposed for controlled drug delivery demonstrate ability as a potential strategy to overcome these limitations [6]. Recently, cubosomes as a surrogate nanocarrier drug delivery system to liposome has been investigated [7]. These are binary systems, especially made up monoolein–water and are three-dimensional nanostructure with hydrophobic and hydrophilic domains that

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Original Article

Formulation and *in vitro / in vivo* Evaluation of Novel Biodegradable Microspheres for Treatment of Hormone Responsive Cancers

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ABSTRACT

Objectives: The present work relates with developing long acting controlled release poly(DL-lactide-co-glycolic acid) (PLGA) microspheres of Goserelin acetate for treatment of breast and prostate cancer. **Methods:** Microspheres were prepared by using biodegradable polymers PLGA 50:50 and PLGA 75:25 employing modified emulsification method by using static mixer. Evaluate the effect of process and formulation variables on the characteristics of microspheres were studied. Particle size distribution, surface morphology, encapsulation efficiency, *in vitro* drug release and *in vivo* drug release profile in Wistar rats were investigated. **Results:** Preparative variables such as concentrations of stabilizer, drug-polymer ratio, stirring rate and ratio of internal to external phases were found to be important factors for the preparation of Goserelin acetate loaded PLGA microspheres. These changes were also reflect *in vitro* and *in vivo* drug release profiles. The result indicated that the morphology of Goserelin acetate PLGA microspheres presented as spherical shape with smooth surface, homogenous drug distribution and the particle size distributed from 88.11 to 116.78 µm. *In vitro* and *in vivo* release profile showed controlled initial burst release followed by one month sustained release profile of the Goserelin acetate loaded PLGA microspheres. **Conclusion:** The process and formulation variables could be effectively modified to achieve the desired characteristics and one month sustained release of Goserelin acetate loaded biodegradable polymeric microspheres showed potential for treatment of hormone responsive cancers.

Key words: Breast cancer, Prostate cancer, Goserelin acetate, Microspheres, poly(D, L-lactide-*co*-glycolide).

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INTRODUCTION

The basic principle for controlled drug delivery system is to change the biopharmaceutical, pharmacokinetics and pharmacodynamics properties of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and physiological parameter inherent in preferred route of administration.[1] The primary goals of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patients compliance.[2] This is achieved by higher management of plasma drug levels and fewer frequent dosing. In general, the dosing interval is also magnified either by modifying the drug molecule to decrease the rate of elimination (K_{cl}) or by modifying the release rate of a dosage form to decrease the rate of absorption (K_a). Both the approaches look for decrease fluctuations in plasma level throughout multiple dosing, permitting the dosing interval to extend while not either over dosing or beneath dosing.[3]

The controlled drug delivery can be designed according to various routes of administration.[4] Although oral administration of drugs could be wide accepted route of drug delivery, bioavailability of drugs usually varies as a result of gastrointestinal absorption, degradation by first-pass effect and hostile surrounding of gastrointestinal tract. Transdermal administration for percutaneous absorption of drug is limited by the impermeable nature of the stratum corneum.[5] Therefore, in such situation, the parenteral route is the most viable approach, of the various ways in which biodegradable polymeric microspheres are one of the better means of controlled drug release over a longer period of time to achieve long-term parenteral drug delivery.[6]

Microspheres formulations are particularly well suited for parenteral route of administration and consist of polymeric materials in which active agents are encapsulated at high efficiency.[7] Biodegradable microspheres are made of biodegradable products, which can be injected with as syringe into the body and once injected, solidify to form a semi-solid deposit.[8] Drug is gradually release on erosion or by diffusion from the particles. These systems offer certain unique advantages, which has sparked people's interest. In addition to ease of use, these include targeted delivery for a site-specific action, longer delivery times, reduced medication dose with corresponding reduction in potential undesirable side effects common to most types of systemic delivery and enhanced patient compliance and comfort.[9] Poly (glycolic acid) (PGA), poly (lactic acid) (PLA) and its copolymers poly (DL-lactide-co-glycolic acid) (PLGA), have attracted attention due to their remarkable features such as biodegradability, biocompatibility andsafety.[10]

Biodegradable Microspheres are usually prepared by various methods such as Emulsification, Spray drying, Phase separation (Conservation), Solvent extraction, Evaporation base processes and Supercritical technology.[11] Emulsification extraction method is a common technique for preparation of controlled release biodegradable microparticles. Emulsification is critical step in microencapsulation process and has

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Original Article

Development of inhalable cubosome nanoparticles of Nystatin for effective management of Invasive Pulmonary Aspergillosis

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ABSTRACT

Background and Aims: Invasive pulmonary aspergillosis (IPA) is an imperative concern in the present era due to its high occurrence and mortality rate in severely immunocompromised patients. The present study was designed to develop, optimize and characterize encapsulated nystatin (NYS) cubosome nanoparticles as an inhalable system, a viable alternative for effective management of IPA.

Methods: A dry lipidic film comprising glycerol monooleate (GMO), Span 83, Poloxamer (P-407) and dispersed NYS was subjected to ultrasound sonication to produce colloidal dispersion of cubosomes. The process and formulation variables were screened using Plackett Burman design and further optimized by Box Behnken design by evaluating its effect on particle size, polydispersity index (PDI), zeta potential and entrapment efficiency.

Results: The optimized NYS cubosomes were nearly spherical with some irregular polyangular symmetry as visualized by transmission electron microscopy (TEM). Further, small angle X-ray scattering (SAXS) affirmed Pn3m cubic mesophasic structure. The optimized nanoparticles had particle size 263.5 nm, zeta potential -14.4 mV, PDI 0.283 and entrapment efficiency 82%. The *in-vitro* cytotoxicity assay indicated that NYS cubosomes reduced cell cytotoxicity in contrast to pure drug post 48h. *In-vitro* haemolytic assay denoted lower toxicity of formulation as compared to free drug. In-vitro drug release studies highlighted, slow but continuous release from NYS cubosomes until 48h and showcased Higuchi release kinetics. Likewise, NYS cubosome demonstrated higher antifungal activity compared to drug suspended in phosphate buffer.

Conclusion: Thus, non-invasive feature and contemplated target specificity of nystatin loaded cubosome nanoparticles pave a mode for its prospect as pulmonary delivery to combat IPA.

Keywords: Nystatin, cubosome nanoparticles, aspergillosis, drug design, pulmonary

INTRODUCTION

Lipidic, polymeric and polyelectrolyte complex based nanoparticulate drug delivery lately has been widely studied as potential carriers for delivery of numerous drug candidates such as anticancer (Chishti, Jagwani, Dhamecha, Jalalpure, & Dehghan, 2019), peptide (on Halling Laier et al., 2018; Poddar & Sawant, 2017), antifungals (Furedi et al., 2017), antivirals (Mandal, Prathipati, Belshan, & Destache, 2019) and antibacterials (Carneiro et al., 2019; Rani et al., 2018). The prevalence rate of invasive pulmonary aspergillosis (IPA) is high in severely immunocompromised patients suffering from HIV, cancer, critically ill patients, organ transplant patients and in individuals with known history of chronic obstructive pulmonary disease (Szalewski, Hinrichs, Zinniel, & Barletta, 2018). The management of IPA still remains a challenge as most of the antifungal used in its treatment present resistance or pose a high toxicity profiles (Kosmidis & Muldoon, 2017). Nystatin (NYS) a broad

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Title

ID 14. Microwave-assisted Grafting of Locust Bean Gum for Sustained Release Drug Delivery System: Process Optimization and Product Evaluation.

Authors

Lahoti, S. R; Kausar, Sana; Mokale, S. N; Chavan, Y. B

Abstract

Introduction: Modification of natural materials by graft copolymerization using various monomers offers the opportunities to tailor their physical as well as chemical properties yielding functional macromolecules that may find a wide range of applications. In the literature, many conventional and traditional methods of grafting are reported. However, these conventional methods are having many limitations like slow reaction, low yield, require high amounts of reactants and non-environmental friendly. In order to overcome these limitations, we used optimized microwave assisted technique with reaction time less than 5 minutes and more than 95% yield. Objectives: The first objective is to optimize the process of microwave-assisted grafting of locust bean gum using Design of Experiment, with respect to various critical process parameters whilst the second objective is to characterize/evaluate the effectiveness and safety of the product as sustained release matrix former. Materials and Methods: It involved microwave assisted synthesis of polyacrylamide-grafted-locust bean gum using ceric ammonium sulphate as an initiator and optimization of process using 23 factorial design. The grafted polymer was evaluated by FTIR, NMR, SEM, XRD, DSC, elemental analysis, acute toxicity studies followed by histopathological evaluation, biodegradability and hemolytic potential studies. Results: The grafted polymer was found to be non-toxic and biodegradable with sustained release potential over a period of 12hourswith matrix release model. The safety was confirmed by acute toxicity studies followed by histopathological evaluation. The grafted gum was found to be biodegradable and non-toxic. Conclusion: The resulted polymer was having tailor-made properties (depending upon degree of grafting), which is very useful in formulation and development of sustained release dosage form of many API molecules.

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ORIGINAL ARTICLE

Immunomodulatory dose of clindamycin in combination with ceftriaxone improves survival and prevents organ damage in murine polymicrobial sepsis

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Received: 4 January 2020 / Accepted: 17 April 2020

Abstract

Sepsis is a life-threatening organ dysfunction resulting from inflammatory responses instigated by toxins secreted by bacteria. Immunomodulatory effect of clindamycin is earlier reported in a murine lipopolysaccharide (LPS)-induced sepsis model. There are no studies demonstrating the immunomodulatory effect of clindamycin in combination with ceftriaxone in a clinically relevant murine polymicrobial sepsis model induced by cecal ligation and puncture (CLP). Ceftriaxone is combined to control the bacterial growth. Following 3 h of CLP challenge, Swiss albino mice were administered vehicle, ceftriaxone alone (100 mg/kg, subcutaneously), and in combination with clindamycin at immunomodulatory dose (200 mg/kg, intraperitoneally). Survival was assessed for 5 days, and bacterial count and biochemical and physiological parameters were measured after 18 h of CLP challenge. Ceftriaxone alone caused significant reduction in bacterial count in blood, peritoneal fluid, lung, liver, and kidney homogenate which was not further substantially reduced by ceftriaxone and clindamycin combination. Day 5 survival was greatly improved by combination compared with ceftriaxone alone which was also evident through marked drop in blood glucose, total white blood cell (WBC) count, and body temperature. The combination group significantly mitigated the cytokine (tumor necrosis factor (TNF)-α and interleukin (IL)-6) and myeloperoxidase (MPO) levels in plasma, lung, liver, and kidney of CLP-challenged mice, which further helped in significantly suppressing the elevated levels of liver and kidney function parameters. Clindamycin at immunomodulatory dose in combination with ceftriaxone attenuated organ damage and improved survival of septic mice by suppressing infection, inflammatory responses, and oxidative stress.

Keywords Sepsis · Survival · Organ damage · Cytokine · Myeloperoxidase · Bacterial count

Introduction

Sepsis is a life-threatening systemic inflammatory condition resulting from severe bacterial infection and poor immunity (Song et al. 2019). This condition is primarily triggered by bacterial cell wall components or endotoxins released during infections that are responsible for secreting proinflammatory cytokines and reactive oxygen species (ROS) implicated in organ dysfunction and associated mortality (Nau and Eiffert 2002; Wibke et al. 2013; Burkovskiy et al. 2013).

The murine CLP model of sepsis is mostly used to evaluate the immunomodulatory activity of drugs as this model closely resembles the human condition of sepsis (Dejager et al. 2011). Several publications report the use of ceftriaxone and clindamycin combination in the murine CLP sepsis model to improve survival and control bacterial growth (Hollenberg et al. 2001, 2000; Barichello et al. 2007; Ritter et al. 2004). Ceftriaxone, a broad-spectrum cephalosporin antibiotic, is used as it is active against Gram-negative bacteria, while clindamycin is combined due to activity against aerobic Gram-positive and anaerobic bacteria. Despite broad coverage offered by both ceftriaxone and clindamycin in combination, the survival benefit was not significant in these studies (Hollenberg et al. 2001, 2000; Barichello et al. 2007; Ritter et al. 2004). The probable reasons could be inadequate drug exposures due to lower doses of either drugs or inability to control the inflammatory responses. It should be noted that clindamycin besides having antibacterial activity is also

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ID 240. Development of Novel Anti-Cancer Agent Targeting Angiogenesis in Colorectal Cancer.

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- **Author(s):** Mokale, Santosh N.; Ingole, Kiran; More, Shweta; Sakle, Nikhil; Dhawale, Sachin

- **Abstract:** Introduction: Computer-aided drug design techniques were adopted to design a series of novel (E)-N-(N- (benzoyloxybenzilidine)-5-chloro pyrimidine-2- amine as VEGFR and c-MET kinase inhibitors. Objectives: To design new chemical entities for dual kinases inhibitors action (VEGFR and c-MET), to synthesis and perform spectral analysis (IR, 1H, 13C NMR, Mass spectra), and to screen the compounds for their proposed dual kinase inhibitor activity against COLO-205 and HT-29 cell lines. Materials and Methods: The designed compounds were synthesized to afford the desired series followed by evaluating their in vitro anti-cancer activities. The reaction was carried out by microwave assisted synthesis method. Synthesized compounds were characterized by standard methods of spectroscopy after purification. Results: Among the synthesized compounds, K-1, K-2, K-3, K-4, K-5, K-6, K-7 and K-8 were found to show potent cytotoxic against receptor on COLO-205 cellline, and K-3, K-4 and K-5 on HT-29 cell line. The in-vitro anti-cancer activity result showed that the compounds have protuberant affinity toward VEGFR and c-MET receptors as standard drug pazopanib. Conclusion: The above results revealed that (E)-N-(N-(benzoyloxybenzilidine)-5-chloro pyrimidine-2- amine hybridized with various heterocyclic scaffolds could be a potential anti-cancer agent.

Synthesis, Pharmacological Screening and Docking Analysis of Some Novel Pyrazole Chalchones as Anti-Cancer Agents

Proceedings of International Conference on Drug Discovery (ICDD) 2020

Posted: 4 Feb 2020

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Date Written: February 1, 2020

Abstract

Breast cancer still remains a leading killer among women worldwide. Estrogens are well known to play crucial role in breast cancer development. ER-α is well characterized as a mediator of cell proliferation in breast cancer cells. Due to the development of drug resistance, undesired side effects, relapses and recurrences of cancer, there is a need to develop safe, potent and tissue selective anti-breast cancer agents with novel mode of action. So we have decided to adopt combination chemotherapy to treat cancer. This strategy has resulted in a combination of pharmacophoric moieties of different bioactive substances such as pyrazole, chalcone and amine side chain led us to discover a novel class of substituted pyrazole-chalcone hybrids, which have been designed and docked with (PDB:1ERR) by using Maestro11.6, It shows efficient interaction with the given protein, which could be with an improved affinity, efficacy and modified selectivity profile with different mode of action and reduce undesirable side effects.

Keywords: Breast cancer, Estrogen Receptor-α, pyrazole, chalcone

JEL Classification: I:123

Design and Development of Hybrid Inhibitor to Synchronously Act on Four Biochemically Distinct Target for Suppression of Tumor Growth in Synergistic Manner.

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Date Written: February 6, 2020

Abstract

Abstract: Cancer is a generic term for a large group of disorder that can affect any part of the body. Conventionally, anticancer agents designed to hit single biological targets have been the main approach in therapeutics development, but these drugs often have limited clinical utility. To explore this, we have proposed a novel strategy with a single molecule designed to synchronously act on four biochemically distinct target such as HDAC, TACE, EGFR and HER2. The concurrent blockade of HDAC, TACE and RTK pathways represents a novel approach to cancer therapy and may provide high efficacy and overcome limitations in the treatment of certain cancers.

A series of novel-substituted hydroxamic acid analogs were synthesized and evaluated for anticancer activity against MCF-7, MDA-MB-231, IMR-32 and HT-29 cancer cell lines. The synthesized derivatives show good anticancer activity as compared to standard. Western blot analysis was performed on selected compound earn the desired results. The study also suggests that these analogs can serve as better therapeutic agents against cancer and can provide starting point for building more potent analogs in future.

Molecular modeling studies of synthesized series includes QSAR, Docking and ADME properties of target compounds were analysed using Schrodinger software v11.6. The synthesized derivatives shows good binding interaction with the respective receptor.

Keywords: HDAC, EGFR, TACE, HER2, Molecular Modeling

JEL Classification: I23

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WILEY

ARTICLE

Novel approach in the synthesis of imidazo [1, 2-*a*] pyridine from phenyl acrylic acids

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Abstract

This paper describes highly efficient concise method for the synthesis of imidazo[1,2-*a*] pyridine. It is a first report employing, amino pyridines, copper nitrate, and phenyl acrylic acids in the synthesis of imidazo[1,2-*a*] pyridine. The silent features of the devised protocol include the high yield, milder reaction conditions, and shorter reaction time.

1 | INTRODUCTION

The nitrogen-containing imidazo [1,2-*a*] pyridine compounds have great synthetic applications owing to its varied biological activities viz. anti-inflammatory,[1–4] anticancer,[5–7] antiulcer,[8] anti-viral,[9–13] anti-bacterial,[14–17] and antituberculosis.[18–20] These derivatives act as cardiotonic agents,[21] GABA and benzodiazepine receptor agonists,[22,23] and β-amyloid formation inhibitors.[24] A variety of synthetic strategies have been developed for the construction of imidazo [1,2-*a*]pyridine scaffolds.[25–34] The most explored approaches embrace: (a) condensation of 2-amino pyridine with α-haloketone compounds,[25,33] α-diazoketone compounds,[26] α-tosyloxyketone compounds,[27,34] (b) coupling of 2-amino pyridine with nitroolefins,[28,35] (c) three component coupling of 2-amino pyridine, aldehyde with nitroalkane,[29,36] isonitrile,[30,37,38] alkynes,[31,39] and alkynecarboxylic acid.[32] However, there is scarcity of general methods to synthesize imidazo [1,2-*a*] pyridine derivatives from commercially available or readily accessible materials. The interesting advantage of our protocol compared with the above-mentioned established protocol lies in our starting material cinnamic acid. The established protocol[25] employs 2-bromoacetophenone, which has environmental hazard issues as it is a lachrymatic compound making it difficult to handle, it is toxic upon inhalation, ingestion, and skin absorption and costly when compared with phenyl acrylic acid/cinnamic acid hence we employed cinnamic acid in our protocol. Our protocol is a first report, which provides an alternative synthetic starting material—cinnamic acid for synthesis of such molecules. The fascinating feature of these scaffolds led us[40] toward the development of new methods for their synthesis. The nitroolefins are usually synthesized by using viz. silver nitrate,[41] tert-butyl nitrate,[42] and copper nitrate[43] but its further designing into bioactive molecule was not yet explored. Herein, it prompted us to synthesize nitroimidazopyridines, wherein in situ conversion of nitroolefins to the imidazo[1,2-*a*] pyridine was achieved in ease. In addition, it would open plethora of such

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Article

Article

A Validated Stability-Indicating Liquid Chromatographic Method for the Determination of Lorcaserin and Related Impurities in DRUG Substance Supported by Quality by Design

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Abstract

Lorcaserin (LOR) is selective and potent antiobesity drug that targets the activation of the serotonin $5HT_{2C}$ receptor. Here a novel, specific, sensitive stability indicating method was developed and validated for the quantitative determination of LOR and its process-related impurities using quality by design principles. By applying experimental design, the authors examine the multifactorial effect of parameters on the critical resolution pair and generated design space representing the robust design. LOR was subjected to stress condition and found stable at all condition, only found significant degradation at oxidative stress condition. The chromatographic separation of degradation product and its process-related impurities were achieved on a Phenomenox Luna phenyl-hexyl column (150 × 4.6 mm × 5 µm), with mobile phase consisting of 10 mM ammonium formate containing 0.1% ammonia solution; pH adjusted to 2.8 with trifluoroacetic acid as solvent A and methanol/acetonitrile (5/95) as solvent B delivered with gradient program at a flow rate of 1.0 mL/min, column temperature was maintained at 25°C and analytes were monitored at 220 nm. The injection volume was 5 µL. The developed RP-LC method was validated and found linear, accurate, specific, selective, precise and robust. The structure of impurities was confirmed by direct mass analysis.

Introduction

Lorcaserin (LOR) is chemically (R) 8- chloro-1- methyl 2,3,4,5-tetrahydro-1H-3-benzazepine, which is a novel, selective and potent antiobesity drug that targets the activation of the serotonin $5HT_{2C}$ receptor and is intended to promote weight loss in obese population by acting as agonist at the intended target (1, 2). LOR is marketed as a salt form called Belviq. Obesity is a life threatening disorder in which there is an increased risk of morbidity and mortality arising from concomitant diseases such as type II diabetes, hypertension, stroke and cancer. $5HT_{2C}$ has been reasonably demonstrated to underlie the anorexigenic effect of LOR (3, 4). It also has some abuse potential and is listed as a Schedule IV drug in the Controlled Substances Act (5).

The recommended dosage for initial monotherapy is 10 mg/day, administered orally in the form of tablet; LOR is not official in IP, BP and USP, it is enantiomerically active R-enantiomer shows higher affinity than S-enantiomer (6, 7). It is available as hydrochloride salt form having pKa of 9.53 with the partition coefficient (log P) of 2.56, freely soluble in water, methanol, acetonitrile and dimethyl sulphoxide. The structures and chemical names of LOR hydrochloride and its related impurities are presented in Figure 1. Lorcaserin

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A network pharmacology-based approach to explore potential targets of *Caesalpinia pulcherima*: an updated prototype in drug discovery

Nikhil S. Sakle, Shweta A. More & Santosh N. Mokale✉

Caesalpinia pulcherima **(CP) is a traditional herb used for the treatment of asthma, bronchitis, cancer, anti-bacterial, anti-fungal and as abortifacient. In the present study, bioactive components and potential targets in the treatment of breast cancer validated through in silico, in vitro and in vivo approach. The results for the analysis were as among 29 components, only four components were found active for further study which proved the use of CP as a multi-target herb for betterment of clinical uses. The results found by PPI states that our network has significant interactions which include the ESR-1, ESR-2, ESRRA, MET, VEGF, FGF, PI3K, PDK-1, MAPK, PLK-1, NEK-2, and GRK. Compound-target network involves 4 active compound and 150 target genes which elucidate the mechanisms of drug action in breast cancer treatment. Furthermore, on the basis of the above results the important proteins were fetched for the docking study which helps in predicting the possible interaction between components and targets. The results of the western blotting showed that CP regulates ER and EGFR expression in MCF-7 cell. In addition to this animal experimentation showed that CP significantly improved immunohistological status in MNU induced carcinoma rats. Network pharmacology approach not only helps us to confirm the study of the chosen target but also gave an idea of compound-target network as well as pathways associated to the CP for treating the complex metabolic condition as breast cancer and they importance for experimental verification.**

Breast cancer (BC) is the malignant growth that begins in the breast cells. BC is the widespread cancer in India (in women) which accounts for 14% of all the cancers in women[1,2]. In general, 1 in 28 women are prone to have BC during her life span. The frequency rates in India begin to rise in the early thirties and peak at the age of 50–64 years[3]. In urban areas, 1 in 22 women are likely to have BC during her life span as compared to rural areas where 1 in 60 women develop BC in her life span[4]. Duration of survival of cancer patients is an important sign for knowing the result of treatment in any study. Since the 1990s, due to regular efforts in the diagnosis and treatment, the overall survival time of patients has been enhanced[5]. In cancer multiple genes participate which gradually alters the normal healthy cells into cancerous cells. Cancers have the capacity to develop resistance to conventional chemotherapy[6]. Thus, it is essential to recognize new therapeutic agents or promising targets. In current cancer therapy, new generations of drugs have targeted cancer specific proteins that are expressed in different cancers. Target specific cancer therapy minimizes the side effect profiles of conventional cytotoxic drugs[7]. In targeted therapy attempts are being made to design ligands with maximum selectivity to act on specific drug targets. Network pharmacology (NP) is an emerging discipline useful in drug discovery, which combines genomic technologies and system biology through computational biological tool. Network pharmacology, is an approach capable of describing complex relationships among biological systems, drugs and diseases[8]. It also clarifies the possible mechanisms of complex bio-actives through large data set analysis and determines the synergistic effects in cancer treatment[9]. Traditional Chinese medicine (TCM) is combination of complex herbal formulation and has been used for more than thousands of years in the treatment of different diseases and disorders for the prolongation of life expectancy in different parts of the world[10]. The network-target-based network pharmacology is a promising approach for the next-generation mode of drug

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Review article

Cardiovascular drug delivery: A review on the recent advancements in nanocarrier based drug delivery with a brief emphasis on the novel use of magnetoliposomes and extracellular vesicles and ongoing clinical trial research

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ABSTRACT

Cardiovascular diseases have become an ever-increasing threat to human life in today's world due to many different factors. Although many drugs with different mechanisms are available, they still have many drawbacks like poor water solubility, unwanted side effects, high metabolism and repeated dosing, to name a few. Liposomal systems being one of the most widely studied drug delivery carriers have seen some up-and-coming developments as of today and possess the ability to counter the above issues. With advancing technology in these modern times, the use of liposomes derived from cellular origins or modifying their structure has demonstrated some newer applications which could act as potential treatment options for cardiovascular diseases in the future. This review discusses the recent developments and advancements in the liposomes and other nanocarrier drug delivery to heart diseases with a special emphasis on the use of magnetoliposomes and extracellular vesicles. Their limitations, along with future prospects, have also been detailed. Moreover, latest updates on the clinical development of nano drug delivery for cardiac diseases is also provided.

1. Introduction

Cardiovascular diseases (CVDs) are the type of diseases which involves heart or blood vessels. Some examples include angina pectoris, myocardial infarction (MI), atherosclerosis and stroke. Angina pectoris is a type of heart condition characterized by chest pain resulting from a reduced oxygen supply to the heart muscles [1,2]. Although there are many causes for cardiovascular diseases, atherosclerosis and hypertension are most common. Also, as the age increases, the cardiovascular function alters due to changes in the physiology and morphology of the body leading to an increased risk of causing diseases at older age even in symptomless healthy persons [3].

Since 1970, CVDs have been a leading cause of deaths worldwide at a large scale. The mortality rates have been declined in many developed countries; however, in developing countries, the mortality rates have been increasing at an alarming rate [1,2,4]. It is generally recommended to adopt precautionary measures at an early age in life as the precursors of cardiovascular disease like atherosclerosis also start developing very early in life [5]. Hence an increased emphasis on developing healthy habits like exercise, balanced diet and eliminating smoking habits etc. is necessary.

Research in novel drug delivery has garnered much attention in the past few decades for fabrication and development of drug-loaded nanocarriers for applications in different diseases.

Ideal prerequisites of a drug delivery system are to deliver the drugs at a rate supporting the body needs and their transport directly to the target organ where it could achieve an efficient to exert its effects. As conventional drug delivery systems don't meet these demands, the need for novel drug delivery systems arises as they can achieve a sustained or controlled release profiles. This decreases the concentration of the active dose ultimately reducing the side-effects of the drugs [6,7]. Specific targeting can also be achieved by employing carrier attached with

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Int. J. Pharm. Investigation, 2020;10(2):167-172 Original Article

Development and Characterization of Tacrolimus Liposomal Gel for Industrial Application

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ABSTRACT

Objective: The objective of the present study was to prepare tacrolimus liposomal gel formulations using ethanolic injection technique for efficacious and cost-effective treatment of atopic dermatitis. **Methods:** The liposomes were prepared using ethanolic injection technique at the drug concentration of 0.1% w/v and optimized by varying the lipid component/ cholesterol ratio and by monitoring particle size, polydispersity and entrapment efficiency. The optimized composition was incorporated into 0.5% Carbopol Ultrez 10 gel for topical application. The developed liposomal gel was evaluated with respect to physicochemical parameters such as pH, viscosity, rheometery and spreadability. Stability study was performed at different temperatures (4°C, 25°C and 40°C) to evaluate the long-term stability. *In vitro* permeation of tacrolimus gel was studied using freshly excised rat skin on Franz diffusion cell. The therapeutic efficacy study was performed on allergic contact dermatitis model in rats. **Results:** Stable tacrolimus liposomal gel was successfully formulated using ethanolic injection technique. *In-vitro* permeation study indicated higher release of the drug (69.7%) as compared to free drug in hydroalcoholic solution (32.8%) and marketed ointment (63.7%). The formulation also showed shear thinning performance, which is a required property of topical formulation. The therapeutic efficacy study in rats indicated that liposomal gel containing 0.1% tacrolimus exhibited better activity as compared to 0.1% marketed tacrolimus ointment. **Conclusion:** The study indicated that tacrolimus can be effectively incorporated in liposomes by commercially viable rapid ethanolic injection method and can be more efficient for the treatment of atopic dermatitis.

Key words: Cost-effective, Ethanol injection, Industrially relevant, Phospholipids, Topical delivery.

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INTRODUCTION

The phospholipids used in topical liposomal compositions exhibit similarity with membranes in the epidermis. This enables higher extent of penetration into the epidermal barrier in comparison to other topical dosage forms like creams and ointments. The liposomal encapsulation may also result in sustained drug release of drug due to a slow clearance of drug from the epidermal layer. The sustained release of drug in turn may also minimize systemic absorption of the drug into blood which is not a desirable attribute as far as topical mode of action is concerned.[1,2] The liposomal drug delivery by topical route has resulted in reduction in side-effects, increased effectiveness and a higher patient compliance.[3,4]

Literature suggest that liposomal encapsulation of tacrolimus in topical formulation enhances drug penetration of skin.[5,6] It is also more user friendly to patients in the gel form than the conventional ointment as itis non greasy and sticky when applied on skin.[7,8] Because of these characteristics need of occlusive dressings may be avoided for tacrolimus to be more effective. The reported studies suggest that liposomal encapsulation will be less toxic than free tacrolimus. Tacrolimus is commercially available as a topical ointment, but the ointment has been reported with low and highly variable absorption and doesn't ensure adequate topical delivery of the drug into deeper skin layers.[9,10] It is interesting to note that despite reported positive studies no liposomal product of tacrolimus emerged in the market for topical application so far. The high manufacturing cost associated with liposomal technology is a significant deterrent. There is an evident need of providing of cost effective and industrially relevant solutions.

Ethanol injection is one of the methods for production of liposomes. This technique offers several advantages, e.g., its reproducibility, fast implementation and simplicity. Another advantage of the technique is that it does not cause oxidative alterations or lipid degradation.[11-13] The present study was aimed at developing tacrolimus liposomal formulation using ethanol injection technique which would ultimately lead to affordable and better treatment to vast majority of patient population.

MATERIALS AND METHODS

Materials

Tacrolimus was a gift sample from Concord Biotech (Ahmedabad, India). Lipoid S-75 and Lipoid S PC-3 were gifted by Lipoid, Germany. Absolute Ethanol USP and Cholesterol of purity (≥99%) were procured from Sigma-Aldrich (India). Carbopol® Ultrez 10 NF Polymers was kindly gifted by Lubrizol, USA. 2,4-Dinitrofluorobenzene (DNFB) was purchased from Sisco Research Laboratories, India. The marketed ointment Topgraf, Tacrolimus ointment (0.1%w/w) was from GlaxoSmithKline, India. Acetonitrile and Methanol were purchased from Merck Specialties Pvt. Ltd. (India). All the other reagents and ingredients were of analytical grade.

Preparation and optimization of tacrolimus loaded liposomes

Liposomes were prepared by rapid ethanol injection method.[13] Various product-influencing variables viz. saturated vs unsaturated lipid, Drug

Title

ID 14. Microwave-assisted Grafting of Locust Bean Gum for Sustained Release Drug Delivery System: Process Optimization and Product Evaluation.

Authors

Lahoti, S. R; Kausar, Sana; Mokale, S. N; Chavan, Y. B

Abstract

Introduction: Modification of natural materials by graft copolymerization using various monomers offers the opportunities to tailor their physical as well as chemical properties yielding functional macromolecules that may find a wide range of applications. In the literature, many conventional and traditional methods of grafting are reported. However, these conventional methods are having many limitations like slow reaction, low yield, require high amounts of reactants and non-environmental friendly. In order to overcome these limitations, we used optimized microwave assisted technique with reaction time less than 5 minutes and more than 95% yield. Objectives: The first objective is to optimize the process of microwave-assisted grafting of locust bean gum using Design of Experiment, with respect to various critical process parameters whilst the second objective is to characterize/evaluate the effectiveness and safety of the product as sustained release matrix former. Materials and Methods: It involved microwave assisted synthesis of polyacrylamide-grafted-locust bean gum using ceric ammonium sulphate as an initiator and optimization of process using 23 factorial design. The grafted polymer was evaluated by FTIR, NMR, SEM, XRD, DSC, elemental analysis, acute toxicity studies followed by histopathological evaluation, biodegradability and hemolytic potential studies. Results: The grafted polymer was found to be non-toxic and biodegradable with sustained release potential over a period of 12hourswith matrix release model. The safety was confirmed by acute toxicity studies followed by histopathological evaluation. The grafted gum was found to be biodegradable and non-toxic. Conclusion: The resulted polymer was having tailor-made properties (depending upon degree of grafting), which is very useful in formulation and development of sustained release dosage form of many API molecules.

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Thin layer chromatography as a simple and quick in-process tool for qualitative and semi-quantitative determination of unentrapped drugs in liposomal formulations

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ABSTRACT: Control of free or unentrapped drug is one of the key quality attributes for liposomal drug delivery systems. Conventional methodologies for estimating unentrapped drug in liposomal formulations require prior separation, which are time-consuming and complex. There is a need for a quick in-process analytical technique, which can enable monitoring of drug loading during various stages of product development and manufacturing. A novel simple and rapid TLC procedure was developed for evaluating entrapment efficiency in liposomal formulations. The method is based on differential radial migration of free and entrapped drug on silica gel TLC plates. The method can be employed either as a simple visual qualitative tool in the early screening studies or in a semi-quantitative mode for detection of free and unentrapped drugs. In case of doxorubicin hydrochloride, a deep-red coloured molecule, the method enabled free drug detection up to the levels as low as 2.5%. This method precluded the need of developing the plate further with the mobile phase. The method was used successfully in product development or as an in-process monitoring tool. The method's potential for characterizing entrapment efficiency was evaluated for less intensely coloured or UV absorbing drug candidates such as amphotericin B liposome and curcumin liposome. The preliminary results post derivatization with ninhydrin reagent or visualization under UV light indicated applicability of technique in general for liposomal delivery systems of various other drugs. According to the best of the author's knowledge, there has been no reports on the evaluation of drug entrapment using such TLC based technique so far.

KEYWORDS: Liposomal formulation; Unentrapped or free drug; Thin layer chromatography; Supramolecular characterization.

1. INTRODUCTION

The concept of using liposomal formulations as site-specific advanced drug carriers have brought drastic improvements in the field of nanomedicines since the first description of liposomes in 1961 [1]. Amongst the various carrier systems, liposomes have generated great interest because of their versatility in terms of size, charge, surface modifications, etc. [2, 3]. Liposomes, as the name suggests, are closed vesicles made up of central aqueous core surrounded by spherical phospholipid-based bilayers [4, 5]. The liposomal mode of drug delivery has been successful in the encapsulation of a vast range of drug [1, 5]. This entrapment can be advantageous as the liposomal carriers protect us from the local effects and site-specific drug toxicity while also protecting normal tissue from damage. Moreover, a more targeted therapy can be exercised in this field. Drugs like doxorubicin hydrochloride, Amphotericin B and many others that otherwise cause toxicity to the host in their free and unentrapped forms are the suitable candidates for liposomal drug delivery [6, 7, 8].

In view of growing significance of liposomal delivery systems, the drug regulatory agencies across the world are encouraging cost effective generic vessions of blockbuster liposomal formulation like AmbisomeTM (Astellas pharma us inc) and DoxilTM (Baxter healthcare corp. US). However, the commercial liposome technology is quite complex involving multistep processes like high pressure homogenisation, drug loading/ size optimization, lyophilization etc. Obtaining pharmaceutical and therapeutic equivalence forms the biggest challenge as even ostensibly alike generic compositions with slight differences in the manufacturing

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ORIGINAL RESEARCH

De-novo design and synthesis of conformationally restricted thiazolidine-2,4-dione analogues: highly selective PPAR-γ agonist in search of anti-diabetic agent

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Abstract

In the present investigation, design, molecular docking simulations, and synthesis of few 2,4-thiazolidinedione for selective modulation of PPAR-gamma are reported. Further evaluation of anti-diabetic activity of few thiazolidine-2,4-diones is assessed using cell line analysis. The structures of the synthesized compounds were confirmed on the basis of FT-IR, ^{1}H-NMR, and mass analyses. Acute toxicity study was done to by using Trypan blue assay and MTT assay of the synthesized compounds. Synthesized compounds were evaluated for their antihyperglycemic effect by glucose absorption assay. The compound code TZD4 showed highest percentage of glucose absorption by 3T3-L1 cells compared with control.

Keywords Type 2 diabetes · Molecular docking · Conformationally restricted TZD · Cell line analysis

Introduction

Diabetes is a global burden and it is increasing across the world because of various reasons [1]. Thiazolidinediones, act via insulin resistance, are one of the novel approach for the management of type 2 diabetes as "insulin sensitizers" [2]. Pioglitazone and rosiglitazone, two new thiazolidinedione, were approved in the year 1999 by US FDA for the management of type 2 diabetes. But use of these drugs is limited because of reasons like congestive heart failure and weight gain. These laments need for discovery of new and safe agents from the thiazolidinedione class anti-diabetic. Further, current available drugs in the market not effectively useful in upholding long-term glycemic control in most of the patients, even when used alone or in combination. This leads to development of fatal complications. Even large number of drugs available, about 63% of diabetic patients, does not succeed to achieve HbA1c levels of < 7% as advised by the ADA, and hence at high risk of developing abovementioned complications. Ongoing oral hypoglycemic agents are associated with potential adverse effects described earlier. Consequently, there is need of novel anti-diabetic agents that should have similar degree of efficacy with a potential to reduce long-term complications of type 2 diabetes and without troublesome side effects [3].

Thiazolidinediones are modulators of protein PPARγ, which are known for the regulation of transcription of insulin-responsive gene which is involved in the control of glucose synthesis, its transport, and thereby utilization. Several new insulin sensitizers are currently under investigation [4]. The thiazolidinediones (TZD) alternatively known as "glitazones" that improve metabolic control among the patients with type 2 diabetes. Their glucose-lowering effect is mediated via improvement of sensitivity of insulin. For this reason, they are also referred to as "insulin sensitizers." These agents are known for their ability for reduction of resistance of insulin in the adipose tissue: muscle and liver. TZDs act as anti-diabetic agent by activating PPARγ, a nuclear receptor. TZD-induced activation of PPARγ alters the transcription of numerous genes which are in engaged

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Original Article

Solvent Drop Grinding Approach Assisted Development of Glimepiride Co-crystals: Solubility Enhancement Journey of BCS Class-II Product

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ABSTRACT

Background: Glimepiride has limited aqueous solubility and majorly suffers from bioavailability issues that eventually reduce the pharmacotherapeutic potentials of the moiety. **Materials and Methods:** For the possible augmentation of all the crucial factors, co-crystals were developed using a Generally Recognized As Safe (GRAS) co-former (caffeine) in the presence of few drops of solvent (acetone) by employing a very simple green approach (solvent drop grinding method). The pharmacokinetic study of the co-crystals was performed in Wistar albino rats, the data was compared with free drug form and pharmacokinetic parameters were determined. The fabricated co-crystal product was comprehensively characterized through sophisticated analytical techniques that ascertained the complete product formation. **Results:** The formation of the glimepiride crystal with the co-former was confirmed through FTIR, DSC, XRD and SEM. From the pharmacokinetic study in rats, the procured data expressed several-folds higher plasma drug concentration which can be correlated with increased bioavailability of glimepiride. **Conclusion:** This study will positively inspire researchers working in the field of solubility/bioavailability enhancement due to the simplicity of the method, green approach and positive results which will open several future avenues of drug applications.

Key words: Glimepiride, Caffeine, Co-crystal, Bioavailability, Solubility, Green technique.

INTRODUCTION

The concept of solubility enhancement of a therapeutically active moiety is essentially required in the modern days as it directly influences the drug bioavailability profile.[1] In general, the United States Food and Drug Administration (USFDA) approved drug molecules belonging to the Class-II (low solubility, high permeability) and Class-IV (low solubility, low permeability) of Biopharmaceutics Classification System (BCS) exclusively suffers from this phenomenon.[2] At present, several methods and techniques are available for the solubility enhancement of which solid dispersion, inclusion particle size reduction,[3-6] complex formation, micellar solubilization, hydrotrophy, cryogenic techniques, crystal engineering, supercritical fluid process, nanosuspensions, etc. are the most prominent one.[7]

Glimepiride (Figure 1A) is a second-generation, BCS Class-II, once-daily orally administered sulfonylurea class of drug that is recommended primarily for treating Type-2 diabetes mellitus (T2DM).[8] This insulin secretagogue directly stimulates the release of insulin (by depolarization of ATP-sensitive potassium channels) from

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CHEMISTRY & BIOLOGY INTERFACE

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Synthesis, evaluation and molecular docking of 1,2,3-triazolyl chalcones as potential antifungal and antioxidant agents

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Abstract: A series of new 1,2,3-triazolyl chalcones were efficiently synthesized and screened for in *vitro* antifungal activity against five different fungal strains such as *Candida albicans*, *Fusarium oxysporum, Aspergillus flavus*, *Aspergillus niger* and *Cryptococcus neoformans*. All the synthesized chalcones displayed potential antifungal activity against most of the tested fungal strains. Especially, compounds **9b, 9c, 9d** and **9g** are the most active chalcones and displayed excellent MIC values as compared to standard antifungal drug Miconazole. Based on the structural similarity to known triazole inhibitors of sterol 14α-demethylase (CYP51), molecular docking study was performed to gauze the binding affinity of these chalcones and gains an insight into the plausible mechanism of antifungal action. The synthesized chalcones were also evaluated for in *vitro* antioxidant activity. All compounds exhibited moderate to excellent antioxidant activity, particularly compounds **9e, 9f, 9g** and **9h** exhibited excellent antioxidant activity in comparison with standard butylated hydroxytoluene (BHT). Furthermore, the synthesized chalcones were analyzed for ADME properties and showed the potential to build up as good oral drug candidates.

Keywords: 1,2,3-triazole, Chalcone, Antifungal activity, Antioxidant activity, Molecular docking study, ADME prediction.

1. Introduction

The incidences of multidrug-resistant fungal infections in recent years have increased dramatically and commonly seen in patients with weak immune systems [1]. An increasing number

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FORMULATION AND EVALUTION OF HERBAL TABLET FOR LIVER ALIMENTS

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ABSTRACT

Nature is gift of god and it provide human not only food, water and shelter but also it provide the medicine which help to cure the diseases and disorder. Liver one of the important organ of human body which helps in various metabolism of body. Any disease or disorders of liver affect the human body. Nature provides plenty of solution to problem related to liver. The article content information regarding formulation contain combination of three plants (T.cordifolia, T.perphura, B.diffusia).They are extracted using various solvents (95% ethanol, 50% Hydro-alcoholic).The phytochemical characterization and T.L.C of extracts is done using rutin as a standard. The tablets are formulated using design expert software. The extract and tablet are evaluated for various parameters

Keywords: T. cordifolia, T. perphura, B. diffusia, 95% ethanol, 50% Hydro- Alcoholic solvent

I. INTRODUTION

Natures is the gift's of God's. It not only provide us food , shelter, but also provide us medicines which are effective as well as less harmful to the human body . Nature provides plenty of solution to problem related to liver. Liver act as a factory of human body where metabolism of various material from gastro intestinal tract take place . The zenobiotics compounds from the gastro intestinal tract is transported to the liver and due to the metabolism of xenobiotics compounds causes hepatotoxicity (LIVER DISEASES).Hepatotoxicity are classified as 1) Hepatocellular injury 2) Cholestatic injury 3) Mixed injury.

1) Tinosproa Cordifolia: It belong to the **Family:** Menispernaceae **Synonym:** Gilo, Gurcha. **Description:** Leave a simple alternative exstipulate, heart shape. Stem are rather succulent with long filiform fleshy aerial root arisng from the branch. Bark are creamy white to grey brown .**Chemical Composition:** It contain alkaloids, gylcosides, steroids, sesquiterpenoids, aliphatic compounds, essential oils, mixture of fatty acids and polysaccharides.

2) Tephrosia purpurea: It belongs to **Family**: Fabiciae **Synonym**: Sarpunkha, Untoali. **Description:** Tephrosia purpurea is a small shrub that grows up to 1.5 meters tall. It has bi-pinnate leaf with 7-15 leaflets. The peas like flower are white to purple and arranged in inflorescences that are upto 25cm long.The pods are straight and somewhat up curved at the terminal end and may ranged from 20-45 mm in length and 3-5 mm breath. **Chemical constituents**: The plant contain flavonoids such as rutin, purpurin etc.

3) Boerhavia diffusa: It belongs to **Family**: Nyctaginaceae **Synonym:** Punarnava, Lal punarnava. **Description**: **Stem:** Greenish purple, stuff, slender, cylindrical, swollen at the node branches from common stalk, often more than a meter long. **Root:** Well developed , fairly long, cylindrical, 0.2-1.5 cm in diameter, yellowish brown to brown colour , surface soft to tough but rough due to minute longitudinal striation. **Flowers:** Very small, pink color, shortly stalked. Fruit: One seeded nut, 6mm long Clavate, rounded, broadly and bluntly 5 ribbed, viscidly glandular. **Chemical composition:** B. DUFFSIAE contains a large number of compounds such as flavonoids, alkaloids, steroids, triterpenoids, lipids, carbohydrate, protein, glycoprotein, fixed oils and inorganic salts.

II. MATERIAL AND METHOD

The tinoospora cordifolia (stem) was purchased from the local market shop of jawahar chowk najagarph, New Delhi. The tephrosia purpurea was collected from the area of 'Dr BABASAHEB AMBEDKAR MARATHWADA UNIVERSITY AURANGABAD'. The B.diffusa was collected from the Botanical garden Rauza bagh Aurangabad.

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Punica granatum Peel Extract Ameliorates Doxorubicin Induced Cardiotoxicity

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Punica granatum Peel Extract Ameliorates Doxorubicin Induced Cardiotoxicity

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Abstract: Doxorubicin (DOX) usefulness is limited due to its cardiotoxic effects. In the present study the protective effects of ethanolic peel extract of *Punica granatum* (EPEPG) against DOX-induced cardiotoxicity in rats was investigated. We studied the effect of ethanolic peel extract of *Punica granatum* (100 mg/kg body weight, p.o.) and vitamin E as reference standard drug on doxorubicin induced cardiotoxicity by testing the heart weight/body weight ratio, biochemical parameters and histopathological changes. The biochemical parameters, which were measured in the blood were blood glutathione, creatine kinase (CK-MB) and lactate dehydrogenase (LDH) and in heart were, tissue glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA) in all the animals. Before and after treatment with (EPEPG, 100 mg/kg) reduced the activity of both creatine kinase (CK-MB) and lactate dehydrogenase (LDH) enzymes, and significantly decreased the levels of malondialdehyde (MDA). It also increased the levels of reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) in tissue and blood glutathione. Histopathological examination of heart tissue showed that treatment (before and after) with (EPEPG) ameliorated the effect of DOX administration on cardiac tissue; cardiac myocytes looked more or less similar to those of control. The above observations suggest that DOX induced cardiotoxicity occurs due to oxidative stress and ethanolic peel extract of *Punica granatum* has produced cardio protective activity.

Key words: Ethanolic peels extract *P. granatum,* doxorubicin, cardiotoxicity, antioxidant.

Introduction

Doxorubicin appears to be especially effective in the therapy of solid tumors and is considered one of the most important drugs currently used in cancer chemotherapy [1]. Several hypotheses have been proposed to explain the cardiotoxic effect of anthracyclines. Doxorubicin induced myocardial dysfunction has been suggested to involve free radical formation [2] and lipid peroxidation [3]. The involvement of free radical formation has been suggested for the mechanism of doxorubicin induced cardiotoxicity, where doxorubicin produces reactive oxygen species that damage myocardial tissue by nonspecific oxidation of membrane and cytosol molecules, ultimately leading to cell death. Handa and Sato first showed that the metabolism of doxorubicin and other quinone containing compounds could lead to free radical generation in a microsomal NADPH- oxidase system [4].

Punica granatum Linn, pomegranate (Punicaceae), a common fruit in the Mediterranean and Iran, is widely used for therapeutic formulae, cosmetics, and food seasoning. The pomegranate fruit, which was readily purchased from conventional remedy markets, was regularly used as an astringent [5], for parasites elimination [6] and as a fever reducing agent. The pharmacological functions of pomegranate include antioxidation [7], anti-lipoperoxidation [8].

Pomegranate juice and peel contains antioxidants such as soluble polyphenols, tannins, and

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IMPROVING BIOAVAILABILITY OF CEFUROXIME AXETIL BY INCREASING RETENTION TIME IN STOMACH WITH THE HELP OF NATURAL POLYMER: FORMULATION AND EVALUATION

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Dr. Babasaheb Ambedkar Marathwada University,

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ABSTRACT

In the present research, an attempt was made to develop gastric retentive tablets of Cefuroxime Axetil (CA) using PMG (Pomegranate) peel powder as release retarded material. Cefuroxime Axetil (CA) is 1-acetoxyethyl ester of a b-lactamase-stable cephalosporin, cefuroxime with a broad spectrum of activity against Gram-positive and Gram-negative microorganisms. After oral administration CA is absorbed and rapidly hydrolyzed by esterases to produce cefuroxime. The 1-acetoxyethylester group at 4th position of CA ensures lipophilicity and promotes the absorption of cefuroxime but at the same time compromises on solubility and hence, the prodrug shows poor and variable oral bioavailability. CA exists in crystalline as well as amorphous forms; of these, latter exhibits higher bioavailability owing to improved solubility. CA is known to have good absorption from upper parts of GIT. Thus, retaining CA in this region for longer time would be beneficial in improving its bioavailability, which makes CA suitable candidate for formulating it as a gastric retentive dosage form for improved bioavailability. The formulation of floating tablets of CA was prepared by direct compression technique. All ingredients except sodium bicarbonate and magnesium stearate were first sifted. These sifted ingredients were mixed well. Then separately sodium bicarbonate and Magnesium stearate are sifted, the drug was mixed well with sifted sodium bicarbonate and then subsequently mixed with sifted magnesium stearate. The above mixture was compressed on Karnavati mini tab eight-station tableting machine using 12 mm flat faced punch. Floating tablets of Cefuroxime Axetil containing PMG peel powder shows good retention. The sodium bicarbonate and citric acid were used as effervescent agents which shows good effervescence. The tablets prepared were evaluated and found to have acceptable physicochemical properties.

From the present study carried out on CA floating tablets using PMG peel powder as a sustained release polymer and sodium bicarbonate as gas generating agent, the in vitro release data of optimized formulation was treated with mathematical equations and was concluded that drug release followed zero-order kinetics with anomalous transport mechanism. Based on the results it can be concluded that floating tablets of Cefuroxime Axetil containing PMG peel powder provides a better option for sustained release action and improved bioavailability.

KEYWORDS: Floating tablets; Cefuroxime Axetil; Retentive material; GRDDS.

INTRODUCTION

Oral drug delivery is the most favored route among the diverse types of drug delivery systems for systemic effects due to ease of administration, patient compliance, economical and non-invasive methods. Sustained release dosage form releases the drug at a slow rate through the oral route. Hence, it is highly desirable to develop sustained drug

Int. J. Pharm. Investigation, 2020;10(3):368-373 Original Article

Improving Bioavailability of Cefpodoxime Proxetil by Increasing Retention Time in Stomach with the Help of Natural Polymer: Formulation and Evaluation

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ABSTRACT

Background: Cefpodoxime proxetil is an orally administered, extended-spectrum, semi-synthetic antibiotic of the cephalosporin class. Cefpodoxime proxetil has a short elimination half-life and also possesses high solubility, chemical, enzymatic stability and absorption profiles in acidic pH which makes Cefpodoxime proxetil suitable candidate for formulating it as a gastroretentive dosage form for improved bioavailability. **Methods:** The formulation of floating tablets of Cefpodoxime proxetil was prepared by the direct compression technique using Pomegranate peel powder as release retarded material. The floating tablets of Cefpodoxime proxetil are prepared by applying design of experiment in that 3^2 Factorial Design was selected. *In vivo* gastro-retention of the optimized floating formulation was determined by X-ray imaging studies on healthy rabbits. **Results:** The F3 Formulation containing Pomegranate peel powder peel powder of 50mg and sodium bicarbonate 100 mg has shown sustained release for 24 hr. The Floating lag time of all the prepared batches was found to be from 49±0.5 to 57±0.5 in sec. The minimum lag time was 49 sec. The *in vitro* release data of optimized formulation was treated with mathematical equations and was concluded that drug release followed zero-order kinetics with anomalous transport mechanism. *In vivo* Gastroretention of the optimized formulation F3 determined by X-ray imaging studies on healthy rabbits shows retention of the tablet in stomach for sufficient period of time. **Conclusion:** The prepared gastro retentive floating tablet formulation using Pomegranate peel powder as rate control polymer shows better-floating properties and effective gastro retention when Pomegranate peel powder and drug is used in the ration of 1:2.5. Hence CFP floating tablet formulation can be a suitable alternative to immediate release CFP tablets to increase gastricresidence time and thereby improving its bioavailability.

Key words: Floating Tablets, Cefpodoxime Proxetil, Pomegranate Peel Powder, Gastroretentive Drug Delivery, Natural Polymer, Bio-availability.

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INTRODUCTION

The administration of active moiety through oral route among other types of drug delivery systems is the most chosen way for achieving systemic effects owing to its comfortable management, good patient compliance and cheap method. Persistent release dosage form releases the active moiety at a slow rate through the oral route. It is exceedingly alluring to create supported medication conveyance frameworks, which discharges the medication at a modified rate to accomplish ideal dynamic particle fixations at the site of activity. These frameworks have weaknesses like non-appropriateness for the active moiety having site-explicit ingestion in the upper part of the GIT, precipitation of active moiety, debasement of the active moiety in the distal part of GIT. This has resulted in the development of gastric retention delivery systems which overpowers the drawbacks connected with continued-release formulations.[1]

A bubbly floating gastro-retentive dosage form is developed for CFP and assessed in rodents. The outcomes showed a potential for development of gastro retentive dosage using Eudragit S100 polymer.[2] It has also been demonstrated successfully the release of the drug CFP from mucoadhesive gastro retentive tablets using Sodium Alginate and Chitosan in a controlled manner.[3]

Literature also confirms the advantages, restrictions, showcased dosage form and patents of floating and non-floating gastro-retentive drug delivery system.[4-6]

The formulator's has highlighted the benefits of gastro-retentive drug delivery system including the organic and formulation factors influencing gastric maintenance and ways to deal with configuration of single-unit and multiple unit floating systems.[7]

CFP is an orally administered extended-spectrum; semi-synthetic antibiotic of the cephalosporin class has a short elimination half-life. It has high solubility, chemical and enzymatic stability. It is absorbed well in acidic pH which makes it suitable candidate for formulating in a gastro retentive dosage form for improving bioavailability. PMG peel powder is used as a polymer in formulations as support release material. It contains Phenolic composites like punicalagins, gallic acid, catechin, epigallocatechin gallate, quercetin, rutin, anthocyanidin's and different flavonoids and acts as a neutral polymer.[8]

MATERIALS

CFP was received as a gift sample from Lupin Pharma Ltd., Aurangabad. Pomegranate peel powder was purchased from Heilen Biopharm. Hydroxy propyl methyl cellulose K4M, Acacia, Sodium bicarbonate,

Review article

Computer aided drug design: A mini-review

Barrawaz Aateka Y*, Shahajan S Baig, Bawazir Abubakar Salam

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Refer This Article

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Keywords

QSAR, molecular modeling, Computational optimization, receptor and ligand, Drug designing

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ABSTRACT

New drug discovery and development process is considered much complex process which is time consuming and resources accommodating too. So computer aided drug design are being broadly used to enhance the effectiveness of the drug discovery and development process which ultimately saves time and resources. Various approaches to Computer aided drug design are evaluated to shows potential techniques in accordance with their needs. Two approaches are considered to designing of drug first one is structure-based and second one is Ligand based drug designs. In this review, we are discussing about highly effective and powerful techniques for drug discovery and development as well as various methods of Computer aided drug design like molecular docking at virtual screening for lead identification, QSAR, molecular homology, de-novo design, molecular modeling and optimization. It also elaborate about different software used in Computer aided drug design, different application of Computer aided drug design etc. Major objectives of Computer aided drug design are to commence collaborative foundation of research activities and to discover new chemical entities for novel therapeutics drugs.

INTRODUCTIION

New drug discovery and drug development is much time-consuming, lengthy, expensive and highly unpredictable risky process that has little peers in global commercial market. And that's why this approach of computer aided drug design is used in pharmaceutical sectors to enhance the process. Especially cost effective approach by using computer tools in the lead optimization phase of drug development is considerable. On average, 10 to 15 years and $ 500 to 800 million are required to introduce a drug to the market, and the synthesis and testing of lead analogues is great contributor that total budget [1]. Henceforth, by using computational tools in successful optimization which can save broad chemical space with reduced amount of compounds that has to be synthesized and tested in vitro. Computational optimization of an affected compound involves an analysis based on the structure of coupling postures and energy profiles for impact analogues, ligand-based detection for compounds with similar chemical structure or improved predicted biological activity, or favorable affinity prediction. Optimization of the metabolism and pharmacokinetics of the drug or absorption, distribution, metabolism, excretion and toxicity potential properties. Cost of biological characterization of compound and synthesis is more higher than compared to very much low cost of CADD make a make more acceptability diversity of chemical space [2].

CADD is capable to accelerate the rate of new drugs by using a much additional targeted search than conventional high-throughput screening (HTS) and optimization of lead compounds to enhance ADME. Design new compounds by either "growing" one functional group after the other as parent molecules or by joining fragments into new chemo types [3].

CADD can be categorized into two approaches: Structure-based and Ligand-based on knowledge of target protein structure for interactions energies calculation for all compounds to be tested are done by structure based CADD which is functioning on information of the target proteins structure which further expose the activeness of molecules through chemical similarities search or quantitative or predictive construction [4,5,6,7].

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Review Article

OLD DRUG WITH NEW MILESTONE: CHLOROQUINE AND HYDROXYCHLOROQUINE IN SARS-COV-2 (COVID-19) WITH MULTIFACETED EFFECTS IN OTHER DISEASES

Barrawaz Aateka Yahya[1]*, Baig Shahajan Shabbir[2], Dr Bawazir Abubakar Salam[1]

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Keywords
Hydroxychloroquine, , Diabetes mellitus, Severe Acute Respiratory Syndrome Coronavirus-2, Disease-Modifying Antirheumatic Drugs, COVID 19.

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ABSTRACT

Hydroxychloroquine is one of the oldest and widely used anti-malarial drug which can be beard easily with cost and well leeway, also these drugs have been greet to have efficacy in autoimmune-related diseases like rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine is known to be a disease-modifying antirheumatic drug, for this, it has been approved firstly in the year 1955 by the United state of food and drug administration. Hydroxychloroquine and chloroquine are recently shown several activities like glucose-lowering effects along with prophylactic use, Dyslipidemia, anticancer, anti-platelet, antithrombotic, antiviral, endothelial dysfunction. Because of the recent outbreak of world has diverted towards these molecules and initiated global clinical trials on Chloroquine and Hydroxychloroquine. So this article focused on the multifaceted effect of Hydroxychloroquine and chloroquine mainly concerning corona. Considering the anti-hyperglycemic potential, anti-inflammatory activity and, pleiotropic effects such as lipid-lowering action, anti-platelet action, antithrombotic action, endothelial dysfunctioning, orbital sarcoidosis, and nephroprotective action, HCQ may emerge as a cost-effective therapeutic option for uncontrolled diabetes patients in alone therapy or combinations. Chloroquine and Hydroxychloroquine have been proved its efficacy towards the recent spread of pandemic disease novel coronavirus.

INTRODUCTIION

Hydroxychloroquine (HCQ) is obtained from the bark of the Cinchona plant and used to treat different desperate conditions including malaria [1]. During 1950, Quinacrine which is derivative of HCQ has shown less retinal toxic effects and more positive usage than CQ, thus further HCQ was commonly used in conditions like RA and SLE. The triple-drug combination of methotrexate and sulfasalazine along with HCQ has always been preferred in RA considering its safety, tolerability, and costing [2,3].

HCQ is also beneficial to improve cardiovascular profile in RA condition since it can lead to further since RA leads to early mortality and morbidity [4]. Several previous studies have established the beneficial effect of HCQ in the treatment of diabetes mellitus [5,6,7,8]. Because of Mortality and morbidity rate due to cardiovascular risk, HCQ is elucidated to have anti-platelet and antithrombotic properties [9,10,11] So there is a strong need of safe and effective drug therapy which can perform multifaceted effects considering the outbreak of global pandemic disease. Currently, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and novel coronavirus (COVID 19) outbreak was identified and firstly reported in Wuhan city of China at

Int. J. Pharm. Investigation, 2020;10(3):368-373 Original Article

Improving Bioavailability of Cefpodoxime Proxetil by Increasing Retention Time in Stomach with the Help of Natural Polymer: Formulation and Evaluation

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INTRODUCTION

The administration of active moiety through oral route among other types of drug delivery systems is the most chosen way for achieving systemic effects owing to its comfortable management, good patient compliance and cheap method. Persistent release dosage form releases the active moiety at a slow rate through the oral route. It is exceedingly alluring to create supported medication conveyance frameworks, which discharges the medication at a modified rate to accomplish ideal dynamic particle fixations at the site of activity. These frameworks have weaknesses like non-appropriateness for the active moiety having site-explicit ingestion in the upper part of the GIT, precipitation of active moiety, debasement of the active moiety in the distal part of GIT. This has resulted in the development of gastric retention delivery systems which overpowers the drawbacks connected with continued-release formulations.[1]

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MATERIALS

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Int. J. Pharm. Investigation, 2020;10(2):192-196 *Original Article*

Stabilization of Rosuvastatin Calcium Formulation by Prevention of Intermolecular Esterification: An Experimental Design

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ABSTRACT

Background: Rosuvastatin calcium is the most effective molecule for the treatment and management of Hypercholesterolemia. This drug easily degrades by exposure to moisture and light and forms unstable formulation by formation of oxidation products, this degradation accelerates in acidic environment of the formulation. The acid form of Rosuvastatin calcium which is the active moiety has a tendency of conversion into lactone form Inactive moiety through "intermolecular esterification" in acidic environment. Synthetic alkalising agents such as tribasic magnesium phosphate is usually added in the tablet formulation to overcome this degradation, but alkalizing agents are harmful to gastric mucosa. **Methods:** Natural stabilizers such as Xanthan Gum, Chitosan and Guar Gum are used for stabilization. Selection of optimum stabilizer and drug/stabilizer ratio is obtained by quality by design approach by implementing 3^2 factorial design. Xanthan gum and Chitosan were selected as Critical quality attributes and material attributes with fixed Rosuvastatin Calcium concentration. **Results:** Tablets consisting of Xanthan Gum and Chitosan in 1:1.4 ratios exhibited maximum stabilization after stability study with 99% assay and dissolution was enhanced by more than 20% i.e. 98% within 30 min as compared to marketed tablets. Statistical test by Analysis of Variance revealed that the model is significant with *p* value <0.0001 and F-value of 50.58 that the model terms are significant for one factor i.e. the concentration of chitosan as natural stabilizer. **Conclusion:** The stabilisation of Rosuvastatin calcium was achieved by natural stabilizer i.e. chitosan with QBD approach and the stable tablet formulation was successfully prepared.

Key words: Rosuvastatin calcium, Quality by Design, Design of Experiment, Natural stabilizers, Chitosan, Xanthan Gum.

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INTRODUCTION

Cardiac diseases such as atherosclerosis is the leading cause of death in the world and one of the most significant factor for these diseases is total/ high density lipoprotein (HDL) cholesterol ratio. Rosuvastatin calcium (RVS) inhibits the activation of the enzyme named HMG-CoA reductase, which is responsible for cholesterol synthesis in the body and prevents cholesterol formation.[1] An important problem about RVS is conversion from acid form into lactone form through "intermolecular esterification" that take place between the carboxylic acid and hydroxyl groups that are present on the β and δ carbons. This reaction takes place in acidic environment and basic agents reverse the reaction. This phenomenon decreases the stability of the compound and as a result lowers the shelf life of the product. Various synthetic stabilisers such as tribasic calcium phosphate, tribasic magnesium phosphate salts were used to stabilise RVS compositions. However, high amounts of alkaline agents' intake harms to gastric mucosa and causes stomach problems in patients.[2] Thus there is a need for new and stable formulation for the most effective and the most frequently used medicament of statin group.[3] The use of natural stabilizers such as various biopolymers and natural gums with higher alkaline nature can be used instead of these harmful alkalising agents to avoid such gastric irritation problems.[4]

MATERIALS AND METHODS

Materials

RVS is obtained as a gift sample by Lupin Ltd, Pune. The excipients such as Crospovidone, microcrystalline cellulose, Chitosan, Guar gum and Xanthan gum are purchased from Fisher scientific and marketed formulation of RVS was purchased from local market.

Methods

Characterisation of Procured Drug

Rosuvastatin Calcium is characterised for its purity by determining various parameters such as: Colour, odour, appearance and melting point which was determined with the help of Thiele's tube using capillary method.[5] In addition to this Fourier transform infrared (FTIR)analysis was performed and its spectrum was taken from JASCO IR spectrometer (PS 400). The drug sample was mixed with dried KBr in mortar and pestle and then filled in the sample holder.[6] For UV-Spectrophotometric analysis of Rosuvastatin, calibration curve was plotted. The solvent system selected was methanol and phosphate buffer pH 6.8. Accurately weighed Rosuvastatin 10mg was dissolved in 100ml of methanol to produce a stock solution of 100µg/m. Aliquots of 1,2,3,4 and 5ml of the stock solution corresponding to 10-50µg/ml were taken in a series of 10ml volumetric flask and volume was made up.[7] Absorption maximum was determined and linear equation was calculated from calibration curve.[8]

Characterisation of Marketed Formulation

The marketed tablet of Rosuvastatin was evaluated for the physical Characteristics such as thickness, diameter, hardness, friability and weight variation test according to the Indian Pharmacopeia (IP) 2007.

Int. J. Pharm. Investigation, 2020;10(3):294-299 *Original Article*

Formulation and Evaluation of Gastro-Bilayer Floating Tablets of Losartan Potassium as Immediate Release Layer and Ramipril Hydrochloride as Sustained Release Floating Layer

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ABSTRACT

Objectives: A sustained release Gastro-bilayer floating tablets with reduced dosing frequency and increased drug bioavailability is developed. The dosage form is suitable for the release of two drugs simultaneously in a single dosage unit i.e. Losartan Potassium and Ramipril Hydrochloride. The SeDeM system for selection of powder blend for direct compression gave the parameter index value of ≥0.5 which is considered as best in terms of compression properties. The prepared dosage form provided sustained effect of the drug for 12 hr by Non-Fickian, controlled diffusion and swollen matrix. Peppa's release model is best suited for the final formulation of batches. Optimized formulation exhibited floating time of 12 hr and floating lag time of less than 1 min. *In-vitro* dissolution studies shows 96% of the both the drugs release. The swelling and erosion of polymers is studied by Scanning Electron Microscopy. The data obtained from Analysis of variance demonstrated the significance of the model with a *P*-value of less than 0.05. **Methods:** SeDeM system was adopted on powder blend before direct compression for preparation of tablet, the hydroxyl propyl methyl cellulose was used as a rate-controlling polymer and a mixture of citric acid and Sodium bicarbonate formed the floating layer. **Results:** Radius values through SeDeM diagram was plotted and index values are calculated and resulted in an index value of ≥0.5. The pre-compression and post compressional parameters are as per Indian Pharmacopeia specifications. The best formulation for gastric bilayer tablet had a combination of Hydroxy propyl methyl cellulose K15M and Sodium Carboxy methyl cellulose which gave 99.57% drug dissolution within 12 hr. **Conclusion:** Gastro-Bilayer Floating Tablets of Losartan as Immediate Release layer and Ramipril as sustained-release floating layer are successfully developed. The problem of poor solubility of drugs can be solved by optimization of blend through SeDeM expert System. Hydroxy propyl methyl cellulose K15M, K4M and Carbopol 934 are helpful in achieving the sustained effect of the drug for 12 hr by Non-Fickian, controlled diffusion and swollen matrix. Peppa's release model is best suited for the final formulation batches based on the drug release mechanisms.

Key words: Gastro-Bilayer Floating Tablets, Losartan Potassium, Ramipril Hydrochloride, SeDeM, Sustained Release Floating Layer.

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INTRODUCTION

The aim of the study is to formulate controlled release Gastro-bilayer floating tablets that will reduce the dosing frequency and increase drug bioavailability for treatment of chronic hypertension.[1] The dosage form is suitable for release of two different types of drugs, wherein one layer is of immediate release which releases Losartan Potassium and the second sustained release layer is of Ramipril Hydrochloride in a single dosage unit. This type of dosage form has many advantages over the conventional single-layered Tablets. Losartan potassium is an angiotensin II receptor antagonist and Ramipril Hydrochloride is angiotensin-converting enzyme-inhibitor when these two drug are used in combination blocks total production of angiotensin mostly responsible for hypertension.[2] The advantages of such bilayer dosage form is mentioned in most of the literature and further up till now this type of combination formulation is still not available therefore such type of dosage form is developed.[3] Formulating bilayer dosage form may contribute to cost-effectiveness by eliminating different coatings required to get sustained-release action.[4] SeDeM expert system is a predictive tool that can be applied for evaluation of suitability, critical quality attributes and the behavior of the drug material and excipients used for the formulation development of bilayer tablets by direct compression having an impact on the final product.[5] This system provides a physical profile of powder material intended to be used and suggests their flow performance. SeDeM expert system technique may reduce the number of preformulation trials and may be coined as time-saving and cost saving in the prediction of deficient part in powder blend as compared to conventional trial and error approaches or software-based prediction models.[6]

MATERIAL

Ramipril Hydrochloride was obtained as a gift sample from Lupine pharmaceutical Industries, Aurangabad, India. Losartan Potassium was purchased from Aristo Laboratories, Mumbai, India. Hydroxy propyl methyl cellulose, Carbopol 934p and Polyvinyl Pyrrolidone-K30 were obtained from the Shreya life Sciences as gift samples.

METHODS

Preparation of Gastro-bilayer floating matrix Tablets

Preparation of Immediate-release layer

The immediate-release layer of Losartan potassium was prepared by mixing drug along with the different excipients and SeDeM expert system applied for evaluation of suitability, critical quality attributes and the behavior of the drug material and excipients used for the

Int. J. Pharm. Investigation, 2020;10(3):368-373 Original Article

Improving Bioavailability of Cefpodoxime Proxetil by Increasing Retention Time in Stomach with the Help of Natural Polymer: Formulation and Evaluation

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ABSTRACT

Background: Cefpodoxime proxetil is an orally administered, extended-spectrum, semi-synthetic antibiotic of the cephalosporin class. Cefpodoxime proxetil has a short elimination half-life and also possesses high solubility, chemical, enzymatic stability and absorption profiles in acidic pH which makes Cefpodoxime proxetil suitable candidate for formulating it as a gastroretentive dosage form for improved bioavailability. **Methods:** The formulation of floating tablets of Cefpodoxime proxetil was prepared by the direct compression technique using Pomegranate peel powder as release retarded material. The floating tablets of Cefpodoxime proxetil are prepared by applying design of experiment in that 3^2 Factorial Design was selected. *In vivo* gastro-retention of the optimized floating formulation was determined by X-ray imaging studies on healthy rabbits. **Results:** The F3 Formulation containing Pomegranate peel powder peel powder of 50mg and sodium bicarbonate 100 mg has shown sustained release for 24 hr. The Floating lag time of all the prepared batches was found to be from 49±0.5 to 57±0.5 in sec. The minimum lag time was 49 sec. The *in vitro* release data of optimized formulation was treated with mathematical equations and was concluded that drug release followed zero-order kinetics with anomalous transport mechanism. *In vivo* Gastroretention of the optimized formulation F3 determined by X-ray imaging studies on healthy rabbits shows retention of the tablet in stomach for sufficient period of time. **Conclusion:** The prepared gastro retentive floating tablet formulation using Pomegranate peel powder as rate control polymer shows better-floating properties and effective gastro retention when Pomegranate peel powder and drug is used in the ration of 1:2.5. Hence CFP floating tablet formulation can be a suitable alternative to immediate release CFP tablets to increase gastricresidence time and thereby improving its bioavailability.

Key words: Floating Tablets, Cefpodoxime Proxetil, Pomegranate Peel Powder, Gastroretentive Drug Delivery, Natural Polymer, Bio-availability.

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INTRODUCTION

The administration of active moiety through oral route among other types of drug delivery systems is the most chosen way for achieving systemic effects owing to its comfortable management, good patient compliance and cheap method. Persistent release dosage form releases the active moiety at a slow rate through the oral route. It is exceedingly alluring to create supported medication conveyance frameworks, which discharges the medication at a modified rate to accomplish ideal dynamic particle fixations at the site of activity. These frameworks have weaknesses like non-appropriateness for the active moiety having site-explicit ingestion in the upper part of the GIT, precipitation of active moiety, debasement of the active moiety in the distal part of GIT. This has resulted in the development of gastric retention delivery systems which overpowers the drawbacks connected with continued-release formulations.[1]

A bubbly floating gastro-retentive dosage form is developed for CFP and assessed in rodents. The outcomes showed a potential for development of gastro retentive dosage using Eudragit S100 polymer.[2] It has also been demonstrated successfully the release of the drug CFP from mucoadhesive gastro retentive tablets using Sodium Alginate and Chitosan in a controlled manner.[3]

Literature also confirms the advantages, restrictions, showcased dosage form and patents of floating and non-floating gastro-retentive drug delivery system.[4-6]

The formulator's has highlighted the benefits of gastro-retentive drug delivery system including the organic and formulation factors influencing gastric maintenance and ways to deal with configuration of single-unit and multiple unit floating systems.[7]

CFP is an orally administered extended-spectrum; semi-synthetic antibiotic of the cephalosporin class has a short elimination half-life. It has high solubility, chemical and enzymatic stability. It is absorbed well in acidic pH which makes it suitable candidate for formulating in a gastro retentive dosage form for improving bioavailability. PMG peel powder is used as a polymer in formulations as support release material. It contains Phenolic composites like punicalagins, gallic acid, catechin, epigallocatechin gallate, quercetin, rutin, anthocyanidin's and different flavonoids and acts as a neutral polymer.[8]

MATERIALS

CFP was received as a gift sample from Lupin Pharma Ltd., Aurangabad. Pomegranate peel powder was purchased from Heilen Biopharm. Hydroxy propyl methyl cellulose K4M, Acacia, Sodium bicarbonate,

ID 240. Development of Novel Anti-Cancer Agent Targeting Angiogenesis in Colorectal Cancer.

- **Source:** Journal of Pharmacy & Bioallied Sciences . 2020 Supplement, Vol. 12, p933-933. 1/3p.

- **Author(s):** Mokale, Santosh N.; Ingole, Kiran; More, Shweta; Sakle, Nikhil; Dhawale, Sachin

- **Abstract:** Introduction: Computer-aided drug design techniques were adopted to design a series of novel (E)-N-(N- (benzoyloxybenzilidine)-5-chloro pyrimidine-2- amine as VEGFR and c-MET kinase inhibitors. Objectives: To design new chemical entities for dual kinases inhibitors action (VEGFR and c-MET), to synthesis and perform spectral analysis (IR, 1H, 13C NMR, Mass spectra), and to screen the compounds for their proposed dual kinase inhibitor activity against COLO-205 and HT-29 cell lines. Materials and Methods: The designed compounds were synthesized to afford the desired series followed by evaluating their in vitro anti-cancer activities. The reaction was carried out by microwave assisted synthesis method. Synthesized compounds were characterized by standard methods of spectroscopy after purification. Results: Among the synthesized compounds, K-1, K-2, K-3, K-4, K-5, K-6, K-7 and K-8 were found to show potent cytotoxic against receptor on COLO-205 cellline, and K-3, K-4 and K-5 on HT-29 cell line. The in-vitro anti-cancer activity result showed that the compounds have protuberant affinity toward VEGFR and c-MET receptors as standard drug pazopanib. Conclusion: The above results revealed that (E)-N-(N-(benzoyloxybenzilidine)-5-chloro pyrimidine-2- amine hybridized with various heterocyclic scaffolds could be a potential anti-cancer agent.

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A network pharmacology-based approach to explore potential targets of *Caesalpinia pulcherima*: an updated prototype in drug discovery

Nikhil S. Sakle, Shweta A. More & Santosh N. Mokale✉

Caesalpinia pulcherima **(CP) is a traditional herb used for the treatment of asthma, bronchitis, cancer, anti-bacterial, anti-fungal and as abortifacient. In the present study, bioactive components and potential targets in the treatment of breast cancer validated through in silico, in vitro and in vivo approach. The results for the analysis were as among 29 components, only four components were found active for further study which proved the use of CP as a multi-target herb for betterment of clinical uses. The results found by PPI states that our network has significant interactions which include the ESR-1, ESR-2, ESRRA, MET, VEGF, FGF, PI3K, PDK-1, MAPK, PLK-1, NEK-2, and GRK. Compound-target network involves 4 active compound and 150 target genes which elucidate the mechanisms of drug action in breast cancer treatment. Furthermore, on the basis of the above results the important proteins were fetched for the docking study which helps in predicting the possible interaction between components and targets. The results of the western blotting showed that CP regulates ER and EGFR expression in MCF-7 cell. In addition to this animal experimentation showed that CP significantly improved immunohistological status in MNU induced carcinoma rats. Network pharmacology approach not only helps us to confirm the study of the chosen target but also gave an idea of compound-target network as well as pathways associated to the CP for treating the complex metabolic condition as breast cancer and they importance for experimental verification.**

Breast cancer (BC) is the malignant growth that begins in the breast cells. BC is the widespread cancer in India (in women) which accounts for 14% of all the cancers in women[1,2]. In general, 1 in 28 women are prone to have BC during her life span. The frequency rates in India begin to rise in the early thirties and peak at the age of 50–64 years[3]. In urban areas, 1 in 22 women are likely to have BC during her life span as compared to rural areas where 1 in 60 women develop BC in her life span[4]. Duration of survival of cancer patients is an important sign for knowing the result of treatment in any study. Since the 1990s, due to regular efforts in the diagnosis and treatment, the overall survival time of patients has been enhanced[5]. In cancer multiple genes participate which gradually alters the normal healthy cells into cancerous cells. Cancers have the capacity to develop resistance to conventional chemotherapy[6]. Thus, it is essential to recognize new therapeutic agents or promising targets. In current cancer therapy, new generations of drugs have targeted cancer specific proteins that are expressed in different cancers. Target specific cancer therapy minimizes the side effect profiles of conventional cytotoxic drugs[7]. In targeted therapy attempts are being made to design ligands with maximum selectivity to act on specific drug targets. Network pharmacology (NP) is an emerging discipline useful in drug discovery, which combines genomic technologies and system biology through computational biological tool. Network pharmacology, is an approach capable of describing complex relationships among biological systems, drugs and diseases[8]. It also clarifies the possible mechanisms of complex bio-actives through large data set analysis and determines the synergistic effects in cancer treatment[9]. Traditional Chinese medicine (TCM) is combination of complex herbal formulation and has been used for more than thousands of years in the treatment of different diseases and disorders for the prolongation of life expectancy in different parts of the world[10]. The network-target-based network pharmacology is a promising approach for the next-generation mode of drug

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ORIGINAL ARTICLE

Mapping the Impact of a Polar Aprotic Solvent on the Microstructure and Dynamic Phase Transition in Glycerol Monooleate/Oleic Acid Systems

Gliserol Monooleat/Oleik Asit Sistemlerinde Polar Aprotik Çözücünün Mikroyapı ve Dinamik Faz Geçişine Etkisinin Haritalanması

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ABSTRACT

Objectives: The impact of incorporating a polar aprotic solvent, dimethyl sulfoxide (DMSO), in glycerol monooleate/oleic acid systems was evaluated briefly to map its influence on the gel microstructure and dynamic phase transition in controlling the performance of a polyene antifungal drug delivery system.

Materials and Methods: An *in situ* gelling fluid precursor system (IGFPS) exhibiting inverse lyotropic liquid crystalline phases was developed by simple solution add-mixture method. Polarized light microscopy, small angle X-ray scattering (SAXS), differential scanning calorimetry (DSC), and oscillatory rheological assessments were performed to ascertain microstructural modulations. The developed system was examined for minimum gelling volume, gelling time, swelling behavior, mucoadhesion, *in vitro* antifungal activity, and *in vitro* drug release.

Results: The SAXS study identifies the coexistence of Im3m cubic phase with HCP P63/mmc hexagonal structures. The SAXS and DSC data highlight DMSO's unique ability to work both as a kosmotropic or chaotropic solvent and to be a function of its concentration. The *in vitro* antifungal test results indicate the concentration of DMSO to be a controlling factor in drug release and diffusion. The *in vitro* drug release kinetic studies reveal that most of the gel samples follow the matrix model and anomalous type release as implied by Peppas model.

Conclusion: Finally, the antifungal IGFPS formulated was found to have the required low viscosity, responsive sol-gel phase transition, appreciative mechanical properties, and desirable antifungal effect with sustained drug release performance.

Key words: Dimethyl sulfoxide, glycerol monooleate, microstructure, oleic acid, small angle X-ray scattering

ÖZ

Amaç: Bir polien antifungal ilaç taşıyıcı sistem performansını kontrol etmek için polar aprotik çözücü olan dimetil sülfoksit'in (DMSO), gliserol monooleat/oleik asit sistemlerine dahil edilmesinin, jel mikroyapısı ve dinamik faz geçişi üzerindeki etkisi araştırılmıştır.

Gereç ve Yöntemler: İnvers liyotropik sıvı kristalin (LLC) fazları sergileyen in situ jelleşen öncü sıvı sistemi (IGFPS), basit çözelti ilave etme yöntemi ile geliştirilmiştir. Polarize ışık mikroskopisi (PLM), küçük açılı X-ışını saçılması (SAXS), diferansiyel tarama kalorimetrisi (DSC) ve reolojik osilatör ölçümleri mikroyapısal modifikasyonları belirlemek için yapılmıştır. Geliştirilen sistem, minimum jelleşme hacmi, jelleşme süresi, şişme davranışı, mukoyapışkanlık, *in vitro* antifungal aktivite ve *in vitro* ilaç salımı açısından incelenmiştir.

Bulgular: SAXS çalışması, Im3m kübik fazın HCP P63/mmc altıgen yapılarla bir arada varlığını tanımlamıştır. SAXS ve DSC verileri, DMSO'nun hem bir kozmotropik hem de kaotropik çözücü olarak görev yaptığını ve işlevini konsantrasyon bağımlığı olarak gerçekleştirdiğini gösterdiğinden DMSO'nun eşsiz yeteneğini vurgulamıştır. *İn vitro* antifungal test sonuçları, DMSO konsantrasyonunun ilaç salımı ve difüzyonunda kontrol edici bir faktör olduğunu göstermiştir. *İn vitro* ilaç salım kinetik çalışmaları, jel örneklerinin çoğunun matris modeli ve Peppas modelinin belirttiği gibi anormal tip salım kinetiğini takip ettiğini ortaya koymuştur.

Sonuç: Sonuç olarak, formüle edilen antifungal IGFPS'nin, gerekli düşük viskoziteye, duyarlı sol-jel faz geçişine, istenen mekanik özelliklere ve sürekli ilaç salım performansı ile arzu edilen antifungal etkiye sahip olduğu bulunmuştur.

Anahtar kelimeler: Dimetil sülfoksit, gliserol monooleat, mikroyapı, oleik asit, küçük açılı X-ışını saçılması

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Research Article

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Ocular delivery of natamycin based on monoolein/span 80/poloxamer 407 nanocarriers for the effectual treatment of fungal keratitis

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ABSTRACT: A 3^2 factorial design was used to develop Natamycin cubosome nanoparticles with enhanced corneal permeation, so as to effectively treat ocular fungal keratitis. Probe sonication technique was deployed to disperse the dry lipidic film to obtain colloidal dispersion. The colloidal dispersion was characterized for critical quality attributes such as particle size, poly dispersibility index (PDI), zeta potential and entrapment efficiency. The optimized batch exhibited a particle size of 158.2 nm, zeta potential -40 mV, PDI 0.328 in addition, entrapment efficiency of 99.85%. The *in vitro* drug release of natamycin from optimized cubosome demonstrated a cumulative %drug release of 84.29% at the end of 8 hours. The optimized cubosomal dispersion exhibited enhanced *in vitro* antifungal activity against *Candida albicans* and *Aspergillus fumigatus* as compared to a pure drug suspension. The optimized formulation was further analyzed for polarized light microscopy (PLM), transmission electron microscopy (TEM) and small angle X-ray scattering (SAXS) to state the morphology of formed cubosome nanoparticles and was noted to be Im3m bicontinous cubic mesophasic structure. X-ray diffraction (XRD) studies affirmed the complete encapsulation of natamycin into cubosome vesicles. *Ex vivo* corneal permeation studies of optimized formulation revealed enhanced corneal permeation in comparison to a pure drug suspension. The ocular irritation studies performed on rabbits indicated the cubosome to be non-irritant. Finally, the developed natamycin cubosome nanoparticles demonstrated sustained drug release and increased corneal penetration. Thus, these cubosome nanocarriers present a propitious delivery system for effective management of ocular fungal keratitis.

KEYWORDS: Natamycin; cubosome; ocular fungal keratitis; nanoparticles; factorial design.

1. INTRODUCTION

Fungal keratitis is a severe ocular infection characterized by decreased vision, photophobia, feathery-edged infiltrates and satellite lesions across the cornea that leads to cataclysmic visual fallouts [1]. The causative agent is a species of fungi such as yeasts (*Candida*), filamentous with septae (*Aspergillus*, *Fusarium*, *Cladosporium*, *Curvularia*) and filamentous with non-septated (*Rhizopus*) [2]. Natamycin is BCS class II drug and due to its high molecular weight, corneal permeation is low. The conventional therapy for natamycin surfaces some notable drawbacks such as high dosing frequency, longer time period treatment cycles (4–6 weeks) and due to fast removal by nasopharyngeal drainage residence time at the ocular mucosa is short [3]. Extensive efforts have been directed towards the enhancement of ophthalmic drug bioavailability by exploring novel drug delivery strategies [3]. The delivery alternatives aim at improving both the precorneal residence time and in boosting the trans-corneal permeation of the drug [4, 5]. Thus, the challenge faced in designing a successful delivery can only be overcomed by circumventing the shielding barriers of the eye without enduring any tissue injury.

Nanocarriers or nanoparticulate systems proposed for controlled drug delivery demonstrate ability as a potential strategy to overcome these limitations [6]. Recently, cubosomes as a surrogate nanocarrier drug delivery system to liposome has been investigated [7]. These are binary systems, especially made up monoolein–water and are three-dimensional nanostructure with hydrophobic and hydrophilic domains that

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Original Article

Development of inhalable cubosome nanoparticles of Nystatin for effective management of Invasive Pulmonary Aspergillosis

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ABSTRACT

Background and Aims: Invasive pulmonary aspergillosis (IPA) is an imperative concern in the present era due to its high occurrence and mortality rate in severely immunocompromised patients. The present study was designed to develop, optimize and characterize encapsulated nystatin (NYS) cubosome nanoparticles as an inhalable system, a viable alternative for effective management of IPA.

Methods: A dry lipidic film comprising glycerol monooleate (GMO), Span 83, Poloxamer (P-407) and dispersed NYS was subjected to ultrasound sonication to produce colloidal dispersion of cubosomes. The process and formulation variables were screened using Plackett Burman design and further optimized by Box Behnken design by evaluating its effect on particle size, polydispersity index (PDI), zeta potential and entrapment efficiency.

Results: The optimized NYS cubosomes were nearly spherical with some irregular polyangular symmetry as visualized by transmission electron microscopy (TEM). Further, small angle X-ray scattering (SAXS) affirmed Pn3m cubic mesophasic structure. The optimized nanoparticles had particle size 263.5 nm, zeta potential -14.4 mV, PDI 0.283 and entrapment efficiency 82%. The *in-vitro* cytotoxicity assay indicated that NYS cubosomes reduced cell cytotoxicity in contrast to pure drug post 48h. *In-vitro* haemolytic assay denoted lower toxicity of formulation as compared to free drug. In-vitro drug release studies highlighted, slow but continuous release from NYS cubosomes until 48h and showcased Higuchi release kinetics. Likewise, NYS cubosome demonstrated higher antifungal activity compared to drug suspended in phosphate buffer.

Conclusion: Thus, non-invasive feature and contemplated target specificity of nystatin loaded cubosome nanoparticles pave a mode for its prospect as pulmonary delivery to combat IPA.

Keywords: Nystatin, cubosome nanoparticles, aspergillosis, drug design, pulmonary

INTRODUCTION

Lipidic, polymeric and polyelectrolyte complex based nanoparticulate drug delivery lately has been widely studied as potential carriers for delivery of numerous drug candidates such as anticancer (Chishti, Jagwani, Dhamecha, Jalalpure, & Dehghan, 2019), peptide (on Halling Laier et al., 2018; Poddar & Sawant, 2017), antifungals (Furedi et al., 2017), antivirals (Mandal, Prathipati, Belshan, & Destache, 2019) and antibacterials (Carneiro et al., 2019; Rani et al., 2018). The prevalence rate of invasive pulmonary aspergillosis (IPA) is high in severely immunocompromised patients suffering from HIV, cancer, critically ill patients, organ transplant patients and in individuals with known history of chronic obstructive pulmonary disease (Szalewski, Hinrichs, Zinniel, & Barletta, 2018). The management of IPA still remains a challenge as most of the antifungal used in its treatment present resistance or pose a high toxicity profiles (Kosmidis & Muldoon, 2017). Nystatin (NYS) a broad

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Int. J. Pharm. Investigation, 2020;10(2):192-196 *Original Article*

Stabilization of Rosuvastatin Calcium Formulation by Prevention of Intermolecular Esterification: An Experimental Design

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ABSTRACT

Background: Rosuvastatin calcium is the most effective molecule for the treatment and management of Hypercholesterolemia. This drug easily degrades by exposure to moisture and light and forms unstable formulation by formation of oxidation products, this degradation accelerates in acidic environment of the formulation. The acid form of Rosuvastatin calcium which is the active moiety has a tendency of conversion into lactone form Inactive moiety through "intermolecular esterification" in acidic environment. Synthetic alkalising agents such as tribasic magnesium phosphate is usually added in the tablet formulation to overcome this degradation, but alkalizing agents are harmful to gastric mucosa. **Methods:** Natural stabilizers such as Xanthan Gum, Chitosan and Guar Gum are used for stabilization. Selection of optimum stabilizer and drug/stabilizer ratio is obtained by quality by design approach by implementing 3^2 factorial design. Xanthan gum and Chitosan were selected as Critical quality attributes and material attributes with fixed Rosuvastatin Calcium concentration. **Results:** Tablets consisting of Xanthan Gum and Chitosan in 1:1.4 ratios exhibited maximum stabilization after stability study with 99% assay and dissolution was enhanced by more than 20% i.e. 98% within 30 min as compared to marketed tablets. Statistical test by Analysis of Variance revealed that the model is significant with *p* value <0.0001 and F-value of 50.58 that the model terms are significant for one factor i.e. the concentration of chitosan as natural stabilizer. **Conclusion:** The stabilisation of Rosuvastatin calcium was achieved by natural stabilizer i.e. chitosan with QBD approach and the stable tablet formulation was successfully prepared.

Key words: Rosuvastatin calcium, Quality by Design, Design of Experiment, Natural stabilizers, Chitosan, Xanthan Gum.

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INTRODUCTION

Cardiac diseases such as atherosclerosis is the leading cause of death in the world and one of the most significant factor for these diseases is total/ high density lipoprotein (HDL) cholesterol ratio. Rosuvastatin calcium (RVS) inhibits the activation of the enzyme named HMG-CoA reductase, which is responsible for cholesterol synthesis in the body and prevents cholesterol formation.[1] An important problem about RVS is conversion from acid form into lactone form through "intermolecular esterification" that take place between the carboxylic acid and hydroxyl groups that are present on the β and δ carbons. This reaction takes place in acidic environment and basic agents reverse the reaction. This phenomenon decreases the stability of the compound and as a result lowers the shelf life of the product. Various synthetic stabilisers such as tribasic calcium phosphate, tribasic magnesium phosphate salts were used to stabilise RVS compositions. However, high amounts of alkaline agents' intake harms to gastric mucosa and causes stomach problems in patients.[2] Thus there is a need for new and stable formulation for the most effective and the most frequently used medicament of statin group.[3] The use of natural stabilizers such as various biopolymers and natural gums with higher alkaline nature can be used instead of these harmful alkalising agents to avoid such gastric irritation problems.[4]

MATERIALS AND METHODS

Materials

RVS is obtained as a gift sample by Lupin Ltd, Pune. The excipients such as Crospovidone, microcrystalline cellulose, Chitosan, Guar gum and Xanthan gum are purchased from Fisher scientific and marketed formulation of RVS was purchased from local market.

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Characterisation of Procured Drug

Rosuvastatin Calcium is characterised for its purity by determining various parameters such as: Colour, odour, appearance and melting point which was determined with the help of Thiele's tube using capillary method.[5] In addition to this Fourier transform infrared (FTIR)analysis was performed and its spectrum was taken from JASCO IR spectrometer (PS 400). The drug sample was mixed with dried KBr in mortar and pestle and then filled in the sample holder.[6] For UV-Spectrophotometric analysis of Rosuvastatin, calibration curve was plotted. The solvent system selected was methanol and phosphate buffer pH 6.8. Accurately weighed Rosuvastatin 10mg was dissolved in 100ml of methanol to produce a stock solution of 100µg/m. Aliquots of 1,2,3,4 and 5ml of the stock solution corresponding to 10-50µg/ml were taken in a series of 10ml volumetric flask and volume was made up.[7] Absorption maximum was determined and linear equation was calculated from calibration curve.[8]

Characterisation of Marketed Formulation

The marketed tablet of Rosuvastatin was evaluated for the physical Characteristics such as thickness, diameter, hardness, friability and weight variation test according to the Indian Pharmacopeia (IP) 2007.

Int. J. Pharm. Investigation, 2020;10(3):368-373 Original Article

Improving Bioavailability of Cefpodoxime Proxetil by Increasing Retention Time in Stomach with the Help of Natural Polymer: Formulation and Evaluation

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ABSTRACT

Background: Cefpodoxime proxetil is an orally administered, extended-spectrum, semi-synthetic antibiotic of the cephalosporin class. Cefpodoxime proxetil has a short elimination half-life and also possesses high solubility, chemical, enzymatic stability and absorption profiles in acidic pH which makes Cefpodoxime proxetil suitable candidate for formulating it as a gastroretentive dosage form for improved bioavailability. **Methods:** The formulation of floating tablets of Cefpodoxime proxetil was prepared by the direct compression technique using Pomegranate peel powder as release retarded material. The floating tablets of Cefpodoxime proxetil are prepared by applying design of experiment in that 3^2 Factorial Design was selected. *In vivo* gastro-retention of the optimized floating formulation was determined by X-ray imaging studies on healthy rabbits. **Results:** The F3 Formulation containing Pomegranate peel powder peel powder of 50mg and sodium bicarbonate 100 mg has shown sustained release for 24 hr. The Floating lag time of all the prepared batches was found to be from 49±0.5 to 57±0.5 in sec. The minimum lag time was 49 sec. The *in vitro* release data of optimized formulation was treated with mathematical equations and was concluded that drug release followed zero-order kinetics with anomalous transport mechanism. *In vivo* Gastroretention of the optimized formulation F3 determined by X-ray imaging studies on healthy rabbits shows retention of the tablet in stomach for sufficient period of time. **Conclusion:** The prepared gastro retentive floating tablet formulation using Pomegranate peel powder as rate control polymer shows better-floating properties and effective gastro retention when Pomegranate peel powder and drug is used in the ration of 1:2.5. Hence CFP floating tablet formulation can be a suitable alternative to immediate release CFP tablets to increase gastricresidence time and thereby improving its bioavailability.

Key words: Floating Tablets, Cefpodoxime Proxetil, Pomegranate Peel Powder, Gastroretentive Drug Delivery, Natural Polymer, Bio-availability.

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INTRODUCTION

The administration of active moiety through oral route among other types of drug delivery systems is the most chosen way for achieving systemic effects owing to its comfortable management, good patient compliance and cheap method. Persistent release dosage form releases the active moiety at a slow rate through the oral route. It is exceedingly alluring to create supported medication conveyance frameworks, which discharges the medication at a modified rate to accomplish ideal dynamic particle fixations at the site of activity. These frameworks have weaknesses like non-appropriateness for the active moiety having site-explicit ingestion in the upper part of the GIT, precipitation of active moiety, debasement of the active moiety in the distal part of GIT. This has resulted in the development of gastric retention delivery systems which overpowers the drawbacks connected with continued-release formulations.[1]

A bubbly floating gastro-retentive dosage form is developed for CFP and assessed in rodents. The outcomes showed a potential for development of gastro retentive dosage using Eudragit S100 polymer.[2] It has also been demonstrated successfully the release of the drug CFP from mucoadhesive gastro retentive tablets using Sodium Alginate and Chitosan in a controlled manner.[3]

Literature also confirms the advantages, restrictions, showcased dosage form and patents of floating and non-floating gastro-retentive drug delivery system.[4-6]

The formulator's has highlighted the benefits of gastro-retentive drug delivery system including the organic and formulation factors influencing gastric maintenance and ways to deal with configuration of single-unit and multiple unit floating systems.[7]

CFP is an orally administered extended-spectrum; semi-synthetic antibiotic of the cephalosporin class has a short elimination half-life. It has high solubility, chemical and enzymatic stability. It is absorbed well in acidic pH which makes it suitable candidate for formulating in a gastro retentive dosage form for improving bioavailability. PMG peel powder is used as a polymer in formulations as support release material. It contains Phenolic composites like punicalagins, gallic acid, catechin, epigallocatechin gallate, quercetin, rutin, anthocyanidin's and different flavonoids and acts as a neutral polymer.[8]

MATERIALS

CFP was received as a gift sample from Lupin Pharma Ltd., Aurangabad. Pomegranate peel powder was purchased from Heilen Biopharm. Hydroxy propyl methyl cellulose K4M, Acacia, Sodium bicarbonate,

Int. J. Pharm. Investigation, 2020;10(3):294-299 *Original Article*

Formulation and Evaluation of Gastro-Bilayer Floating Tablets of Losartan Potassium as Immediate Release Layer and Ramipril Hydrochloride as Sustained Release Floating Layer

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ABSTRACT

Objectives: A sustained release Gastro-bilayer floating tablets with reduced dosing frequency and increased drug bioavailability is developed. The dosage form is suitable for the release of two drugs simultaneously in a single dosage unit i.e. Losartan Potassium and Ramipril Hydrochloride. The SeDeM system for selection of powder blend for direct compression gave the parameter index value of ≥0.5 which is considered as best in terms of compression properties. The prepared dosage form provided sustained effect of the drug for 12 hr by Non-Fickian, controlled diffusion and swollen matrix. Peppa's release model is best suited for the final formulation of batches. Optimized formulation exhibited floating time of 12 hr and floating lag time of less than 1 min. *In-vitro* dissolution studies shows 96% of the both the drugs release. The swelling and erosion of polymers is studied by Scanning Electron Microscopy. The data obtained from Analysis of variance demonstrated the significance of the model with a *P*-value of less than 0.05. **Methods:** SeDeM system was adopted on powder blend before direct compression for preparation of tablet, the hydroxyl propyl methyl cellulose was used as a rate-controlling polymer and a mixture of citric acid and Sodium bicarbonate formed the floating layer. **Results:** Radius values through SeDeM diagram was plotted and index values are calculated and resulted in an index value of ≥0.5. The pre-compression and post compressional parameters are as per Indian Pharmacopeia specifications. The best formulation for gastric bilayer tablet had a combination of Hydroxy propyl methyl cellulose K15M and Sodium Carboxy methyl cellulose which gave 99.57% drug dissolution within 12 hr. **Conclusion:** Gastro-Bilayer Floating Tablets of Losartan as Immediate Release layer and Ramipril as sustained-release floating layer are successfully developed. The problem of poor solubility of drugs can be solved by optimization of blend through SeDeM expert System. Hydroxy propyl methyl cellulose K15M, K4M and Carbopol 934 are helpful in achieving the sustained effect of the drug for 12 hr by Non-Fickian, controlled diffusion and swollen matrix. Peppa's release model is best suited for the final formulation batches based on the drug release mechanisms.

Key words: Gastro-Bilayer Floating Tablets, Losartan Potassium, Ramipril Hydrochloride, SeDeM, Sustained Release Floating Layer.

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INTRODUCTION

The aim of the study is to formulate controlled release Gastro-bilayer floating tablets that will reduce the dosing frequency and increase drug bioavailability for treatment of chronic hypertension.[1] The dosage form is suitable for release of two different types of drugs, wherein one layer is of immediate release which releases Losartan Potassium and the second sustained release layer is of Ramipril Hydrochloride in a single dosage unit. This type of dosage form has many advantages over the conventional single-layered Tablets. Losartan potassium is an angiotensin II receptor antagonist and Ramipril Hydrochloride is angiotensin-converting enzyme-inhibitor when these two drug are used in combination blocks total production of angiotensin mostly responsible for hypertension.[2] The advantages of such bilayer dosage form is mentioned in most of the literature and further up till now this type of combination formulation is still not available therefore such type of dosage form is developed.[3] Formulating bilayer dosage form may contribute to cost-effectiveness by eliminating different coatings required to get sustained-release action.[4] SeDeM expert system is a predictive tool that can be applied for evaluation of suitability, critical quality attributes and the behavior of the drug material and excipients used for the formulation development of bilayer tablets by direct compression having an impact on the final product.[5] This system provides a physical profile of powder material intended to be used and suggests their flow performance. SeDeM expert system technique may reduce the number of preformulation trials and may be coined as time-saving and cost saving in the prediction of deficient part in powder blend as compared to conventional trial and error approaches or software-based prediction models.[6]

MATERIAL

Ramipril Hydrochloride was obtained as a gift sample from Lupine pharmaceutical Industries, Aurangabad, India. Losartan Potassium was purchased from Aristo Laboratories, Mumbai, India. Hydroxy propyl methyl cellulose, Carbopol 934p and Polyvinyl Pyrrolidone-K30 were obtained from the Shreya life Sciences as gift samples.

METHODS

Preparation of Gastro-bilayer floating matrix Tablets

Preparation of Immediate-release layer

The immediate-release layer of Losartan potassium was prepared by mixing drug along with the different excipients and SeDeM expert system applied for evaluation of suitability, critical quality attributes and the behavior of the drug material and excipients used for the

Int. J. Pharm. Investigation, 2020;10(2):192-196 *Original Article*

Stabilization of Rosuvastatin Calcium Formulation by Prevention of Intermolecular Esterification: An Experimental Design

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Department of Quality Assurance, Y.B. Chavan College of Pharmacy, Rauza Bagh, Aurangabad, Maharashtra, INDIA.

ABSTRACT

Background: Rosuvastatin calcium is the most effective molecule for the treatment and management of Hypercholesterolemia. This drug easily degrades by exposure to moisture and light and forms unstable formulation by formation of oxidation products, this degradation accelerates in acidic environment of the formulation. The acid form of Rosuvastatin calcium which is the active moiety has a tendency of conversion into lactone form Inactive moiety through "intermolecular esterification" in acidic environment. Synthetic alkalising agents such as tribasic magnesium phosphate is usually added in the tablet formulation to overcome this degradation, but alkalizing agents are harmful to gastric mucosa. **Methods:** Natural stabilizers such as Xanthan Gum, Chitosan and Guar Gum are used for stabilization. Selection of optimum stabilizer and drug/stabilizer ratio is obtained by quality by design approach by implementing 3^2 factorial design. Xanthan gum and Chitosan were selected as Critical quality attributes and material attributes with fixed Rosuvastatin Calcium concentration. **Results:** Tablets consisting of Xanthan Gum and Chitosan in 1:1.4 ratios exhibited maximum stabilization after stability study with 99% assay and dissolution was enhanced by more than 20% i.e. 98% within 30 min as compared to marketed tablets. Statistical test by Analysis of Variance revealed that the model is significant with *p* value <0.0001 and F-value of 50.58 that the model terms are significant for one factor i.e. the concentration of chitosan as natural stabilizer. **Conclusion:** The stabilisation of Rosuvastatin calcium was achieved by natural stabilizer i.e. chitosan with QBD approach and the stable tablet formulation was successfully prepared.

Key words: Rosuvastatin calcium, Quality by Design, Design of Experiment, Natural stabilizers, Chitosan, Xanthan Gum.

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MATERIALS AND METHODS

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Methods

Characterisation of Procured Drug

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PYRIDINE AND BENZOISOTHIAZOLE BASED PYRAZOLINES: SYNTHESIS, CHARACTERIZATION, BIOLOGICAL ACTIVITY, MOLECULAR DOCKING AND ADMET STUDY

Pintu G. Pathare[a], Sunil U. Tekale[a], Manoj G. Damale[b], Jaiprakash N. Sangshetti[c], Rafique U. Shaikh[d], László Kótai[e], Rajendra P. Pawar[a]*

Keywords: Pyrazolines; antioxidant; antimicrobial; molecular docking.

Synthesis, characterization, antioxidant and antimicrobial activities of novel pyrazolines and phenylpyrazoline containing substituted pyridine and piperazine benzoisothiazole moieties have been reported. When these synthesized compounds were exposed for antioxidant screening, some among them exhibited prominent DPPH radical scavenging activity and superoxide radical (SOR) scavenging activity where ascorbic acid used as standard. During the antimicrobial screening compounds, some derivatives were found to be very active against *Cryptococcus neoformans*, which was supported on the basis of higher free binding energies with methionyl-tRNA synthetase.

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INTRODUCTION

Pyrazolines, a class of five-membered heterocycles, is recognized for never-ending research and development in terms of therapeutic potential. As a result, pyrazolines have become an obvious core of numerous drugs having diverse activities.[1] The broad spectrum of activities shown by the pyrazolines encourages searchers to modify their structures by building with some biologically important heterocyclic compounds like alkyl, aromatic, heterocyclic rings and other groups at different positions on the ring which helps to create a novel class of desired compounds.

Pyrazoline and its analogs act as significant pharmacies and synthons in the field of organic chemistry and drug designing. They are well-acknowledged for pharmacologically interesting heterocyclic systems through recent literature survey.[2] Pyrazolines possess a wide range of biological properties such as anticancer,[3-5] anti-inflammatory,[6] antibacterial,[7] anti-depressive and anticonvulsant,[8] antimicrobial,[9] antinociceptives[10] and enzyme inhibitors.[11] Thus pyrazolines are well recognized for various biological activities.[12,13] Hence, synthesis of new heterocycles bearing pyrazolines remains the core area of research. Numerous methods were developed for the synthesis of pyrazoline and their synthetic counterparts, among which the classical method involves cyclization of the Michael acceptor unit (chalcone) with hydrazine hydrate or phenylhydrazine in the presence of cyclizing agents like acetic acid or simple heating procedure.[14]

Thus, considering the biological significance of pyrazolines and in continuation of our efforts in the development of biologically active entities;[15-17] in the present work, we report the synthesis, characterization, antimicrobial and antioxidant activities of some novel pyrazolines bearing pyridine and benzoisothiazole containing piperazine moiety.

The results of biological activities were supported by molecular docking studies. ADMET study was performed to know the drug-likeness and toxicity profile of the synthesized compounds.

MATERIALS AND METHODS

Melting points were recorded in an electrothermal melting point apparatus and were uncorrected. The consumption of starting material and formation of the products was monitored on silica precoated thin layer chromatography plate using 40 % ethyl acetate : n-hexane as the mobile phase. FTIR spectra were recorded using KBr pellets (100 mg) on Shimadzu FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer and chemical shifts were expressed in δ ppm with reference to tetramethylsilane (TMS) as the internal standard.

In the antimicrobial activity, the zones of inhibition and the antioxidant activity performed spectrophotometrically were expressed as mean ± SD of three replicates.

General procedure for the synthesis of pyrazolines

A mixture of chalcone (0.7g, 0.16 mol) and hydrazine hydrate (1.0 mL) or phenylhydrazine in ethanol (1.0 mL) was stirred for 2 h at 25-35 °C. Sometimes heating at 45-50 °C was required for dehydration. The precipitated solid was filtered off to get a crude product which was crystallized with hot ethanol to get pure white color material.

PYRIDINE AND BENZOISOTHIAZOLE BASED PYRAZOLINES: SYNTHESIS, CHARACTERIZATION, BIOLOGICAL ACTIVITY, MOLECULAR DOCKING AND ADMET STUDY

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Punica granatum Peel Extract Ameliorates Doxorubicin Induced Cardiotoxicity

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Abstract: Doxorubicin (DOX) usefulness is limited due to its cardiotoxic effects. In the present study the protective effects of ethanolic peel extract of *Punica granatum* (EPEPG) against DOX-induced cardiotoxicity in rats was investigated. We studied the effect of ethanolic peel extract of *Punica granatum* (100 mg/kg body weight, p.o.) and vitamin E as reference standard drug on doxorubicin induced cardiotoxicity by testing the heart weight/body weight ratio, biochemical parameters and histopathological changes. The biochemical parameters, which were measured in the blood were blood glutathione, creatine kinase (CK-MB) and lactate dehydrogenase (LDH) and in heart were, tissue glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA) in all the animals. Before and after treatment with (EPEPG, 100 mg/kg) reduced the activity of both creatine kinase (CK-MB) and lactate dehydrogenase (LDH) enzymes, and significantly decreased the levels of malondialdehyde (MDA). It also increased the levels of reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) in tissue and blood glutathione. Histopathological examination of heart tissue showed that treatment (before and after) with (EPEPG) ameliorated the effect of DOX administration on cardiac tissue; cardiac myocytes looked more or less similar to those of control. The above observations suggest that DOX induced cardiotoxicity occurs due to oxidative stress and ethanolic peel extract of *Punica granatum* has produced cardio protective activity.

Key words: Ethanolic peels extract *P. granatum,* doxorubicin, cardiotoxicity, antioxidant.

Introduction

Doxorubicin appears to be especially effective in the therapy of solid tumors and is considered one of the most important drugs currently used in cancer chemotherapy [1]. Several hypotheses have been proposed to explain the cardiotoxic effect of anthracyclines. Doxorubicin induced myocardial dysfunction has been suggested to involve free radical formation [2] and lipid peroxidation [3]. The involvement of free radical formation has been suggested for the mechanism of doxorubicin induced cardiotoxicity, where doxorubicin produces reactive oxygen species that damage myocardial tissue by nonspecific oxidation of membrane and cytosol molecules, ultimately leading to cell death. Handa and Sato first showed that the metabolism of doxorubicin and other quinone containing compounds could lead to free radical generation in a microsomal NADPH- oxidase system [4].

Punica granatum Linn, pomegranate (Punicaceae), a common fruit in the Mediterranean and Iran, is widely used for therapeutic formulae, cosmetics, and food seasoning. The pomegranate fruit, which was readily purchased from conventional remedy markets, was regularly used as an astringent [5], for parasites elimination [6] and as a fever reducing agent. The pharmacological functions of pomegranate include antioxidation [7], anti-lipoperoxidation [8].

Pomegranate juice and peel contains antioxidants such as soluble polyphenols, tannins, and

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Research Article

FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING FILM OF ROSUVASTATIN CALCIUM USING QBD APPROACH

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ABSTRACT

The aim of the present study was to design the mouth dissolving film of Rosuvastatin calcium (RC) by applying quality by design (QbD) approach. The mouth dissolving film was prepared using solvent casting method. The critical quality attributes (CQAs) and quality target product profiles (QTPP) of RC mouth dissolving films were defined based on previous studies. Plackett-Burman experimental design was used for initial screening of process and formulation variables. The screened variables were further optimized using 3^2 full factorial designs. The variables influencing formulation of film was HPMC E5 and PVP K30. The design space was determined using statistical tool and optimized formulations were prepared within the design space. The optimized films showed all the evaluation parameters within the QTPP. The results indicated that as long as formulation variables remain within the design space, mouth dissolving film of RC with desired characteristics and quality requirement could be formulated.

Keywords: Plackett-Burman; Rosuvastatin calcium; 3^2 full factorial design; quality by design; Mouth dissolving film.

INTRODUCTION

The oral route of drug administration is the most preferred route of drug delivery amongst all the routes of drug administration. Oral mouth dissolving film (MDF) is gaining popularity because of high patient compliance in treating paediatric and geriatric patients and provides immediate release as it offers quick onset of action[1,2]. The film dissolve or disintegrate quickly in the oral cavity and the fast dissolving action is due to quick wetting of the film in the moist oral cavity, leading to fast dissolving action. This also prevents choking or spitting out problems associated with solid oral dosage forms[3,4].

The MDF can be formulated using a variety of film formers and other excipients and the most common technique for its preparation is using solvent casting[4]. Variety of polymers and their different grades can be used in the formation of MDF depending upon the need of disintegration time, drug loading and mechanical properties[4]. Plasticizers added in MDF improve the flexibility and reduces the brittleness of the strip. They significantly enhance film forming properties through a reduction in the glass transition temperature of the polymers[5]. Variability in type and grade of polymer and plasticizer concentration may impact the MDF critical quality attributes (CQA) such as thickness, % elongation at break, yield stress, Young's modulus, folding endurance and dissolution rate of the film. The present study was carried out to investigate the impact of the formulation and process variables on the quality of mouth dissolving film using Quality by Design (QbD) approach.

Rosuvastatin is a synthetic, high potent third generation statin with cholesterol-lowering activity. Rosuvastatin competitively inhibits hydroxyl methyl glutaryl-coenzyme A (HMG-CoA) reductase which catalyses the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis, therefore, it is used for high cholesterol, blood lipid metabolic disorder and pure high triglyceride blood disease treatment[6,7]. Clinical studies have proven that fast disintegrating tablets can enhance patient compliance, provide an immediate onset time of action, and increase bioavailability[8]. Hence it was decided to use Rosuvastatin as a model candidate for oral dissolving film.

Quality by Design (QbD) is a scientific approach for product development. It ensures the quality of the product systematically by providing thorough understanding the compatibility of all the components and processes involved in manufacturing. QbD provides detailed insight on quality throughout the development process[8].

Typically, it involves identification of quality target product profile (QTTP) that are critical from the patient's perspective and helps in establishing the relationship between formulation/manufacturing variables and CQAs to consistently deliver a drug product to the patient[9]. In addition to the mechanical properties (yield stress, % elongation at the break and Young's modulus), a short disintegration time and fast drug dissolution constitute the desired QTPP of Rosuvastatin MDF product.[10] It is also important to identify critical material attributes (CMA) and critical process parameters (CPP) based on process and product understanding.

The aim of the present study was to design and optimize the Rosuvastatin calcium MDFs by using QbD. In the present study, Rosuvastatin calcium MDFs was developed, and a design space was established through a factorial design for optimization using Design Expert 9.0.3.1 software (Stat-Ease, Minneapolis, MN, USA). In our preliminary study, we investigated factors that could

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MDPI

Article

Preparation, Optimization, and In Vivo Evaluation of Nanoparticle-Based Formulation for Pulmonary Delivery of Anticancer Drug

Nazimuddin Chishti [1], Satveer Jagwani [2], Dinesh Dhamecha [2], Sunil Jalalpure [2,3] and Mohamed Hassan Dehghan [4,*]

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Abstract: *Background and Oobjectives:* Lung cancer, a pressing issue in present-day society due to its high prevalence and mortality rate, can be managed effectively by long-term delivery of anticancer agents encapsulated in nanoparticles in the form of inhalable dry powder. This approach is expected to be of strategic importance in the management of lung cancer and is a developing area in current research. In the present investigation, we report on the formulation and characterization of docetaxel inhalable nanoparticles as a viable alternative for effective treatment of non-small cell lung cancer as a long-term delivery choice. *Materials and Methods:* Poloxamer (PLX-188) coated poly(lactic-co-glycolic acid) (PLGA) nanoparticles containing docetaxel (DTX-NPs) were prepared by simple oil in water (o/w) single emulsification-solvent evaporation process. The nanoparticles were collected as pellet by centrifugation, dispersed in mannitol solution, and lyophilized to get dry powder. *Results:* Optimized DTX-NPs were smooth and spherical in morphology, had particle size around 200 nm, zeta potential around −36 mV, and entrapment efficiency of around 60%. The in vitro anticancer assay was assessed and it was observed that nanoparticle-based formulation exhibited enhanced cytotoxicity when compared to the free form of the drug post 48 h. On examining for in vitro drug release, slow but continuous release was seen until 96 h following Higuchi release kinetics. DTX-NPs were able to maintain their desired characteristics when studied at accelerated conditions of stability. *Conclusions:* In-vivo study indicated that the optimized nanoparticles were well retained in lungs and that the drug level could be maintained for a longer duration if given in the form of DTX-NPs by the pulmonary route. Thus, the non-invasive nature and target specificity of DTX-NPs paves the way for its future use as a pulmonary delivery for treating non-small cell lung cancer (NSCLC).

Keywords: PLGA nanoparticles; Lyophilization; non-small cell lung cancer; pulmonary

1. Introduction

Administration of drug loaded nanoparticles by inhalation route is being exploited far and wide for delivery of chemotherapeutics [1–3], insulin, proteins and peptides, antibiotics, vaccines, etc. [4,5]. Inhalable nanoparticles have been a useful approach for systemic drug delivery such as in pain

Synthesis, Biological Investigation and Docking Study of Novel Chromen Derivatives as Anti-Cancer Agents

Authors: Dube, Pritam N.; Sakle, Nikhil S.; Dhawale, Sachin A.; More, Shweta A.; Mokale, Santosh N.
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Background: According to the latest global cancer data, cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. Among that female breast cancer ranks as the fifth leading cause of death (627000 deaths, 6.6%). The main causative factor involved in breast cancer development and progression is the Estrogen Receptor (ER) which is the essential target for anti-cancer drug discovery. Since millennia ER-α has been considered as an oncology mark for the treatment of breast cancer.

Methods: A series of novel 6-methyl-3-(3-oxo-1-phenyl-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propyl)-2Hchromen-2-one was designed, synthesized and screened for their anti-breast cancer activity against estrogen receptor-positive MCF-7, ZR-75-1 and negative MDA-MB-435 human breast cancer cell lines. Estrogen level of all the potent cytotoxic compounds were measured on day 30 of intoxication was compared with the control and N-

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ORIGINAL ARTICLE

Caesalpinia pulcherrima Arrests Cell Cycle and Triggers Reactive Oxygen Species-Induced Mitochondrial-Mediated apoptosis and Necroptosis via Modulating Estrogen and Estrogen Receptors

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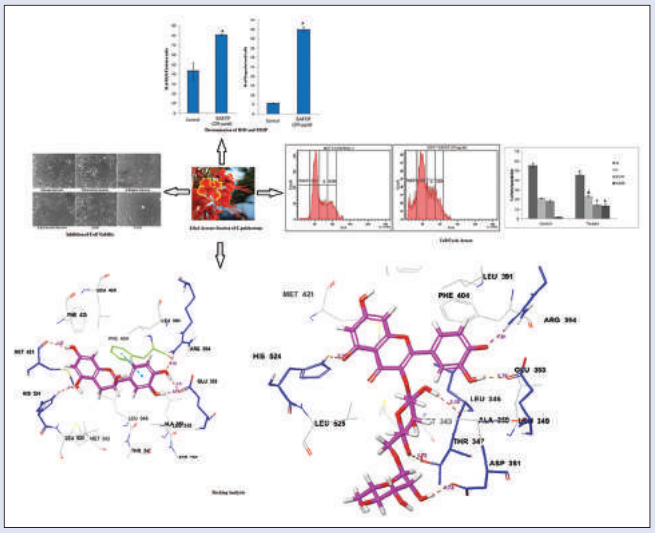
ABSTRACT

Background: *Caesalpinia pulcherrima* belonging to the family *Fabaceae* is used in India as a traditional medicine for a variety of ailments. Globally, traditional medicines are presently being used for the treatment of cancer. **Objective:** The present study was aimed at investigating the chemomodulatory potential of *C. pulcherrima* flowers in breast cancer and explaining its possible mechanism. **Materials and Methods:** The cytotoxic potential of ethyl acetate fraction of *C. pulcherrima* (EAFCP) flower was tested in MCF-12A (normal breast), MCF-7 (estrogen receptor [ER] positive), and MDA-MB-453 (human epidermal growth factor receptor 2 positive) human breast cancer cells by sulforhodamine B assay. Chemomodulatory potential was evaluated *in vivo* against N-methyl-N-nitrosourea (MNU)-induced mammary carcinoma in female Sprague Dawley® rats. The mechanism for anticancer potential was screened by *in vitro* studies involving Annexin V-FITC assay (apoptosis), cell cycle patterns, intracellular reactive oxygen species, and mitochondrial membrane potential measurement (FACS based) followed by docking study on estrogen receptor-alpha (ER-α). **Results:** The fractions showed perceptible cell growth inhibition potency (IC_{50} <50 μg/ml) in MCF-7 breast cancer cells. In MNU-treated animals, antioxidant enzymes and histological examination showed statistically significant ($P < 0.001$) changes. Treatment of MCF-7 cells with EAFCP reduced cell growth rate by a mechanism associated with both apoptotic and necrotic cell death. Molecular docking study further showed that rutin and catechin have a comparable binding affinity for the ER-α. **Conclusion:** In this study, we confirmed that EAFCP was most effective in reducing cell viability, scavenging physiological oxidant species, and causing mitochondria-mediated apoptosis and necroptosis in MCF-7 cell by selectively modulating the functions of ER-α.

Key words: Antioxidant, breast cancer, estrogen receptor modulator, high-performance liquid chromatography, histopathology

SUMMARY

- Ethyl acetate fraction of Caesalpinia pulcherrima (EAFCP) flower showed cytotoxic potential against breast cancer cells by sulforhodamine B assay. The anticancer and antioxidant potential of EAFCP flower was evaluated against N-methyl-N-nitrosourea-induced mammary cancer in female Sprague Dawley rats. The in vitro results of the present study showed that EAFCP can induce mitochondrial-mediated apoptosis and necroptosis through reactive oxygen species generation with loss of mitochondrial membrane potential in MCF-7 via modulating the functions of estrogen receptor-alpha *in silico*.



Abbreviations used: EAFCP: Ethyl acetate fraction of *Caesalpinia pulcherrima*; MNU: N-methyl-N-nitrosourea; ROS: Reactive oxygen species; ER-α: Estrogen receptor-α; HPLC: High-performance liquid chromatography; TBARS: Thiobarbituric acid-reactive substances; HP: Hydroperoxides; LPO: Lipid peroxidation; CAT: Catalase; SOD: Superoxide dismutase; NBT: p-nitro blue tetrazolium chloride; GP_X: Glutathione peroxidase; GST: Glutathione-S-transferase; CDNB: 1-Chloro-2,4-dinitrobenzene; GR: Glutathione reductase; GSH: Reduced glutathione; MMP: Mitochondrial membrane potential; H and E: Hematoxylin and eosin; TB: Toluidine blue; LBD: Ligand-binding domain; TAM: Tamoxifen; ADR: Adriamycin; ANOVA: Analysis of variance.

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INTRODUCTION

Breast cancer is one of the most common malignancies in the world and a major cause of cancer-related deaths in women. It has been observed that estrogen level is an important factor in the initiation and development of breast cancer. Estrogen receptor-alpha (ER-α) is a well-characterized mediator in breast cancer for the proliferation of cells.[1] On the other hand, estrogens and estrogenic compounds are a subject of

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ONE POT BF_3.MeCN CATALYZED SOLVENT FREE SYNTHESIS OF 3,4-DIHYDROPYRIMIDINE-2-ONE ANALOGUES

Ajit A. Kharpe[a], Tukaram S. Choudhare[a], Santosh N. Mokale[b] and Prashant D. Netankar[a]*

Keywords: BF_3.ACN, solvent-free, 3,4-dihydropyrimidine-2-one.

One-pot solvent free three components coupling of aryl aldehydes, β-dicarbonyl compounds, urea or thiourea was performed to afford corresponding 3,4-dihydropyrimidine-2-ones and their sulfur analogs 3,4-dihydro-pyrimidine-2-thiones. It is the first report of BF_3.ACN catalyzed the solvent-free synthesis of pyrimidone analogs.

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INTRODUCTION

The multicomponent reactions (MCRs) are established as a simple, convenient method in synthetic chemistry.[1-3] Furthermore, MCRs are extremely economical, high yielding, less time consuming and with less side reactions.[4-5] Therefore, the design of new MCRs with the green procedure has engaged huge attention, especially in the areas of drug discovery, organic synthesis and material science.

Pyrimidines have extremely biological importance,[6-11] they and their analogs are considered as important bioactive heterocycles[-+]exhibiting interesting biological activities like antiviral,[12] antiprotozoan,[13] anti-proliferative,[14] cytotoxic activity[15] and anti-inflammatory .[16]

As a part of our ongoing efforts to develop new routes for the synthesis of heterocyclic compounds,[17] herein, we like to report a solvent-free single step multicomponent synthesis of 3,4-dihydropyrimidine-2-one and 3,4-dihydropyrimidine-2-thione derivatives.

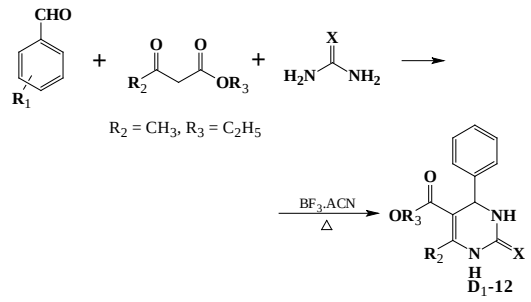

Figure 1. BF_3.ACN catalyzed solvent-free synthesis 3,4-dihydropyrimidine-2-one and 3,4-dihydropyrimidine-2-thione derivatives.

It is the first report of solvent-free condensation of β-keto esters, aryl aldehydes and urea or thiourea in the presence of BF_3.MeCN (BF3*ACN)) as an effective catalyst (**Figure 1)**.

RESULTS AND DISCUSSION

Initially, a mixture of benzaldehyde, ethyl acetoacetate and urea was refluxed in ethanol in the presence of BF_3.ACN (Table 1) to obtain the corresponding 3,4-dihydropyrimidine-2-one derivative. The product was obtained in good yield (90 %). Solvent optimization studies of the above reaction were carried out and are summarized in Table 1. The reaction proceeded very well in solvent-free condition (Table 1, 97%).

Table 1. Solvent optimization for one-pot synthesis 3,4-dihydropyrimidine-2-one in the presence of 10 mol % BF3.MeCN catalyst[a]

Solvent	Condition	Time, min	Yield, %[b]
Ethanol	Reflux	60	90
Water	Reflux	130	85
Water : Ethanol (1:1)	Reflux	120	88
Methanol	Reflux	90	88
Acetonitrile	Reflux	35	92
Solvent Free	90 °C	20	97

a) Experimental conditions: benzaldehyde (2 mmol), urea (3 mmol), ethyl acetoacetate (2 mmol); b) Isolated yield.

Similarly, catalyst optimization studies of the above reaction were also carried out in solvent-free conditions and are summarized in Table 2. When catalyst was used from 5 mol%, 10 mol%, 15 mol% both yield and rate of the reaction was increased. However, the further increment of catalyst amount did not appreciably affect the yield and rate of the reaction. Finally, among all the experimental variations, the 10 mol% BF_3.ACN solvent-free condition at 90 ° C temperature gave the best results with 97% yield (Table 2).

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Current Drug Discovery Technologies, **2019,** *16,* **00-00**

REVIEW ARTICLE

Targeting Small Molecule Tyrosine Kinases by Polyphenols: New Move Towards Anti-tumor Drug Discovery

Nikhil S. Sakle[1], Shweta A. More[1], Sachin A. Dhawale[1] and Santosh N. Mokale[1,*]

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ARTICLE HISTORY

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Abstract: ***Background*****:** Cancer is a complex disease involving genetic and epigenetic alteration that allows cells to escape normal homeostasis. Kinases play a crucial role in signaling pathways that regulate cell functions. Deregulation of kinases leads to a variety of pathological changes, activating cancer cell proliferation and metastases. The molecular mechanism of cancer is complex and the dysregulation of tyrosine kinases like Anaplastic Lymphoma Kinase (ALK), Bcr-Abl (Fusion gene found in patient with Chronic Myelogenous Leukemia (CML), JAK (Janus Activated Kinase), Src Family Kinases (SFKs), ALK (Anaplastic lymphoma Kinase), c-MET (Mesenchymal- Epithelial Transition), EGFR (Epidermal Growth Factor receptor), PDGFR (Platelet-Derived Growth Factor Receptor), RET (Rearranged during Transfection) and VEGFR (Vascular Endothelial Growth Factor Receptor) plays major role in the process of carcinogenesis. Recently, kinase inhibitors have overcome many problems of traditional cancer chemotherapy as they effectively separate out normal, non-cancer cells as well as rapidly multiplying cancer cells.

Methods**:** Electronic databases were searched to explore the small molecule tyrosine kinases by polyphenols with the help of docking study (Glide-7.6 program interfaced with Maestro-v11.3 of Schrödinger 2017) to show the binding energies of polyphenols inhibitor with different tyrosine kinases in order to differentiate between the targets.

Results**:** From the literature survey, it was observed that the number of polyphenols derived from natural sources alters the expression and signaling cascade of tyrosine kinase in various tumor models. Therefore, the development of polyphenols as a tyrosine kinase inhibitor against targeted proteins is regarded as an upcoming trend for chemoprevention.

Conclusion**:** In this review, we have discussed the role of polyphenols as chemoreceptive which will help in future for the development and discovery of novel semisynthetic anticancer agents coupled with polyphenols.

Keywords: Tyrosine kinase, Polyphenols, Docking analysis.

1. INTRODUCTION

Cancer is a complex disease which involves genetic and epigenetic alterations that allow cells to escape normal homeostatic [1]. Signaling pathways play a vital role in higher-level cellular processes, like apoptosis, proliferation and development. Modification in signaling pathways can be fuel for cancer progression as it is intimately involved in cell growth, cell division and cell death [2]. Another most common path in cancer development and progression is mutation in number of genes. Mutated genes are frequently found in different human cancers followed by activation thus cellular abnormality leading to cancer initiation [3]. Tyrosine kinases are the main mediators of the signaling pathway and play vital roles in different biological processes. Normally these signaling pathways avoid deregulated proliferation towards apoptotic stimuli. Recent studies have shown the involvement of tyrosine kinases in the pathogenesis of cancer. In cancer, these signaling cascades are genetically and epigenetically altered. As a result, abnormal enhanced signaling gives these enzymes a leading oncoprotein status, ensuing in the faulty of signaling networks [4].

2. BIOACTIVE NATURAL PRODUCTS FROM PLANTS

Natural Products, particularly plants, have multiple biological functions and are used for the treatment of various diseases in developed and developing countries from ancient

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Chemomodulatory effects of *Alysicarpus vaginalis* extract via mitochondria-dependent apoptosis and necroptosis in breast cancer

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ABSTRACT

The present study intended to assess the anticancer potential of *Alysicarpus vaginalis* ethyl acetate fraction (AVEAF) in breast cancer cell lines (MCF-7 and MDA-MB-453) and against *N*-methyl-*N*-nitrosourea (MNU) induced mammary carcinoma in Sprague-Dawley rats which resemble the human estrogen dependent breast cancer. The SRB assay showed that the maximum growth inhibition rate of AVEAF on MCF-7 cell was 27.12 at 100 µg/ml. Flow cytometry analysis observed that AVEAF induced the cell cycle arrest at the S phases and decreased in mitochondrial membrane potential on the MCF-7 cells. AVEAF elevated intracellular ROS level in the MCF-7 cells which were reversed with *N*-acetycysteine (2 mM) pretreatment indicating that AVEAF induced mitochondrial-mediated apoptosis via augmentation of intracellular ROS. Western blotting exhibited that AVEAF increased the expression of pro-apoptotic protein Bax while decreasing anti-apoptotic proteins Bcl-2 and Bcl-xL expression which promoted the cleavage of caspase-9, PARP1, RIPK 1, and RIPK 3. Additionally, AVEAF exerted anticancer effect on tumor-bearing rats and the tumor inhibition rate is 50%. Data of the study indicate that AVEAF exhibits In Vitro and In Vivo anticancer activities that associate with its ROS-mediated mitochondrial-mediated intrinsic pathway of apoptosis and necroptosis in MCF-7 cells and may serve as a potential against breast cancer.

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Introduction

In the growing era of cancer, breast cancer is the most common cause of death in the women. As of noted, more than 3.1 million women with a history of breast cancer have been reported in the United States (January 2018; U.S. Breast Cancer Statistics, 2019) (1).Whereas current Indian data have shown that one in 22 women develop breast cancer (2). Natural products are complementary and alternative sources widely accepted and used in cancer therapy in developed countries due to the variety in the structure and the biological mechanism of action of their compounds (3). It has been observed that such natural products can function as chemomodulatory and chemopreventive agents that affect the processes of mammary tumorigenesis, like initiation, promotion, and progression (4). Plants are the main source of bioactive metabolites like phenolic, quinones, glucosinolates, terpenoids, and alkaloids with antioxidant and anticancer activities (5). The carcinogens may act through the production of reactiveoxygen species (ROS). Increased production of ROS was found to play key roles in damage and loss of function of tissues and organs (6). ROS may also lead to damage cellular constituents like proteins, DNA, and lipid, thus, initiating various chronic diseases. Traditionally whole plant has been used for the treatment of cytotoxicity, renal calculi, sepsis, diuretic, kidney disorders, skin related problems, leprosy, hepatoprotective, and pulmonary troubles. Exploration of phytoconstituents possessing both antioxidant and anticancer properties is of great remedial importance (7–9).

The present study investigated whether *Alysicarpus vaginalis* ethyl acetate fraction (AVEAF) could serve as a more effective cancer chemomodulatory for plant-derived anticancer agents. The study also aimed to find the possible mechanism of action of this fraction during tumor regression in an efficient way In Vitro and In Vivo model.

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/hnuc

Pharmaceutical Nanotechnology, **2019**, *7,* 343-361

RESEARCH ARTICLE

Formulation Optimization and Biopharmaceutical Evaluation of Imatinib Mesylate Loaded β-cyclodextrin Nanosponges

Milind Kamble[1,*], Zahid Zaheer[1,*], Santosh Mokale[1] and Rana Zainuddin[1]

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Abstract: ***Background*:** Many researchers have prepared and evaluated nanosponges and claimed their advantages as an effective drug carrier, especially it was observed prominently in case of anti-fungal drugs. The materials employed to synthesize nanosponges were mainly crosslinking agents, different beta-cyclodextrin and other cellulose-based polymers. Many of them had used ratio proportions of cross-linking agents, d polymers to synthesize these nanosponges which ultimately produce a porous mesh-like network known as nanosponges where actually drug is encapsulated or loaded.

***Objective*:** In the present investigation, we observed the effect of various levels of cross-linking agents and beta-cyclodextrin concentrations on porosity, drug encapsulation, zeta potential and drug release by employing the quality by design approach to synthesize nanosponges rather than merely keeping both concentrations in proportions.

***Methods*:** We have slightly modified the method reported earlier *i.e*. melting method in which we have used rota evaporator receiver vessel for melting cross-linking agent and beta- cyclodextrin, rotated at 20 RPM at 100°C.

***Results*:** In a quality by design approach, we observed that out of four dependent variables *i.e*. porosity, drug loading, zeta potential and drug release, three significantly depend on the crosslinking of beta-cyclodextrin molecules which is highly appreciated by the amount of cross-linking agent present in the reaction. The pharmacokinetics of Imatinib loaded optimized nanosponges were compared with the reference product to observe the pattern of absorption and disposition.

***Conclusion*:** Nanosponges synthesized by optimization technique could be effective means of anti-cancer drug oral administration as they encapsulate the drug effectively and offer a prolonged release of drug which gradually releases the drug and avoids unnecessary exposure of the drug.

Keywords: Beta-cyclodextrin, crosslinking agents, drug encapsulation, imatinib mesylate, nanosponges, zeta potential.

1. INTRODUCTION

Nanosponges (NSPs) are a novel class of hyper-crosslinked polymer-based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. Cyclodextrin-based NSPs were first prepared by Li and Ma in 1998 [1]. From then many synthetic procedures explored NSPs by tapping different cross-linking agents and by using their different molar ratios [2-4]. NSPs provide prolonged release as well as improve drug bioavailability by modifying the pharmacokinetic parameters of actives as reported by Gursalkar *et al.* [5]. Cyclodextrin-based NSPs

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DEVELOPMENT OF HPLC METHOD FOR DETERMINATION OF TAMSULOSIN USING QUALITY BY DESIGN (QBD) APPROACH

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Keywords: Tamsulosin; QbD approach; RP-HPLC method; Box-Behnken model; ICH guidelines.

An HPLC method for Tamsulosin was developed by using a quality by design (QbD) novel concept. QbD has gained importance in recent times due to regulatory requirements in industrial application. Chromatographic separation of Tamsulosin was carried out by using C_8 column, and mobile phase used was methanol and distilled water (40:60 v/v) for proper separation process. Separation by using water as a solvent is beneficial as it is cost effective process and industrially applicable. In the development of the HPLC method, factors like injection volume, conc. of methanol, the column vent temperature is critical in maintaining. Hence the Box-Behnken optimization model was applied for the main, interaction and quadratic effects of these three factors on the selected response. The effect of these parameters was studied on the tailing factor (resolution). Results were analysed during a surface diagram. Verification of the software-generated result was done by taking six replicates of the run. Finally, the method was validated according to ICH guidelines.

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INTRODUCTION

Tamsulosin (5-[(2R)-2-{[2-(2-ethoxyphenoxy)ethyl]-amino}propyl]-2-methoxybenzene-1-sulfonamide) acts as adrenergic α-antagonists and is maximally used to treat symptomatic benign prostatic hyperplasia (BPH), which will help with the passage of kidney stones, and also for urinary retention. Tamsulosin acts as a selective antagonist at α_{1A} and α_{1B}-adrenoceptors in the prostate, prostatic capsule, prostatic urethra, and bladder neck. The three discrete α_1-adrenoceptor subtypes such as α_{1A}, α_{1B} and α_{1D} were also identified and their distribution differs between human organs and other tissue. It was noted that there are approximately 70% of the α_1-receptors in the human prostate, which were of the α_{1A} subtype. The blockage in these types of receptors will cause relaxation of smooth muscles in the bladder neck and prostate, and which thus decreases urinary outflow resistance in males. [1]

To the best of our knowledge HPLC method using a simple UV detector by applying the QbD approach is not available. As per International Conference on Harmonization (ICH) guidance on pharmaceutical development, "QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process control and which is dependent on quality risk management and its related science.[2] QbD has gained special attention in current times due to regulatory requirements in the research work.

US-FDA has accelerated QbD drive to encourage the risk-based approach and thorough understanding of processes, which is ultimately going to help the regulatory bodies in the review process.

The basic foundation behind QbD is that quality is 'designed' into the process at the onset to the establishment of the method by a thorough understanding of the effect of the various system parameters are studied. Effects are analyzed for their influence on the quality of the product that is desired. This is nothing but ultimately to establish the design space for the method. Design space is defined as a "multidimensional combination and interaction of input variables that have been demonstrated to assure quality."[3]Some of the methods have been reported for the development of the HPLC method for Tamsulosin.[4-14]

MATERIALS AND METHODS

Tamsulosin standard active pharmaceutical ingredient (API) was procured from Hetero Drugs Limited (Hyderabad) and solvents were supplied from Dodal Enterprises and Badar chemicals, Aurangabad. Distilled HPLC grade water was prepared in the quality assurance lab of Y. B. Chavan College of Pharmacy, Aurangabad. The instrument used for HPLC analysis work was performed by using a Shimadzu LC20 model with C_8 column of 4.6×150mm; 5µmplates

Tamsulosin sample preparation

The stock solution of Tamsulosin for optimization of experiments was prepared by accurately weighing 10mg of Tamsulosin and dissolving it in 100 mL of the mobile phase composing of methanol and water 40:60 combination.

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New *N*-phenylacetamide-incorporated 1,2,3-triazoles: [Et_3NH][OAc]-mediated efficient synthesis and biological evaluation†

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A facile, highly efficient, and greener method for the synthesis of new 1,4-disubstituted-1,2,3-triazoles was conducted using [Et_3NH][OAc] as a medium by the implementation of ultrasound irradiation *via* click chemistry, affording excellent yields. The present synthetic method exhibited numerous advantages such as mild reaction conditions, excellent product yields, minimal chemical waste, operational simplicity, shorter reaction time, and a wide range of substrate scope. The synthesized compounds were further evaluated for *in vitro* antifungal activity against five fungal strains, and some of the compounds displayed equivalent or greater potency than the standard drug. A molecular docking study against the modelled three-dimensional structure of cytochrome P450 lanosterol 14α-demethylase was also performed to understand the binding affinity and binding interactions of the enzyme. Furthermore, the synthesized compounds were evaluated for DPPH radical scavenging activity and antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain.

1. Introduction

1,2,3-Triazole, a five-membered heterocyclic ring system, is a very well-known biologically active pharmacophore constructed by the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, which is popular as a click chemistry reaction.[1] Over the last decade, 1,2,3-triazole has become one of the key structural motifs and is used in numerous fields including polymer chemistry,[2] material science,[3] and drug discovery.[4] 1,2,3-triazole-based molecules display various biological activities such as anti-fungal,[5,6] anti-bacterial,[6] anti-tubercular,[7] anti-inflammatory,[8] anti-allergic,[9] anti-HIV,[10] anti-cancer,[11] and anti-phytopathogenic.[12] Some marketed drugs have the 1,2,3-triazole unit in their structure, and these include Cefatrizine (a broad-spectrum antibiotic), Tazobactam (an antibiotic), and Carboxyamidotriazole (CAI) (a calcium channel blocker) (Fig. 1).

Azole drugs have broad-spectrum activities against most yeasts and filamentous fungi and are mostly used in antifungal chemotherapy.[13] Some well-known antifungal agents including fluconazole, voriconazole, ravuconazole, and itraconazole contain a 1,2,4-triazole ring in their structure, as shown in Fig. 2. However, their clinical uses have been restricted by their relatively high risk of toxicity, pharmacokinetic deficiencies, emergence of drug resistance, and undesirable side effects. These antifungal drugs inhibit CYP51, a key enzyme in the biosynthesis of ergosterol, through a mechanism in which the antifungal agent having a triazole scaffold is positioned perpendicular to the porphyrin plane with a ring nitrogen atom (N-4 of triazole) coordinated with a heme iron atom.[14] Over a couple of decades, the incidence of systemic fungal infections has increased due to cancer chemotherapy, organ transplantation, tuberculosis, and immunodeficiency virus (HIV) infection.[15] However, the extensive use of antifungal drugs has led to an increase in the resistance to these drugs.[16] Hence, there is an urgent need for developing new antifungal agents with effective activities, low toxicity, and minimum side effects.

Ionic liquids (ILs) are environment-friendly solvents because of their interesting properties and they can be used as alternatives to harmful organic solvents. Furthermore, they are useful in catalytic reactions[17] and organic synthesis[18] because of their

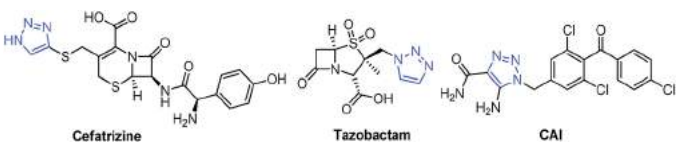

Fig. 1 Structures of drugs containing the 1,2,3-triazole unit.

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New 1,2,3-triazole-linked tetrahydrobenzo[*b*]pyran derivatives: Facile synthesis, biological evaluation and molecular docking study

Smita P. Khare, et al. ***[full author details at the end of the article]***

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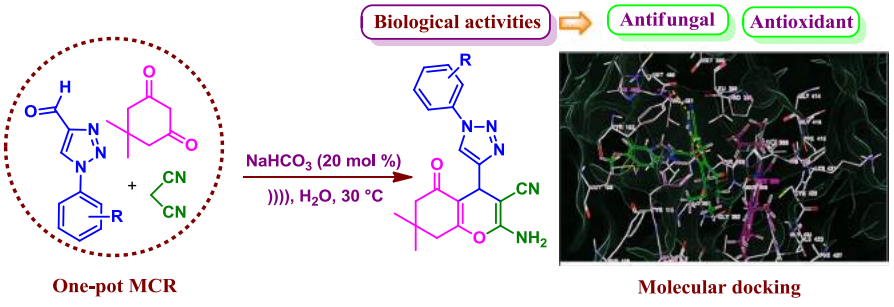
Abstract

An efficient ultrasound-promoted one-pot three-component synthesis of a series of new 1,2,3-triazole-linked tetrahydrobenzo[*b*]pyran derivatives as antifungal and antioxidant agents using $NaHCO_3$ has been described for the first time. The bioassay result indicates that the compounds **7b**, **7c**, **7i** and **7j** displayed excellent antifungal activity with lower MIC = 12.5 µg/mL than the reference drug miconazole. Most of the compounds from the series showed promising antioxidant activity with lower IC_{50} values in the range 12.47 ± 0.60–16.49 ± 0.44 µg/mL in comparison with butylated hydroxy toluene (BHT). Molecular docking studies revealed that most of the newly synthesized compounds showed excellent binding affinity with the potential target sterol 14α-demethylase (CYP51). Moreover, in silico adsorption, distribution, metabolism and excretion (ADME) study shows that the derivatives may possess drug like properties for further development of newer therapeutic agents.

Graphic abstract



Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-019-03906-0) contains supplementary material, which is available to authorized users.

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REVIEW

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SGLT inhibitors as antidiabetic agents: a comprehensive review

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Diabetes is one of the most common disorders that substantially contributes to an increase in global health burden. As a metabolic disorder, diabetes is associated with various medical conditions and diseases such as obesity, hypertension, cardiovascular diseases, and atherosclerosis. In this review, we cover the scientific studies on sodium/glucose cotransporter (SGLT) inhibitors published during the last decade. Our focus on providing an exhaustive overview of SGLT inhibitors enabled us to present their chemical classification for the first time.

1. Introduction

Diabetes mellitus (DM) is a common disorder associated with metabolic dysfunction that affects people all around the world. In 2011, the estimated prevalence of DM was 366 million cases, which are predicted to increase to approximately 552 million by 2030.[1] The growing pervasiveness of diabetes has been linked to an increasing global health burden over the last several decades.[2] DM is often linked to various other chronic conditions and disorders such as obesity, hypertension, cardiovascular diseases or atherosclerosis, resulting in a significant decrease in life expectancy. It also increases the associated

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Abhishek A. Kulkarni graduated from Shri Bhagwan College of Pharmacy, Dr Babasaheb Ambedkar Marathwada University, Aurangabad (MS), India in 2013 with distinction. He received his master's degree in Pharmaceutical Chemistry with distinction from the Y. B. Chavan College of Pharmacy, Aurangabad (MS), India under the guidance of Dr Jaiprakash N. Sangshetti in 2015. He has presented various scientific posters on topics related to Pharmaceutical Chemistry at both state and national level. His area of research includes the design and synthesis of novel heterocyclic coupled bioactive compounds and evaluation of their antileishmanial, antimicrobial and antioxidant activities. He is also working on the one-pot multicomponent synthesis of various bioactive molecules using various reusable catalysts.

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JOURNAL OF THE CHINESE CHEMICAL SOCIETY

ARTICLE

Synthesis and evaluation of pyrazole-incorporated monocarbonyl curcumin analogues as antiproliferative and antioxidant agents

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A series of pyrazole-incorporated monocarbonyl analogues of curcumin were synthesized via Clasien–Schimidt-type condensation and subsequently screened for in vitro antiproliferative and antioxidant activity. The analogues **4c, 5d, 5e, 5g, 6e,** and **6f** showed potential activity against the MDA-MB-231 cell line. The synthesized analogues were also screened for their antioxidant activity. Compounds **5a**, **5e**, **6d,** and **6f** exhibit comparable radical scavenging activity with respect to the standard drug ascorbic acid. Furthermore, a molecular docking study has been conducted for **5d** and **5g** and suggests that these compounds have a potential to become lead molecules in drug discovery and process.

KEYWORDS

antioxidant activity, Antiproliferative activity, molecular docking, Monocarbonyl curcumin analogues

1 | INTRODUCTION

Curcuma longa, a perennial herb of the family *Zingiberaceae,* has been used extensively as an essential spice and traditional medicine in India and China since ancient times.[1] Curcumin is obtained from turmeric, which is yellow-colored powder derived from the rhizomes of *Curcuma longa.* Curcuminoid (Figure 1) exhibits a broad spectrum of pharmacological activities like antimalerial,[2] antioxidant,[3] anti-HIV,[4] anti-inflammatory,[5] anticancer,[6] anti-Parkinson,[7] anti-Alzheimer's,[8] anti-angiogenesis,[9] and free radical-scavenging activity.[10] The clinical usefulness of curcumin is restricted due to its poor oral absorption, low oral bioavailability, and poor pharmacokinetic profile.[11] It is believed that the presence of β-diketone moiety and the active methylene group is responsible for poor oral absorption, weak pharmacokinetics, and instability of curcumin under physiological conditions.[12]

In recent years, efforts have been devoted to the development of structurally modified curcumin analogues/derivatives.[13] Monocarbonyl analogue of curcumin is one of the classes of structurally modified curcuminoids obtained by removing β-diketone moiety and active methylene group from curcumin.[14,15] Monocarbonyl analogues of curcumin (MAC) shows potential antibacterial,[16a] anti-inflammatory,[16b] antioxidant,[16c] anticancer,[16d] antiparasitic,[16e] antileishmanial,[16f] Alzheimer's disease,[16g] HIV-1 IN-LEDGF/p75 interaction,[16h] topoisomerase II alpha inhibitors,[16i] antiobesity,[16j] anti-invasive chemotypes,[16k] lipoxygenase and proinflammatory cytokines,[16l] and anti-tubulin activities.[16m] It is reported that some of the monocarbonyl analogues of curcumin not only have better stability and antitumor activity in vitro but also have a better pharmacokinetic profile in vivo.[17]

Cancer is the leading cause of death worldwide next to cardiovascular disease. World cancer reports demonstrate that millions of deaths occurred due to cancer, and new cases of various cancers are expected to rise by about 70% over the next two decades. It was also observed that more than 60% of world's new annual cases of cancer occur in Asia, Africa, and Central and South America.[18] Hence, keeping in view the seriousness of cancer, the development of novel therapeutic agents against cancer has been a focus for

Chemical Papers
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ORIGINAL PAPER

Synthesis and bioevaluation of α,α′-bis(1H-1,2,3-triazol-5-ylmethylene) ketones

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Abstract
Curcumin is an active component of turmeric that has poor solubility, stability and bioavailability. The monocarbonyl curcumin analogues were modified from curcumin to achieve more stable and active compounds as compared to curcumin. Therefore, we have designed and synthesized a library of 18 compounds of α,α'-bis(1H-1,2,3-triazol-5-ylmethylene) ketones **(8a–o)** and evaluated them for their in vitro antitubercular and antioxidant activities against their respective strains. Results of biological activities reveal that some of the compounds from the series showed good antitubercular as well as antioxidant activities. The compound **8l** was found as the most active antitubercular agent with MIC value 3.125 µg/mL, against *Mtb* H37Rv. Moreover, the compounds, **8c, 8d, 8e** and **8g,** also showed potent antitubercular activity. The compounds **8e** and **8m** displayed potent antioxidant activities with IC_{50} values 15.60 and 15.49 µg/mL, respectively. In support of the bioactivities, in silico ADME properties' prediction has also been carried out in this study.

This work was presented at Exploring New Horizons in Chemical Sciences 2019, an international symposium held in Aurangabad, India on 10-12 January, 2019.

Extended author information available on the last page of the article

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Chem. Biodiversity

Quinoline based monocarbonyl curcumin analogues as potential antifungal and antioxidant agents: Synthesis, Bioevaluation and molecular docking study.

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Abstract: In search of new fungicidal and free radical scavenging agents, we synthesized a focused library of 2-chloroquinoline based monocarbonyl analogues of curcumin (MACs). The synthesized MACs were evaluated for *in vitro* antifungal and antioxidant activity. The antifungal activity was evaluated against five different fungal strains such as *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus Niger*, *Cryptococcus neoformans* respectively. Most of the synthesized MACs displayed promising antifungal activity as compared to standard drug Miconazole. Furthermore, molecular docking study on a crucial fungal enzyme sterol 14α-demethylase (CYP51) could provide insight into the plausible mechanism of antifungal activity. Also, MACs were screened for *in vitro* radical scavenging activity using butylated hydroxyl toluene (BHT) as a standard. Almost all MACs exhibited better antioxidant activity as compared to BHT.

Keywords: Monocarbonyl analogues of curcumin • antifungal activity • antioxidant activity • molecular docking study

Introduction

Multidrug resistance microorganisms have exerted a great threat to human health in last few years. Increase in numbers of stem cell transplantation, organ transplantation, chemotherapy and human immunodeficiency virus infections increased invasive fungal infections.[1] Most of the fungal infections are caused by *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigates*. Candidosis, aspergillosis and cryptococcosis, are three major fungal infections responsible for clinical infections in patients having weak immune system.[2,3] Existing azole based drugs such as Fluconazole, voriconazole, itraconazole and miconazole are some of the widely used broad spectrum antifungal agents.[4] They displayed broad spectrum antifungal potential against most of the filamentous fungi, however some of them are not effective against invasive aspergillosis and also suffered from severe drug resistance.[5,6] Moreover, the broad use of existing azole containing antifungal drugs have caused severe drug resistance.[7] Keeping in view the limited antifungal strategies and paucity of effective drugs, there is an urgent need for the development of novel and effective antifungals to combat the fungal infections.

Antioxidants plays important role in body defense system by reducing or neutralizing the free radicals, that protects the cells from oxidative injury.[8] Recently, it has been observed that reactive oxygen species participates in mechanism of action of triazole containing antifungals.[9] It is important to elucidate possible association among oxidative stress response and antifungal mechanism of action for developing new targets for novel antifungal agents by rational development of antifungal drugs. Hence, antifungal agents with radical scavenging properties can be a good choice in designing new fungicidal agents.

Curcumin is an important phytochemical obtained from rootstalks of the plant *curcuma longa* of the family *Zingiberaceae.* Curcumin is found to exhibit broad spectrum of biological activities,[10–18] but its clinical usefulness is restricted due to low oral bioavailability, poor oral absorption and poor pharmacokinetics.[19] Instability of curcumin is found to decrease by removing central β-diketone and active methylene group.[20] In past few years,enormous efforts have made by medicinal chemists across the globe in the development of structurally modified, therapeutically active curcumin analogues/derivatives.[21] Kathryn M. Nelson and colleagues have recently published a review article on curcumin's essential medicinal chemistry and its analogues, which provides new directions in curcumin science. [22]

Design and Synthesis of New Aryloxy-linked Dimeric 1,2,3-Triazoles *via* Click Chemistry Approach: Biological Evaluation and Molecular Docking Study

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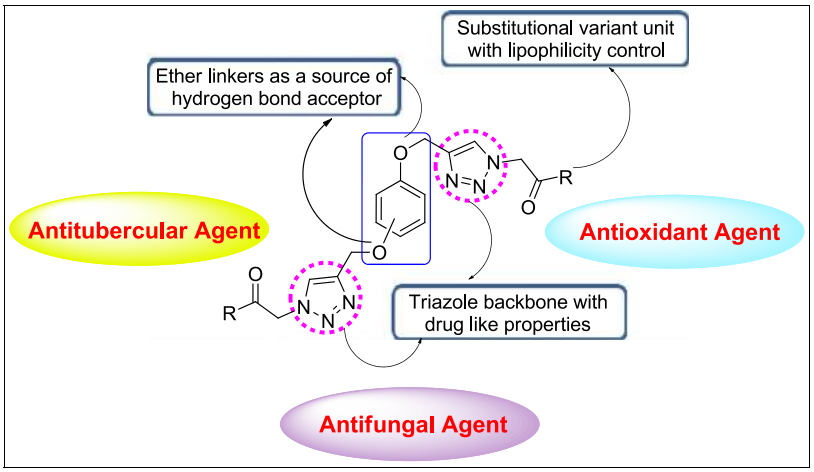

A quest for more potent new antitubercular agents has prompted to design and synthesize aryloxy-linked dimeric 1,2,3-triazoles (**4a**–**j**), from azides (**2a-e**) and bis(prop-2-yn-1-yloxy)benzene (**3a**–**b**) on 1,3-dipolar cycloaddition reaction *via* copper (I)-catalyzed click chemistry approach with good to better yields. The titled compounds (**4a**–**j**) were designed using molecular hybridization approach by assembling various bio-active pharmacophoric fragments in a single molecular framework. All the synthesized compounds have been screened for their *in vitro* antitubercular, antifungal, and antioxidant activities against their respective strains. Among them, **4h** and **4i** show the highest antifungal activity, whereas compounds **4h**, **4i**, and **4j** have revealed promising antitubercular activity against their respective strains. In addition to this, most of the synthesized compounds were found as potent antifungal and antioxidant agents. A significant network of bonded and non-bonded interactions stabilized these molecules into the active site of fungal CYP51 that is realized from the obtained well-placed docking poses and the associated thermodynamic interactions with the enzyme. The synthesized compounds have also been analyzed for absorption, distribution, metabolism, and excretion properties.

INTRODUCTION

Twin drug synthesis is one of the famous classical approaches of a promising rational drug designing [1]. There are two types of twin drugs on the basis of combining two similar or dissimilar moieties known as "identical" and "non-identical" twin drugs, respectively [2]. The identical twin drugs are obtained from dimerization of active pharmacophoric groups and possesses the C_2 symmetry in its structural motif [3]. The main aim of this synthetic approach is to obtain more potent and more selective dimeric drug as compared with monomer. It is very useful when the targeted protein exists with two binding sites [4]. Literature survey also reveals that dimeric compound shows better bioactivities than monomers [5]. Keeping these facts, many researchers focused on the synthesis and bioevaluation of dimeric molecules as shown in Figure 1 [6].

Nowadays, azole class of compounds gain more attention to researchers, especially 1,2,3-triazoles as they

OrganocatalysedDomino Synthesis of New Thiazole-Based Decahydroacridine-1,8-dionesand Dihydropyrido[2,3-d:6,5-d']dipyrimidines in Water as Antimicrobial Agents

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Abstract

Organopromoter, 2-aminoethanesulfonic acid catalyzed synthesis of series of structurally intriguing new hybrids thiazolyl acridine-1,8 (2*H*,5*H*)-diones and dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones for the first time. 2-Aminoethanesulfonic acid is a biobased organopromoter, used to generate four new bonds for the synthesis of new coupled thiazole-Based decahydroacridine-1,8-diones.Superior green credentials, operational simplicity, easy workup and recyclability of the catalyst are the key strengths of this method. Which attributes to broad substrate scope, mild reaction conditions, short reaction time, cost effectiveness, high atom economy and good to excellent yields make the present method a distinct improvement over existing methods. Spectral (IR,^{1}H NMR,^{13}C NMR, Mass) data, and elemental analyses confirmed the structures of the titled products. Series of thiazolyl acridine-1,8 (2*H*,5*H*)-diones and dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraones were screened for their antimicrobial activity against four bacterial and three fungal strains.

Keywords Antimicrobial; Thiazolyl decahydroacridine-1,8-diones; Dihydropyrido[2,3-d:6,5-d']dipyrimidine; Multicomponent; Taurine

Research on Chemical Intermediates
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Supramolecular biomimetic catalysis by β-cyclodextrin for the synthesis of new antimicrobial chromeno[4,3-b] quinolin-isonicotinamides in water

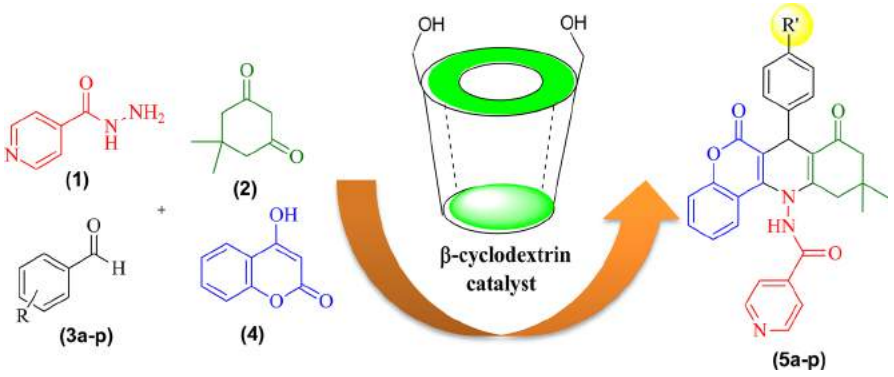
Manisha R. Bhosle, et al. ***[full author details at the end of the article]***

Received: 20 June 2019 / Accepted: 16 September 2019

Abstract

Herein, a fast and convenient protocol for the synthesis of new isoniazid fused chromeno[4,3-b]quinolin was achieved through biomimetic catalysis by cyclodextrin in the water at 60–65 °C. The present investigation involves attractive characteristics such as the use of water as the reaction medium, one-pot conditions, short reaction periods, easy work-up/purification and reduced waste production. This method provides a green route for the synthesis of targeted scaffolds and also a wide substrate scope for several substituted aldehydes to provide good yields of the corresponding products. Furthermore, the catalyst can be easily recovered by simple filtration and reused several times without any substantial loss in activity. Our study also discloses the antimicrobial screening of new chromeno[4,3-b]quinolin-isonicotinamides against four bacterial and three fungal strains.

Graphic Abstract



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Ultrasound assisted rapid synthesis, biological evaluation, and molecular docking study of new 1,2,3-triazolyl pyrano[2,3-*c*]pyrazoles as antifungal and antioxidant agent

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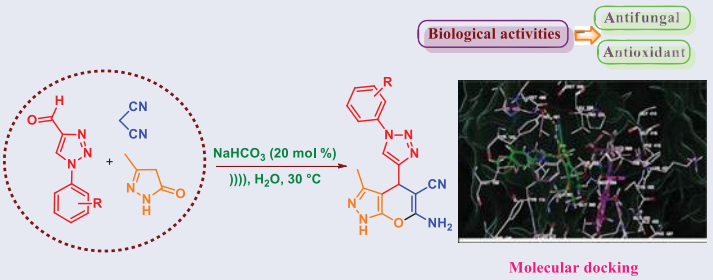
ABSTRACT

In search of new generation of triazole based antifungal agents, synthesis of series of new 1,2,3-triazolyl pyrano[2,3-*c*]pyrazoles under ultrasonic irradiation using $NaHCO_3$ has been reported. The bioevaluation results indicate that, the compounds **7c**, **7d**, **7e**, **7f**, and **7i** displayed excellent antifungal activity with lower MIC $\leq$ 25 μg/mL. Most of the compounds from the series showed potent antioxidant activity with a lower IC_{50} value in the range 09.39 ± 0.42–14.97 ± 0.24 μg/mL, in comparison to butylated hydroxyl toluene (BHT). Molecular docking studies against potential target sterol 14α-demethylase (CYP51) was also performed and showed excellent binding affinity with the target enzyme. Moreover, *in silico* ADME study shows that the derivatives could serve as drug like molecules for further drug development in clinical research.

GRAPHICAL ABSTRACT



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KEYWORDS
Antifungal activity; molecular docking study; multicomponent reactions; pyrano[2,3-*c*]pyrazole; 1,2,3-triazole

Introduction

Over the past few decades, invasive fungal infections among the immunocompromised and critically ill patients are growing rapidly and is becoming a leading cause of

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Comprehensive QSAR studies reveal structural insights into the NR2B subtype selective benzazepine derivatives as *N*-Methyl-*D*-Aspartate receptor antagonists

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ABSTRACT

NMDA receptors are considered as high profile therapeutic target in the treatment of pain and neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's disease. NR2 subunit of NMDA receptor divided into four subunits i.e. NR2A, NR2B, NR2C and NR2D. Restricted distribution of NR2B subunit in the brain makes it potential target. In the present study, new structural insights into benzazepine derivatives as NR2B selective NMDA receptor antagonists have been reported using QSAR modelling. Total five QSAR models were developed using various statistical methods. 2D-QSAR models showed that chi3 and SsssNE-index descriptors are crucial for NMDA receptor antagonistic activity. Chi3 descriptor relates with non-hydrogen heteroatom connected with two or three bonds and SsssNE-index descriptor deals with Electrotopological state indices for number of nitrogen atom connected with three single bonds. Both the descriptors were negatively correlated with all the developed 2D-QSAR models. Significance of these descriptors is extensively studied in present work. In 3D-QSAR studies, steric and electrostatic fields were found to be important for antagonistic effect on NMDA receptors. 3D-QSAR studies clarify the substitution pattern of R group on nitrogen atom of benzazepine core. The substitutions with high electropositive with less or medium steric character are favourable for the activity. All developed models were critically validated to establish their reliability and accuracy for prediction of binding affinity of benzazepine derivatives towards NR2B subunit of NMDA receptor. The present study offered not only highly predictive and reliable QSAR models for benzazepine derivatives but also revealed some of the vital structural observations required for their higher binding affinity towards NR2B subunit of NMDA receptors.

1. Introduction

N-methyl *D*-aspartate receptors (NMDAR) possess ligand-gated ion channel and distributed all over the mammalian central nervous system [1]. NMDARs are pharmacologically very important in neuronal development (neurotransmission), learning and memory [2]. These receptors are activated by the combined presence of the glutamate and glycine [3–6]. In addition to binding of these two agonists, a predepolarization of the cell membrane is required for the opening of the ion channel. They are found in the synaptic and extrasynaptic location. NMDA receptors control the flow of Calcium, Sodium and Pottasium ions across nerve cell membrane. Concentration of Ca^{2+} and Na^{+} ions influx depends on the concentration of K^{+} ion out flux from the cell. Over-activation of NMDA receptors causes excessive glutamate release leading to increase in Ca^{2+} ion concentration in the cell which further potentiate the uncontrolled activation of various Ca^{2+} ion dependant enzymes, nerve cell damage and at last the neuronal cell death. Over-activated NMDA receptors play major role in acute adverse effects such as traumatic brain injury, stroke and also lead to some neurodegenerative disorders i.e. Alzheimer's disease, Parkinson's disease, Huntington's disease) [7,8]. This involvement of NMDA

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ORIGINAL ARTICLE

Quantitative Assessment of Tactile Allodynia and Protective Effects of flavonoids of *Ficus carica* Lam. Leaves in Diabetic Neuropathy

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Submitted: 29-10-2018 Revised: 17-12-2018 Published: 26-04-2019

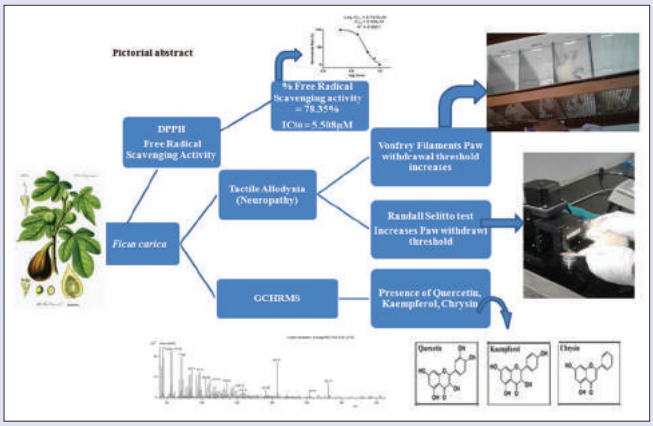
ABSTRACT

Background: Flavonoids, a group of polyphenols responsible for protective role against many diseased conditions, provide antioxidant activity which is the reason for their medicinal properties. Tactile allodynia is a behavioral biomarker of neuropathy that is well estimated by von Frey filaments and Randall–Selitto test. **Objective:** *Ficus carica* Lam. leaves were studied for the conformation of flavonoids in ethyl acetate fraction of methanolic extract (FCEA) using GC-HRMS for the identification of flavonoids. It was analyzed for antioxidant activity by *in vitro* free radical scavenging activity, performed using 2,2-diphenyl-1-picrylhydrazyl (DPPH) followed by blood glucose-level estimation, evaluation of neuropathic pain, and kidney and liver function tests in diabetic rats. **Materials and Methods:** The shade-dried leaves of *F. carica* Lam. were extracted with methanol and after that fractionated using ethyl acetate (FCEA). The characterization of FCEA was established using GC-HRMS. *In vitro* free radical scavenging activity was performed using DPPH assay. Diabetes was induced using streptozotocin (40 mg/kg/intraperitoneally), and effects of FCEA were studied on blood glucose level, neuropathy markers, and liver and kidney functions of diabetic rats. **Results:** GC-HRMS results highlighted the presence of quercetin, kaempferol, and chrysin in FCEA with free radical scavenging activity of 78.35% and IC_{50} value of 5.508 μM. FCEA reduces glucose levels and also shows protective effects in case of diabetic neuropathy as it increases the threshold of withdrawal latency in tactile allodynia and also decreases the serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, blood urea nitrogen, and creatinine levels. **Conclusion:** The protective effects of FCEA against diabetic neuropathy, hepatoprotective and nephroprotective effects might be due to strong antioxidant property of important flavonoids present which is confirmed in the study.

Key words: Chrysin, diabetic neuropathy, kaempferol, quercetin, Randall Selitto, von Frey

SUMMARY

- The research work shows the presence of quercetin, kaempferol, and chrysin in *Ficus carica* Lam. leaves; along with this, it has depicted *in vitro* free radical scavenging activity by 2,2-diphenyl-1-picrylhydrazyl assay method. After quantitative assessment of tactile allodynia, this plant sample has proven protective effects in diabetic neuropathy, and these effects were compared with surgical model of neuropathy by von Frey filaments and Randall–Selitto test.



Abbreviations used: BSTFA: N, O-Bis (trimethylsilyl) trifluoroacetamide; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FCEA: Ethyl acetate fraction from methanolic extract of leaves of *Ficus carica* Lam.; GC-HRMS: Gas chromatography–high-resolution mass spectrometry.

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INTRODUCTION

Polyphenolic substances are ubiquitously found chemical constituents in a variety of plants having medicinal properties.[1-4] A large number of plants contain flavonoids; they further consist of flavones, flavonols, isoflavonoids, anthocyanidins, and chalcones.[2,3] It has a protective role in carcinogenesis,[4,5] inflammation,[4,5] atherosclerosis,[4] thrombosis,[4] diabetes, and cardiovascular diseases[5] and has activities such as antiviral,[4,5] antimicrobial,[4] antihepatotoxic,[4] antiosteoporotic,[4,6] antiulcer,[4] immunomodulatory,[4] antiproliferative,[4,6] and apoptotic[4] as a result of their antioxidant actions.[4-6] In the last few years, gas chromatography–mass spectrometry (GC-MS) has established as a firm platform for analysis of plant's secondary metabolites and phytoconstituents. It is a hyphenated system, a compatible technique

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Novel Benzylidenehydrazide-1,2,3-Triazole Conjugates as Antitubercular Agents: Synthesis and Molecular Docking

Authors: Shaikh, Mubarak H.; Subhedar, Dnyaneshwar D.; Nawale, Laxman; Sarkar, Dhiman; Khan, Firoz A. Kalam; Sangshetti, Jaiprakash N.; Shingate, Bapurao B.
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Abstract | References | Citations | Supplementary Data

Background & Objective: Novel 1,2,3-triazole based benzylidenehydrazide derivatives were synthesized and evaluated for antitubercular activity against Mycobacterium tuberculosis (MTB) H37Ra, M. bovis BCG and cytotoxic activity. Most of the derivatives exhibited promising in vitro potency against MTB characterized by lower MIC values.

Methods: Among all the synthesized derivatives, compound 6a and 6j were the most active against active and dormant MTB H37Ra, respectively. Compound 6d was significantly active against dormant and active M. bovis BCG.

Results: The structure activity relationship has been explored on the basis of anti-tubercular activity data. The active compounds were also tested against THP-1, A549 and Panc-1 cell lines and showed no significant cytotoxicity. Further, the synthesized compounds were found to have potential antioxidant with IC50 range = 11.19-56.64 µg/mL. The molecular docking study of synthesized compounds was performed against DprE1 enzyme of MTB to understand the binding interactions.

Conclusion: Furthermore, synthesized compounds were also analysed for ADME properties and the potency of compounds indicated that, this series can be considered as a starting point for the developement of novel and more potent anti-tubercular agents in future.

Keywords: 1,2,3-Triazole; ADME; antioxidant; antitubercular; cytotoxicity; docking study

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More about this publication?

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Synthesis, bioevaluation and molecular docking study of new piperazine and amide linked dimeric 1,2,3-triazoles

Tejshri R. Deshmukh[a], Smita P. Khare[a], Vagolu S. Krishna[b], Dharmarajan Sriram[b], Jaiprakash N. Sangshetti[c], Vijay M. Khedkar[d], and Bapurao B. Shingate[a]

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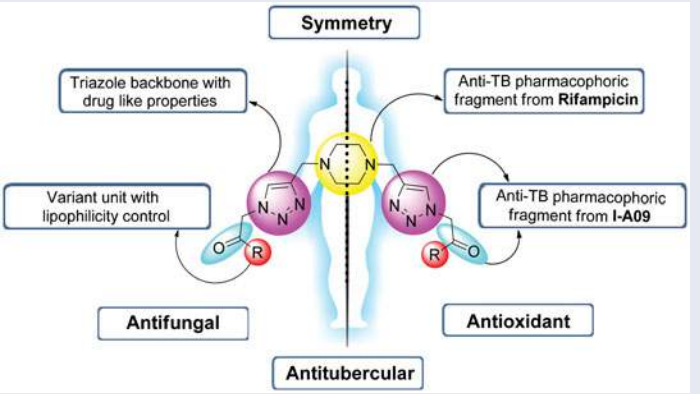
ABSTRACT

In search of more potent new antitubercular agents, a library of novel piperazine tethered dimeric 1,2,3-triazoles were designed by assembling 1,2,3-triazoles and piperazine in a single molecular architectural framework. The titled compounds (**3a–m**) were synthesized by 1,3-dipolar cycloaddition of 1,4-di(prop-2-yn-1-yl)piperazine (**1**) and various azides (**2a–m**) using click chemistry approach with good yields. All the synthesized compounds (**3a–m**) have been screened for their *in vitro* antitubercular, antifungal and antioxidant activities against their respective strains. Among them, **3b**, **3d,** and **3i** have revealed promising antitubercular activity against *Mycobacterium tuberculosis (Mtb)* H37Rv with MIC 12.5 μg/mL. Molecular docking results provided well-clustered solutions to the mode of binding for these molecules into the active site of *Mtb* enoyl reductase (InhA). In addition to this, most of synthesized compounds were found to have potential antifungal as well as antioxidant activity.

GRAPHICAL ABSTRACT



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KEYWORDS
Antifungal activity; antioxidant activity; antitubercular activity; dimeric 1,2,3-triazoles; molecular docking study

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Review article

Sugar alcohol-based polymeric gene carriers: Synthesis, properties and gene therapy applications

Seo Jin Hong[a], Min Hye Ahn[a], Jaiprakash Sangshetti[b], Rohidas B. Arote[a,c,*]

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Sugar alcohol-based polymers

ABSTRACT

Advances in the field of nanomedicine have led to the development of various gene carriers with desirable cellular responses. However, unfavorable stability and physicochemical properties have hindered their applications *in vivo*. Therefore, multifunctional, smart nanocarriers with unique properties to overcome such drawbacks are needed. Among them, sugar alcohol-based nanoparticle with abundant surface chemistry, numerous hydroxyl groups, acceptable biocompatibility and biodegradable property are considered as the recent additions to the growing list of non-viral vectors. In this review, we present some of the major advances in our laboratory in developing sugar-based polymers as non-viral gene delivery vectors to treat various diseases. We also discuss some of the open questions in this field.

Statement of Significance: Recently, the development of sugar alcohol-based polymers conjugated with polyethylenimine (PEI) has attracted tremendous interest as gene delivery vectors. First, the natural backbone of polymers with their numerous hydroxyl groups display a wide range of hyperosmotic properties and can thereby enhance the cellular uptake of genetic materials via receptor-mediated endocytosis. Second, conjugation of a PEI backbone with sugar alcohols via Michael addition contributes to buffering capacity and thereby the proton sponge effect. Last, sugar alcohol based gene delivery systems improves therapeutic efficacy both *in vitro* and *in vivo*.

Contents

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ORIGINAL RESEARCH

Identification of dual site inhibitors of tankyrase through virtual screening of protein-ligand interaction fingerprint (PLIF)–derived pharmacophore models, molecular dynamics, and ADMET studies

Manoj G. Damale[1] · Rajesh Patil[2] · Siddique Akber Ansari[3] · Hamad M. Alkahtani[3] · Abdulrahman A. Almehizia[3] · Shahebaaz K. Pathan[4] · Santosh Chhajed[5] · Jaiprakash Sangshetti[4]

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Abstract

Tankyrases are the group of poly (ADP-ribosyl) polymerases (PARPs) which are the attractive targets in various therapeutic areas such as cancer, antiviral, diabetes, and hormonal imbalance. The selective nature of tankyrase 1 and 2 inhibitors has created solid base to get dual site binders as they bind to induced adenosine binding site and nicotinamide binding site resulting in dual site inhibition. The present work describes the cheminformatics approach to find potential lead molecules as tankyrases dual site inhibitors through pharmacophore model by utilizing protein-ligand interaction fingerprints (PLIF) approach. The constructed pharmacophore model was used in virtually screening of ZINC and Interbioscreen database. Top ten hit molecules of virtual screening were subjected to molecular docking in order gain insights of key interactions at the adenosine and nicotinamide binding sites. The top hits were subjected to molecular dynamics simulation studies to gain deeper insights into probable mechanism of inhibition and stability of the complex. The top hit **ZINC12973507** showed all the features required in key interactions at the active site of tankyrases and this hit molecule can be further explored as a potential drug candidate for dual site inhibition of tankyrases.

Keywords Tankyrase · Protein-ligand interaction fingerprints (PLIF) approach · Pharmacophore · Virtual screening · Molecular docking · Molecular dynamics

Introduction

Poly (ADP-ribose) polymerases (PARPs) are family of around eighteen proteins mainly involved in DNA repair [1]. The damage to DNA strands invokes the catalytic activity of two domains of PARP namely PARP-1 and PARP-2. PARPs utilize NAD^+ as a substrate to generate ADP-ribose polymer. Such ADP-ribosylation is an important event during the post translational modification of residues such as aspartate, glutamate, asparagine, arginine, lysine, cysteine, phosphoserine, and diphthamide of signaling proteins. The PARP5 also named as ADP-ribosyltransferase (ARTD) has wide-ranging roles in cellular processes such as DNA repair, metabolism, gene transcription, Wnt signaling, telomerase maintenance, mitosis, vesicle translocation, proteosomal activity, viral replication, lung fibrogenesis, and myelination. PARP5 is present in two isoforms PARP-5a (ARTD5) and PARP-5b (ARTD6). These two isoforms are now referred as tankyrase1 (TNKS1) and tankyrase2 (TNKS2). These isoforms share 85% sequence identity and structural domain similarity. Tankyrases

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Published online: 05 December 2019

A Review on different formulations of Punica granatum

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Abstract:
Plant based preparations have been used since olden times and playing a role as a curative against different human and animal diseases. The curiosity in conventional medicines has increased in different parts of world. A well known olden fruit named as Punica granatum which is commonly known as Pomegranate, Anar or Dalim in North India whose curative qualities have rebounded and echoed throughout the millennia. It contains numerous valuable ingredients such as flavonoids, ellagitannin, punicalagin, ellagic acid, vitamins and minerals. The main constituents including punicalagins and ellagitannin are responsible for beyond measure health benefits due to its strong antioxidant activity. As well, constituents of pomegranate show health promoting effect through the modulation of physiological and biochemical pathways. Recent evidences suggested that pomegranates fruits, peels and seeds demonstrate therapeutics implications in health management via inhibition of free radical effect and modulation of enzymes activity linked with diseases development. In this review, we summarize the work of different researchers on pomegranate in the different formulations for the different diseases.

Keywords: Punica granatum, Punicalagin, Novel Drug Delivery System, Pomegranates, dosage form, formulations.

Nanoparticles

"Mucoadhesive polyethylenimine–dextran sulfate nanoparticles containing Punica granatum peel extract as a novel sustained release antimicrobial"

Mucoadhesive polyethylenimine–dextran sulfate nanoparticles (PDNPs) were developed for local oral mucosa delivery. Punica granatum peel extract (PGE) was loaded into PDNPs for oral mal odor reduction and caries prevention. PDNPs were constructed using the polyelectrolyte complexation technique employing oppositely charged polymers polyethylenimine (PEI) and dextran sulfate (DS), with PEG 400 as a stabilizer. Under optimal conditions, spherical particles of 500nm with a zeta potential of +28mV were produced. Up to 98%, drug entrapment efficiency was observed. The mass ratio of PEI:DS played a significant role in controlling particle size and entrapment efficacy. PDNPs shown to be a good mucoadhesive drug delivery system as confirmed by *ex vivo wash off test*. In vitro dissolution studies revealed that PGE-loaded PDNPs manifested a prolong release characteristic with a burst release within 5 min. In addition, they remained effectively against oral bacteria. (Waree Tiyaboonchai et al. 2014)

Niosomes

"Formulation and Evaluation of Niosomes Containing Punicalagin from Peels of Punica Granatum"

The objective of the present study is to develop and validate a simple, precise, accurate, and economical analytical method for the estimation of Punicalagin extracted from peels of *Punica granatum*. To perform the compatibility study of drug, Punicalagin with the excipients used in formulating niosomes. To develop a vesicular system like niosomes which act as carriers and hence will help in penetration of drug through skin and provide a prolong release. Punicalagin is chemically named as 2, 3-(S)-hexahydroxydiphenoyl-4,6-(S,S)-gallagyl-D-glucose and belongs to a category of hydrolysable tannin. Thus, to protect its hydrolysis, it is formulated into a nanocarrier system known as niosomes which is based on the preparation of niosomes by using a non-ionic surfactant in varying amounts and keeping the amount of cholesterol constant. The formulations were evaluated on the basis of evaluation parameters and thus optimized for the best formulation. (Priya Hanu and Singh Harmanpreet, 2012)

Pharmaceutical Nanotechnology, **2019**, *7,* 343-361

RESEARCH ARTICLE

Formulation Optimization and Biopharmaceutical Evaluation of Imatinib Mesylate Loaded β-cyclodextrin Nanosponges

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ARTICLE HISTORY

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Abstract: ***Background*:** Many researchers have prepared and evaluated nanosponges and claimed their advantages as an effective drug carrier, especially it was observed prominently in case of anti-fungal drugs. The materials employed to synthesize nanosponges were mainly crosslinking agents, different beta-cyclodextrin and other cellulose-based polymers. Many of them had used ratio proportions of cross-linking agents, d polymers to synthesize these nanosponges which ultimately produce a porous mesh-like network known as nanosponges where actually drug is encapsulated or loaded.

***Objective*:** In the present investigation, we observed the effect of various levels of cross-linking agents and beta-cyclodextrin concentrations on porosity, drug encapsulation, zeta potential and drug release by employing the quality by design approach to synthesize nanosponges rather than merely keeping both concentrations in proportions.

***Methods*:** We have slightly modified the method reported earlier *i.e*. melting method in which we have used rota evaporator receiver vessel for melting cross-linking agent and beta- cyclodextrin, rotated at 20 RPM at 100°C.

***Results*:** In a quality by design approach, we observed that out of four dependent variables *i.e*. porosity, drug loading, zeta potential and drug release, three significantly depend on the crosslinking of beta-cyclodextrin molecules which is highly appreciated by the amount of cross-linking agent present in the reaction. The pharmacokinetics of Imatinib loaded optimized nanosponges were compared with the reference product to observe the pattern of absorption and disposition.

***Conclusion*:** Nanosponges synthesized by optimization technique could be effective means of anti-cancer drug oral administration as they encapsulate the drug effectively and offer a prolonged release of drug which gradually releases the drug and avoids unnecessary exposure of the drug.

Keywords: Beta-cyclodextrin, crosslinking agents, drug encapsulation, imatinib mesylate, nanosponges, zeta potential.

1. INTRODUCTION

Nanosponges (NSPs) are a novel class of hyper-crosslinked polymer-based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. Cyclodextrin-based NSPs were first prepared by Li and Ma in 1998 [1]. From then many synthetic procedures explored NSPs by tapping different cross-linking agents and by using their different molar ratios [2-4]. NSPs provide prolonged release as well as improve drug bioavailability by modifying the pharmacokinetic parameters of actives as reported by Gursalkar *et al.* [5]. Cyclodextrin-based NSPs

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DEVELOPMENT OF HPLC METHOD FOR DETERMINATION OF TAMSULOSIN USING QUALITY BY DESIGN (QBD) APPROACH

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Keywords: Tamsulosin; QbD approach; RP-HPLC method; Box-Behnken model; ICH guidelines.

An HPLC method for Tamsulosin was developed by using a quality by design (QbD) novel concept. QbD has gained importance in recent times due to regulatory requirements in industrial application. Chromatographic separation of Tamsulosin was carried out by using C_8 column, and mobile phase used was methanol and distilled water (40:60 v/v) for proper separation process. Separation by using water as a solvent is beneficial as it is cost effective process and industrially applicable. In the development of the HPLC method, factors like injection volume, conc. of methanol, the column vent temperature is critical in maintaining. Hence the Box-Behnken optimization model was applied for the main, interaction and quadratic effects of these three factors on the selected response. The effect of these parameters was studied on the tailing factor (resolution). Results were analysed during a surface diagram. Verification of the software-generated result was done by taking six replicates of the run. Finally, the method was validated according to ICH guidelines.

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INTRODUCTION

Tamsulosin (5-[(2R)-2-{[2-(2-ethoxyphenoxy)ethyl]-amino}propyl]-2-methoxybenzene-1-sulfonamide) acts as adrenergic α-antagonists and is maximally used to treat symptomatic benign prostatic hyperplasia (BPH), which will help with the passage of kidney stones, and also for urinary retention. Tamsulosin acts as a selective antagonist at α_{1A} and α_{1B}-adrenoceptors in the prostate, prostatic capsule, prostatic urethra, and bladder neck. The three discrete α_1-adrenoceptor subtypes such as α_{1A}, α_{1B} and α_{1D} were also identified and their distribution differs between human organs and other tissue. It was noted that there are approximately 70% of the α_1-receptors in the human prostate, which were of the α_{1A} subtype. The blockage in these types of receptors will cause relaxation of smooth muscles in the bladder neck and prostate, and which thus decreases urinary outflow resistance in males. [1]

To the best of our knowledge HPLC method using a simple UV detector by applying the QbD approach is not available. As per International Conference on Harmonization (ICH) guidance on pharmaceutical development, "QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process control and which is dependent on quality risk management and its related science.[2] QbD has gained special attention in current times due to regulatory requirements in the research work.

US-FDA has accelerated QbD drive to encourage the risk-based approach and thorough understanding of processes, which is ultimately going to help the regulatory bodies in the review process.

The basic foundation behind QbD is that quality is 'designed' into the process at the onset to the establishment of the method by a thorough understanding of the effect of the various system parameters are studied. Effects are analyzed for their influence on the quality of the product that is desired. This is nothing but ultimately to establish the design space for the method. Design space is defined as a "multidimensional combination and interaction of input variables that have been demonstrated to assure quality."[3]Some of the methods have been reported for the development of the HPLC method for Tamsulosin.[4-14]

MATERIALS AND METHODS

Tamsulosin standard active pharmaceutical ingredient (API) was procured from Hetero Drugs Limited (Hyderabad) and solvents were supplied from Dodal Enterprises and Badar chemicals, Aurangabad. Distilled HPLC grade water was prepared in the quality assurance lab of Y. B. Chavan College of Pharmacy, Aurangabad. The instrument used for HPLC analysis work was performed by using a Shimadzu LC20 model with C_8 column of 4.6×150mm; 5µmplates

Tamsulosin sample preparation

The stock solution of Tamsulosin for optimization of experiments was prepared by accurately weighing 10mg of Tamsulosin and dissolving it in 100 mL of the mobile phase composing of methanol and water 40:60 combination.

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Research Article

FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING FILM OF ROSUVASTATIN CALCIUM USING QBD APPROACH

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ABSTRACT

The aim of the present study was to design the mouth dissolving film of Rosuvastatin calcium (RC) by applying quality by design (QbD) approach. The mouth dissolving film was prepared using solvent casting method. The critical quality attributes (CQAs) and quality target product profiles (QTPP) of RC mouth dissolving films were defined based on previous studies. Plackett-Burman experimental design was used for initial screening of process and formulation variables. The screened variables were further optimized using 3^2 full factorial designs. The variables influencing formulation of film was HPMC E5 and PVP K30. The design space was determined using statistical tool and optimized formulations were prepared within the design space. The optimized films showed all the evaluation parameters within the QTPP. The results indicated that as long as formulation variables remain within the design space, mouth dissolving film of RC with desired characteristics and quality requirement could be formulated.

Keywords: Plackett-Burman; Rosuvastatin calcium; 3^2 full factorial design; quality by design; Mouth dissolving film.

INTRODUCTION

The oral route of drug administration is the most preferred route of drug delivery amongst all the routes of drug administration. Oral mouth dissolving film (MDF) is gaining popularity because of high patient compliance in treating paediatric and geriatric patients and provides immediate release as it offers quick onset of action[1,2]. The film dissolve or disintegrate quickly in the oral cavity and the fast dissolving action is due to quick wetting of the film in the moist oral cavity, leading to fast dissolving action. This also prevents choking or spitting out problems associated with solid oral dosage forms[3,4].

The MDF can be formulated using a variety of film formers and other excipients and the most common technique for its preparation is using solvent casting[4]. Variety of polymers and their different grades can be used in the formation of MDF depending upon the need of disintegration time, drug loading and mechanical properties[4]. Plasticizers added in MDF improve the flexibility and reduces the brittleness of the strip. They significantly enhance film forming properties through a reduction in the glass transition temperature of the polymers[5]. Variability in type and grade of polymer and plasticizer concentration may impact the MDF critical quality attributes (CQA) such as thickness, % elongation at break, yield stress, Young's modulus, folding endurance and dissolution rate of the film. The present study was carried out to investigate the impact of the formulation and process variables on the quality of mouth dissolving film using Quality by Design (QbD) approach.

Rosuvastatin is a synthetic, high potent third generation statin with cholesterol-lowering activity. Rosuvastatin competitively inhibits hydroxyl methyl glutaryl-coenzyme A (HMG-CoA) reductase which catalyses the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis, therefore, it is used for high cholesterol, blood lipid metabolic disorder and pure high triglyceride blood disease treatment[6,7]. Clinical studies have proven that fast disintegrating tablets can enhance patient compliance, provide an immediate onset time of action, and increase bioavailability[8]. Hence it was decided to use Rosuvastatin as a model candidate for oral dissolving film.

Quality by Design (QbD) is a scientific approach for product development. It ensures the quality of the product systematically by providing thorough understanding the compatibility of all the components and processes involved in manufacturing. QbD provides detailed insight on quality throughout the development process[8].

Typically, it involves identification of quality target product profile (QTTP) that are critical from the patient's perspective and helps in establishing the relationship between formulation/manufacturing variables and CQAs to consistently deliver a drug product to the patient[9]. In addition to the mechanical properties (yield stress, % elongation at the break and Young's modulus), a short disintegration time and fast drug dissolution constitute the desired QTPP of Rosuvastatin MDF product.[10] It is also important to identify critical material attributes (CMA) and critical process parameters (CPP) based on process and product understanding.

The aim of the present study was to design and optimize the Rosuvastatin calcium MDFs by using QbD. In the present study, Rosuvastatin calcium MDFs was developed, and a design space was established through a factorial design for optimization using Design Expert 9.0.3.1 software (Stat-Ease, Minneapolis, MN, USA). In our preliminary study, we investigated factors that could

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Development and Biopharmaceutical Characterization of BCS Class II Drug – Naproxen by Two Way Complexation Solid Dispersion Technique

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Abstract: The objective of this study was to increase the solubility and bioavailability of Naproxen (NP) by fabricating ternary solid dispersion (tSDs) with water soluble polymer PEG 6000 and crospovidone. tSDs were prepared and optimized by 3^2 full factorial design with PEG 6000 level (X1) and CP level (X2) as independent variables and percent drug release (D80, (Y)) as dependent variable. The optimized tSDs were evaluated for their physicochemical properties which confirmed the formation of tSDs (DSC), SEM suggested smooth surface and compact structures. PXRD revels that drug was still present in crystalline form and was not molecularly dispersed in the complex especially in non-homogeneous part of the tSDs. The optimized tSDs revels that Dissolution rate (Y) was significantly affected by independent variable PEG 6000 (X1) while CP (X2) was insignificant. The transparent characteristics of tSDs was observed as a result of lowered Tg temperature gives higher dissolution rate up to 97.70 % for optimized formulation (F9). The pharmacokinetic study in Han Wistar rats showed that the tSDs had the greatest effect on oral bioavailability of NP *in vivo* test showed that NP (tSDs) presented significantly larger $AUC_{0\text{-}t}$, which was 1.09 folds more than that of marketed formulation. C_{max} of NP (tSDs) also increased from 120 µg/ml to 146 µg/ml compared to that of marketed formulations and generated shortened T_{max} of (1.0 ± 0.416) h, compared to marketed dosage form (2.0 ± 0.456) h.

Key words: Solid dispersion, glass transition temperature, ternary solid dispersion, level optimization, & pharmacokinetics

Introduction

Systemic availability of drug depends on the two important steps. These two steps determine the rate and extend of drug absorption, so called as Rate Limiting Steps. i. e. Drug dissolution and Drug permeation [1]. Drug dissolution is always depends on the solubility of that particular drug which is hydrophobic, poorly aqueous soluble drug like NP, falls under the category of BCS class II drug [2]. The solid dispersion technique for water-insoluble drugs developed by Chiou and Reigelman provides an efficient method to improve the dissolution rate of a drug. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material [3]. Methods used to obtain solid dispersions affects the drugs crystallinity as Mooter *et al.*, revealed that with a 20/80 w/w Itraconazole/Inutec SP1 extrudate (solid solution) a dissolution of 100% could be obtained after 30 min. The same composition prepared by spray drying; however, gave rise to a dissolution of only 50% [4]. The presence of different proportions of PEG systematically lowers the degree of complexed drug NP with β-CD due to competing equilibria gives rise to ternary solid dispersions [5]. The solid dispersions and ternary complexes formed exhibits increased dissolution behaviour as result of metastable amorphous material formed which in turn cooled, it usually crystallizes below the melting temperature, (Tm). When cooling rate is sufficiently fast, the liquid fails to crystallize, and a super cooled state is attained. Further cooling to below the glass transition temperature (Tg) causes the system to fall out of structural equilibrium. Since this state is not physically stable, structural changes occur over time to achieve a more energetically favoured state leads to less dissolution rate [6]. Solid dispersions of PEG6000 and Loperamide prepared by spray drying showed deteriorated dissolution rate on storage at high temperature (40°C and 0% RH) and in conditions of higher relative humidity (25°C and 52% RH) resulting in

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REVIEW

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SGLT inhibitors as antidiabetic agents: a comprehensive review

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Diabetes is one of the most common disorders that substantially contributes to an increase in global health burden. As a metabolic disorder, diabetes is associated with various medical conditions and diseases such as obesity, hypertension, cardiovascular diseases, and atherosclerosis. In this review, we cover the scientific studies on sodium/glucose cotransporter (SGLT) inhibitors published during the last decade. Our focus on providing an exhaustive overview of SGLT inhibitors enabled us to present their chemical classification for the first time.

1. Introduction

Diabetes mellitus (DM) is a common disorder associated with metabolic dysfunction that affects people all around the world. In 2011, the estimated prevalence of DM was 366 million cases, which are predicted to increase to approximately 552 million by 2030.[1] The growing pervasiveness of diabetes has been linked to an increasing global health burden over the last several decades.[2] DM is often linked to various other chronic conditions and disorders such as obesity, hypertension, cardiovascular diseases or atherosclerosis, resulting in a significant decrease in life expectancy. It also increases the associated

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ORIGINAL ARTICLE

Quantitative Assessment of Tactile Allodynia and Protective Effects of flavonoids of *Ficus carica* Lam. Leaves in Diabetic Neuropathy

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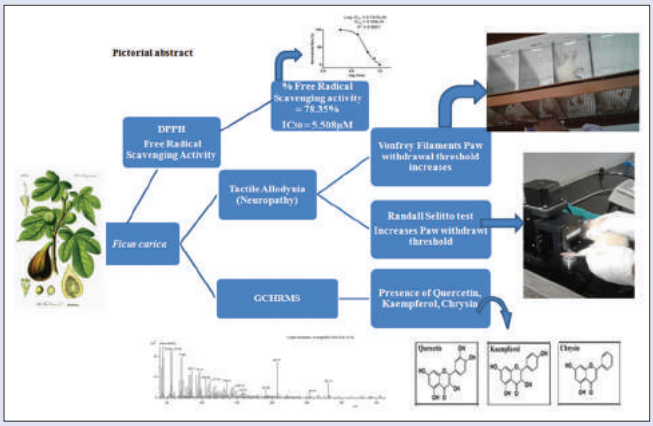
ABSTRACT

Background: Flavonoids, a group of polyphenols responsible for protective role against many diseased conditions, provide antioxidant activity which is the reason for their medicinal properties. Tactile allodynia is a behavioral biomarker of neuropathy that is well estimated by von Frey filaments and Randall–Selitto test. **Objective:** *Ficus carica* Lam. leaves were studied for the conformation of flavonoids in ethyl acetate fraction of methanolic extract (FCEA) using GC-HRMS for the identification of flavonoids. It was analyzed for antioxidant activity by *in vitro* free radical scavenging activity, performed using 2,2-diphenyl-1-picrylhydrazyl (DPPH) followed by blood glucose-level estimation, evaluation of neuropathic pain, and kidney and liver function tests in diabetic rats. **Materials and Methods:** The shade-dried leaves of *F. carica* Lam. were extracted with methanol and after that fractionated using ethyl acetate (FCEA). The characterization of FCEA was established using GC-HRMS. *In vitro* free radical scavenging activity was performed using DPPH assay. Diabetes was induced using streptozotocin (40 mg/kg/intraperitoneally), and effects of FCEA were studied on blood glucose level, neuropathy markers, and liver and kidney functions of diabetic rats. **Results:** GC-HRMS results highlighted the presence of quercetin, kaempferol, and chrysin in FCEA with free radical scavenging activity of 78.35% and IC_{50} value of 5.508 μM. FCEA reduces glucose levels and also shows protective effects in case of diabetic neuropathy as it increases the threshold of withdrawal latency in tactile allodynia and also decreases the serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, blood urea nitrogen, and creatinine levels. **Conclusion:** The protective effects of FCEA against diabetic neuropathy, hepatoprotective and nephroprotective effects might be due to strong antioxidant property of important flavonoids present which is confirmed in the study.

Key words: Chrysin, diabetic neuropathy, kaempferol, quercetin, Randall Selitto, von Frey

SUMMARY

- The research work shows the presence of quercetin, kaempferol, and chrysin in *Ficus carica* Lam. leaves; along with this, it has depicted *in vitro* free radical scavenging activity by 2,2-diphenyl-1-picrylhydrazyl assay method. After quantitative assessment of tactile allodynia, this plant sample has proven protective effects in diabetic neuropathy, and these effects were compared with surgical model of neuropathy by von Frey filaments and Randall–Selitto test.



Abbreviations used: BSTFA: N, O-Bis (trimethylsilyl) trifluoroacetamide; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FCEA: Ethyl acetate fraction from methanolic extract of leaves of *Ficus carica* Lam.; GC-HRMS: Gas chromatography–high-resolution mass spectrometry.

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INTRODUCTION

Polyphenolic substances are ubiquitously found chemical constituents in a variety of plants having medicinal properties.[1-4] A large number of plants contain flavonoids; they further consist of flavones, flavonols, isoflavonoids, anthocyanidins, and chalcones.[2,3] It has a protective role in carcinogenesis,[4,5] inflammation,[4,5] atherosclerosis,[4] thrombosis,[4] diabetes, and cardiovascular diseases[5] and has activities such as antiviral,[4,5] antimicrobial,[4] antihepatotoxic,[4] antiosteoporotic,[4,6] antiulcer,[4] immunomodulatory,[4] antiproliferative,[4,6] and apoptotic[4] as a result of their antioxidant actions.[4-6] In the last few years, gas chromatography–mass spectrometry (GC-MS) has established as a firm platform for analysis of plant's secondary metabolites and phytoconstituents. It is a hyphenated system, a compatible technique

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Original Article

Ameliorative Potential of *Allium cepa* Lam. Leaves on Diabetes Induced and Chronic Constriction Injury Induced Neuropathic Pain in Experimental Rats

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ABSTRACT

Background: Neuropathy can be induced in rats by peripheral injuries, depending on compression of complete or a section of sciatic nerve and chemically by Streptozotocin (STZ). **Materials and Methods:** In the present study neuropathic pain were induced in rats by two methods, chronic constriction injury (surgical model) and STZ (40mg/kg/i.p.) induced diabetes (drug induced model). In both the models, behavioural as well as markers of oxidative stress were studied. Behavioural parameters were tested using vonfrey hair and Randall Selitto analgesiometer whereas biochemical parameter includes glycosylated haemoglobin and markers of oxidative stress. The study was further supported by histopathology of sciatic nerve. Flavonoid rich extract of *Allium cepa* Lam. leaves was administered at three different doses viz. 25, 50 and 100mg/kg/p.o to the rats with neuropathic pain. Both the models of neuropathic pain showed significant alteration in behavioural as well as oxidative stress parameters. **Results:** Treatment of *Allium cepa* leaves extract showed dose dependent improvement in behavioural and biochemical parameters towards normal (p value <0.001, <0.05 and <0.01). The altered histopathological changes in sciatic nerve were also significantly improved as compared to rats with neuropathic pain. **Conclusion:** The neuroprotective effects of the *Allium cepa* leaves extract is a virtue of its strong antioxidant activity.

Key words: *Allium cepa*, Neuropathy, CCI, Oxidative stress, Sciatic nerve.

INTRODUCTION

Different animal models of neuropathy showed a strong correlation of sciatic nerve with neuropathic pain. Peripheral nerve injury models involve surgical procedures at sciatic nerve to induce neuropathy, whereas drug induced neuropathy and disease induced neuropathy are models developed due to oxidative stress, degeneration or neurotoxicity of peripheral nerves *i.e* sciatic nerve.[1] Surgical models targeting nerve result in a chronic mechanical allodynia on injured paw. These models include chronic constriction injury, sciatic nerve cuffing, partial sciatic nerve ligation, spinal nerve ligation or common peroneal nerve ligation.[2] While the disease induced neuropathy commonly include diabetic neuropathy model in research groups,[1] chronic hyperglycemia induces oxidative stress through multiple pathways like redox imbalances, altered protein kinase C activity and mitochondrial overproduction of superoxide[3] and this plays a significant role in development of diabetic complications including diabetic neuropathy.[4] While, sciatic nerve injury is associated with excessive production of reactive oxygen species, calcium ions entry and apoptosis; calcium overload through Transient Receptor Potential (TRP) cation channel and pain

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A Review on different formulations of Punica granatum

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Abstract:
Plant based preparations have been used since olden times and playing a role as a curative against different human and animal diseases. The curiosity in conventional medicines has increased in different parts of world. A well known olden fruit named as Punica granatum which is commonly known as Pomegranate, Anar or Dalim in North India whose curative qualities have rebounded and echoed throughout the millennia. It contains numerous valuable ingredients such as flavonoids, ellagitannin, punicalagin, ellagic acid, vitamins and minerals. The main constituents including punicalagins and ellagitannin are responsible for beyond measure health benefits due to its strong antioxidant activity. As well, constituents of pomegranate show health promoting effect through the modulation of physiological and biochemical pathways. Recent evidences suggested that pomegranates fruits, peels and seeds demonstrate therapeutics implications in health management via inhibition of free radical effect and modulation of enzymes activity linked with diseases development. In this review, we summarize the work of different researchers on pomegranate in the different formulations for the different diseases.

Keywords: Punica granatum, Punicalagin, Novel Drug Delivery System, Pomegranates, dosage form, formulations.

Nanoparticles

"Mucoadhesive polyethylenimine–dextran sulfate nanoparticles containing Punica granatum peel extract as a novel sustained release antimicrobial"

Mucoadhesive polyethylenimine–dextran sulfate nanoparticles (PDNPs) were developed for local oral mucosa delivery. Punica granatum peel extract (PGE) was loaded into PDNPs for oral mal odor reduction and caries prevention. PDNPs were constructed using the polyelectrolyte complexation technique employing oppositely charged polymers polyethylenimine (PEI) and dextran sulfate (DS), with PEG 400 as a stabilizer. Under optimal conditions, spherical particles of 500nm with a zeta potential of +28mV were produced. Up to 98%, drug entrapment efficiency was observed. The mass ratio of PEI:DS played a significant role in controlling particle size and entrapment efficacy. PDNPs shown to be a good mucoadhesive drug delivery system as confirmed by *ex vivo wash off test*. In vitro dissolution studies revealed that PGE-loaded PDNPs manifested a prolong release characteristic with a burst release within 5 min. In addition, they remained effectively against oral bacteria. (Waree Tiyaboonchai et al. 2014)

Niosomes

"Formulation and Evaluation of Niosomes Containing Punicalagin from Peels of Punica Granatum"

The objective of the present study is to develop and validate a simple, precise, accurate, and economical analytical method for the estimation of Punicalagin extracted from peels of *Punica granatum*. To perform the compatibility study of drug, Punicalagin with the excipients used in formulating niosomes. To develop a vesicular system like niosomes which act as carriers and hence will help in penetration of drug through skin and provide a prolong release. Punicalagin is chemically named as 2, 3-(S)-hexahydroxydiphenoyl-4,6-(S,S)-gallagyl-D-glucose and belongs to a category of hydrolysable tannin. Thus, to protect its hydrolysis, it is formulated into a nanocarrier system known as niosomes which is based on the preparation of niosomes by using a non-ionic surfactant in varying amounts and keeping the amount of cholesterol constant. The formulations were evaluated on the basis of evaluation parameters and thus optimized for the best formulation. (Priya Hanu and Singh Harmanpreet, 2012)

Synthesis, Biological Investigation and Docking Study of Novel Chromen Derivatives as Anti-Cancer Agents

Authors: Dube, Pritam N.; Sakle, Nikhil S.; Dhawale, Sachin A.; More, Shweta A.; Mokale, Santosh N.
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Background: According to the latest global cancer data, cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. Among that female breast cancer ranks as the fifth leading cause of death (627000 deaths, 6.6%). The main causative factor involved in breast cancer development and progression is the Estrogen Receptor (ER) which is the essential target for anti-cancer drug discovery. Since millennia ER-α has been considered as an oncology mark for the treatment of breast cancer.

Methods: A series of novel 6-methyl-3-(3-oxo-1-phenyl-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propyl)-2Hchromen-2-one was designed, synthesized and screened for their anti-breast cancer activity against estrogen receptor-positive MCF-7, ZR-75-1 and negative MDA-MB-435 human breast cancer cell lines. Estrogen level of all the potent cytotoxic compounds were measured on day 30 of intoxication was compared with the control and N-

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REVIEW ARTICLE

Targeting Small Molecule Tyrosine Kinases by Polyphenols: New Move Towards Anti-tumor Drug Discovery

Nikhil S. Sakle[1], Shweta A. More[1], Sachin A. Dhawale[1] and Santosh N. Mokale[1,*]

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ARTICLE HISTORY

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Abstract: ***Background*****:** Cancer is a complex disease involving genetic and epigenetic alteration that allows cells to escape normal homeostasis. Kinases play a crucial role in signaling pathways that regulate cell functions. Deregulation of kinases leads to a variety of pathological changes, activating cancer cell proliferation and metastases. The molecular mechanism of cancer is complex and the dysregulation of tyrosine kinases like Anaplastic Lymphoma Kinase (ALK), Bcr-Abl (Fusion gene found in patient with Chronic Myelogenous Leukemia (CML), JAK (Janus Activated Kinase), Src Family Kinases (SFKs), ALK (Anaplastic lymphoma Kinase), c-MET (Mesenchymal- Epithelial Transition), EGFR (Epidermal Growth Factor receptor), PDGFR (Platelet-Derived Growth Factor Receptor), RET (Rearranged during Transfection) and VEGFR (Vascular Endothelial Growth Factor Receptor) plays major role in the process of carcinogenesis. Recently, kinase inhibitors have overcome many problems of traditional cancer chemotherapy as they effectively separate out normal, non-cancer cells as well as rapidly multiplying cancer cells.

Methods**:** Electronic databases were searched to explore the small molecule tyrosine kinases by polyphenols with the help of docking study (Glide-7.6 program interfaced with Maestro-v11.3 of Schrödinger 2017) to show the binding energies of polyphenols inhibitor with different tyrosine kinases in order to differentiate between the targets.

Results**:** From the literature survey, it was observed that the number of polyphenols derived from natural sources alters the expression and signaling cascade of tyrosine kinase in various tumor models. Therefore, the development of polyphenols as a tyrosine kinase inhibitor against targeted proteins is regarded as an upcoming trend for chemoprevention.

Conclusion**:** In this review, we have discussed the role of polyphenols as chemoreceptive which will help in future for the development and discovery of novel semisynthetic anticancer agents coupled with polyphenols.

Keywords: Tyrosine kinase, Polyphenols, Docking analysis.

1. INTRODUCTION

Cancer is a complex disease which involves genetic and epigenetic alterations that allow cells to escape normal homeostatic [1]. Signaling pathways play a vital role in higher-level cellular processes, like apoptosis, proliferation and development. Modification in signaling pathways can be fuel for cancer progression as it is intimately involved in cell growth, cell division and cell death [2]. Another most common path in cancer development and progression is mutation in number of genes. Mutated genes are frequently found in different human cancers followed by activation thus cellular abnormality leading to cancer initiation [3]. Tyrosine kinases are the main mediators of the signaling pathway and play vital roles in different biological processes. Normally these signaling pathways avoid deregulated proliferation towards apoptotic stimuli. Recent studies have shown the involvement of tyrosine kinases in the pathogenesis of cancer. In cancer, these signaling cascades are genetically and epigenetically altered. As a result, abnormal enhanced signaling gives these enzymes a leading oncoprotein status, ensuing in the faulty of signaling networks [4].

2. BIOACTIVE NATURAL PRODUCTS FROM PLANTS

Natural Products, particularly plants, have multiple biological functions and are used for the treatment of various diseases in developed and developing countries from ancient

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Chemomodulatory effects of *Alysicarpus vaginalis* extract via mitochondria-dependent apoptosis and necroptosis in breast cancer

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ABSTRACT

The present study intended to assess the anticancer potential of *Alysicarpus vaginalis* ethyl acetate fraction (AVEAF) in breast cancer cell lines (MCF-7 and MDA-MB-453) and against *N*-methyl-*N*-nitrosourea (MNU) induced mammary carcinoma in Sprague-Dawley rats which resemble the human estrogen dependent breast cancer. The SRB assay showed that the maximum growth inhibition rate of AVEAF on MCF-7 cell was 27.12 at 100 µg/ml. Flow cytometry analysis observed that AVEAF induced the cell cycle arrest at the S phases and decreased in mitochondrial membrane potential on the MCF-7 cells. AVEAF elevated intracellular ROS level in the MCF-7 cells which were reversed with *N*-acetycysteine (2 mM) pretreatment indicating that AVEAF induced mitochondrial-mediated apoptosis via augmentation of intracellular ROS. Western blotting exhibited that AVEAF increased the expression of pro-apoptotic protein Bax while decreasing anti-apoptotic proteins Bcl-2 and Bcl-xL expression which promoted the cleavage of caspase-9, PARP1, RIPK 1, and RIPK 3. Additionally, AVEAF exerted anticancer effect on tumor-bearing rats and the tumor inhibition rate is 50%. Data of the study indicate that AVEAF exhibits In Vitro and In Vivo anticancer activities that associate with its ROS-mediated mitochondrial-mediated intrinsic pathway of apoptosis and necroptosis in MCF-7 cells and may serve as a potential against breast cancer.

ARTICLE HISTORY
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Introduction

In the growing era of cancer, breast cancer is the most common cause of death in the women. As of noted, more than 3.1 million women with a history of breast cancer have been reported in the United States (January 2018; U.S. Breast Cancer Statistics, 2019) (1).Whereas current Indian data have shown that one in 22 women develop breast cancer (2). Natural products are complementary and alternative sources widely accepted and used in cancer therapy in developed countries due to the variety in the structure and the biological mechanism of action of their compounds (3). It has been observed that such natural products can function as chemomodulatory and chemopreventive agents that affect the processes of mammary tumorigenesis, like initiation, promotion, and progression (4). Plants are the main source of bioactive metabolites like phenolic, quinones, glucosinolates, terpenoids, and alkaloids with antioxidant and anticancer activities (5). The carcinogens may act through the production of reactiveoxygen species (ROS). Increased production of ROS was found to play key roles in damage and loss of function of tissues and organs (6). ROS may also lead to damage cellular constituents like proteins, DNA, and lipid, thus, initiating various chronic diseases. Traditionally whole plant has been used for the treatment of cytotoxicity, renal calculi, sepsis, diuretic, kidney disorders, skin related problems, leprosy, hepatoprotective, and pulmonary troubles. Exploration of phytoconstituents possessing both antioxidant and anticancer properties is of great remedial importance (7–9).

The present study investigated whether *Alysicarpus vaginalis* ethyl acetate fraction (AVEAF) could serve as a more effective cancer chemomodulatory for plant-derived anticancer agents. The study also aimed to find the possible mechanism of action of this fraction during tumor regression in an efficient way In Vitro and In Vivo model.

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ORIGINAL ARTICLE

Quantitative Assessment of Tactile Allodynia and Protective Effects of flavonoids of *Ficus carica* Lam. Leaves in Diabetic Neuropathy

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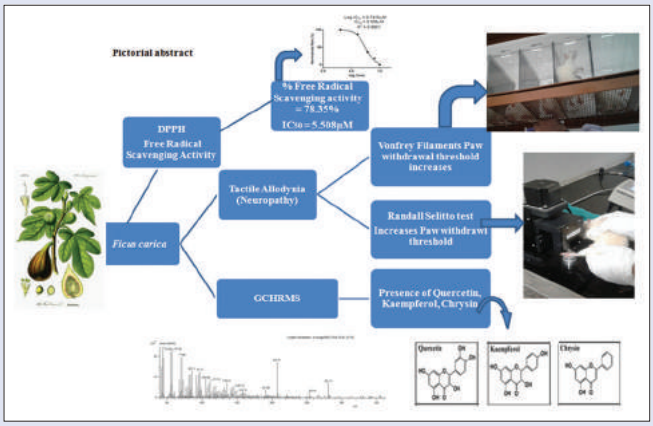
ABSTRACT

Background: Flavonoids, a group of polyphenols responsible for protective role against many diseased conditions, provide antioxidant activity which is the reason for their medicinal properties. Tactile allodynia is a behavioral biomarker of neuropathy that is well estimated by von Frey filaments and Randall–Selitto test. **Objective:** *Ficus carica* Lam. leaves were studied for the conformation of flavonoids in ethyl acetate fraction of methanolic extract (FCEA) using GC-HRMS for the identification of flavonoids. It was analyzed for antioxidant activity by *in vitro* free radical scavenging activity, performed using 2,2-diphenyl-1-picrylhydrazyl (DPPH) followed by blood glucose-level estimation, evaluation of neuropathic pain, and kidney and liver function tests in diabetic rats. **Materials and Methods:** The shade-dried leaves of *F. carica* Lam. were extracted with methanol and after that fractionated using ethyl acetate (FCEA). The characterization of FCEA was established using GC-HRMS. *In vitro* free radical scavenging activity was performed using DPPH assay. Diabetes was induced using streptozotocin (40 mg/kg/intraperitoneally), and effects of FCEA were studied on blood glucose level, neuropathy markers, and liver and kidney functions of diabetic rats. **Results:** GC-HRMS results highlighted the presence of quercetin, kaempferol, and chrysin in FCEA with free radical scavenging activity of 78.35% and IC_{50} value of 5.508 μM. FCEA reduces glucose levels and also shows protective effects in case of diabetic neuropathy as it increases the threshold of withdrawal latency in tactile allodynia and also decreases the serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, blood urea nitrogen, and creatinine levels. **Conclusion:** The protective effects of FCEA against diabetic neuropathy, hepatoprotective and nephroprotective effects might be due to strong antioxidant property of important flavonoids present which is confirmed in the study.

Key words: Chrysin, diabetic neuropathy, kaempferol, quercetin, Randall Selitto, von Frey

SUMMARY

- The research work shows the presence of quercetin, kaempferol, and chrysin in *Ficus carica* Lam. leaves; along with this, it has depicted *in vitro* free radical scavenging activity by 2,2-diphenyl-1-picrylhydrazyl assay method. After quantitative assessment of tactile allodynia, this plant sample has proven protective effects in diabetic neuropathy, and these effects were compared with surgical model of neuropathy by von Frey filaments and Randall–Selitto test.



Abbreviations used: BSTFA: N, O-Bis (trimethylsilyl) trifluoroacetamide; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FCEA: Ethyl acetate fraction from methanolic extract of leaves of *Ficus carica* Lam.; GC-HRMS: Gas chromatography–high-resolution mass spectrometry.

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INTRODUCTION

Polyphenolic substances are ubiquitously found chemical constituents in a variety of plants having medicinal properties.[1-4] A large number of plants contain flavonoids; they further consist of flavones, flavonols, isoflavonoids, anthocyanidins, and chalcones.[2,3] It has a protective role in carcinogenesis,[4,5] inflammation,[4,5] atherosclerosis,[4] thrombosis,[4] diabetes, and cardiovascular diseases[5] and has activities such as antiviral,[4,5] antimicrobial,[4] antihepatotoxic,[4] antiosteoporotic,[4,6] antiulcer,[4] immunomodulatory,[4] antiproliferative,[4,6] and apoptotic[4] as a result of their antioxidant actions.[4-6] In the last few years, gas chromatography–mass spectrometry (GC-MS) has established as a firm platform for analysis of plant's secondary metabolites and phytoconstituents. It is a hyphenated system, a compatible technique

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Original Article

Ameliorative Potential of *Allium cepa* Lam. Leaves on Diabetes Induced and Chronic Constriction Injury Induced Neuropathic Pain in Experimental Rats

Dureshahwar Khan[1], Mubashir Mohammed[1], Aman Upaganlawar[2], Chandrashekhar D. Upasani[2], Hemant D. Une[1,*]

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ABSTRACT

Background: Neuropathy can be induced in rats by peripheral injuries, depending on compression of complete or a section of sciatic nerve and chemically by Streptozotocin (STZ). **Materials and Methods:** In the present study neuropathic pain were induced in rats by two methods, chronic constriction injury (surgical model) and STZ (40mg/kg/i.p.) induced diabetes (drug induced model). In both the models, behavioural as well as markers of oxidative stress were studied. Behavioural parameters were tested using vonfrey hair and Randall Selitto analgesiometer whereas biochemical parameter includes glycosylated haemoglobin and markers of oxidative stress. The study was further supported by histopathology of sciatic nerve. Flavonoid rich extract of *Allium cepa* Lam. leaves was administered at three different doses viz. 25, 50 and 100mg/kg/p.o to the rats with neuropathic pain. Both the models of neuropathic pain showed significant alteration in behavioural as well as oxidative stress parameters. **Results:** Treatment of *Allium cepa* leaves extract showed dose dependent improvement in behavioural and biochemical parameters towards normal (p value <0.001, <0.05 and <0.01). The altered histopathological changes in sciatic nerve were also significantly improved as compared to rats with neuropathic pain. **Conclusion:** The neuroprotective effects of the *Allium cepa* leaves extract is a virtue of its strong antioxidant activity.

Key words: *Allium cepa*, Neuropathy, CCI, Oxidative stress, Sciatic nerve.

INTRODUCTION

Different animal models of neuropathy showed a strong correlation of sciatic nerve with neuropathic pain. Peripheral nerve injury models involve surgical procedures at sciatic nerve to induce neuropathy, whereas drug induced neuropathy and disease induced neuropathy are models developed due to oxidative stress, degeneration or neurotoxicity of peripheral nerves *i.e* sciatic nerve.[1] Surgical models targeting nerve result in a chronic mechanical allodynia on injured paw. These models include chronic constriction injury, sciatic nerve cuffing, partial sciatic nerve ligation, spinal nerve ligation or common peroneal nerve ligation.[2] While the disease induced neuropathy commonly include diabetic neuropathy model in research groups,[1] chronic hyperglycemia induces oxidative stress through multiple pathways like redox imbalances, altered protein kinase C activity and mitochondrial overproduction of superoxide[3] and this plays a significant role in development of diabetic complications including diabetic neuropathy.[4] While, sciatic nerve injury is associated with excessive production of reactive oxygen species, calcium ions entry and apoptosis; calcium overload through Transient Receptor Potential (TRP) cation channel and pain

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DEVELOPMENT OF HPLC METHOD FOR DETERMINATION OF TAMSULOSIN USING QUALITY BY DESIGN (QBD) APPROACH

Jaiprakash N. Sangshetti,[a]* Dhanashree K. Chivte,[a] Mohammed Imran Anees,[a] Mallinath Langade,[b] Faraz Khan,[a] Rana Zainuddin,[a] Zahid Zaheer,[a] Paresh Mahaparale[c]

Keywords: Tamsulosin; QbD approach; RP-HPLC method; Box-Behnken model; ICH guidelines.

An HPLC method for Tamsulosin was developed by using a quality by design (QbD) novel concept. QbD has gained importance in recent times due to regulatory requirements in industrial application. Chromatographic separation of Tamsulosin was carried out by using C_8 column, and mobile phase used was methanol and distilled water (40:60 v/v) for proper separation process. Separation by using water as a solvent is beneficial as it is cost effective process and industrially applicable. In the development of the HPLC method, factors like injection volume, conc. of methanol, the column vent temperature is critical in maintaining. Hence the Box-Behnken optimization model was applied for the main, interaction and quadratic effects of these three factors on the selected response. The effect of these parameters was studied on the tailing factor (resolution). Results were analysed during a surface diagram. Verification of the software-generated result was done by taking six replicates of the run. Finally, the method was validated according to ICH guidelines.

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INTRODUCTION

Tamsulosin (5-[(2R)-2-{[2-(2-ethoxyphenoxy)ethyl]-amino}propyl]-2-methoxybenzene-1-sulfonamide) acts as adrenergic α-antagonists and is maximally used to treat symptomatic benign prostatic hyperplasia (BPH), which will help with the passage of kidney stones, and also for urinary retention. Tamsulosin acts as a selective antagonist at α_{1A} and α_{1B}-adrenoceptors in the prostate, prostatic capsule, prostatic urethra, and bladder neck. The three discrete α_1-adrenoceptor subtypes such as α_{1A}, α_{1B} and α_{1D} were also identified and their distribution differs between human organs and other tissue. It was noted that there are approximately 70% of the α_1-receptors in the human prostate, which were of the α_{1A} subtype. The blockage in these types of receptors will cause relaxation of smooth muscles in the bladder neck and prostate, and which thus decreases urinary outflow resistance in males. [1]

To the best of our knowledge HPLC method using a simple UV detector by applying the QbD approach is not available. As per International Conference on Harmonization (ICH) guidance on pharmaceutical development, "QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process control and which is dependent on quality risk management and its related science.[2] QbD has gained special attention in current times due to regulatory requirements in the research work.

US-FDA has accelerated QbD drive to encourage the risk-based approach and thorough understanding of processes, which is ultimately going to help the regulatory bodies in the review process.

The basic foundation behind QbD is that quality is 'designed' into the process at the onset to the establishment of the method by a thorough understanding of the effect of the various system parameters are studied. Effects are analyzed for their influence on the quality of the product that is desired. This is nothing but ultimately to establish the design space for the method. Design space is defined as a "multidimensional combination and interaction of input variables that have been demonstrated to assure quality."[3]Some of the methods have been reported for the development of the HPLC method for Tamsulosin.[4-14]

MATERIALS AND METHODS

Tamsulosin standard active pharmaceutical ingredient (API) was procured from Hetero Drugs Limited (Hyderabad) and solvents were supplied from Dodal Enterprises and Badar chemicals, Aurangabad. Distilled HPLC grade water was prepared in the quality assurance lab of Y. B. Chavan College of Pharmacy, Aurangabad. The instrument used for HPLC analysis work was performed by using a Shimadzu LC20 model with C_8 column of 4.6×150mm; 5µmplates

Tamsulosin sample preparation

The stock solution of Tamsulosin for optimization of experiments was prepared by accurately weighing 10mg of Tamsulosin and dissolving it in 100 mL of the mobile phase composing of methanol and water 40:60 combination.

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Determination of Losartan potassium & Ramipril hydrochloride in Pharmaceutical Preparation by RP-LC technique

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Abstract

RP-HPLC system has been produced for synchronous estimation of Losartan potassium and Ramipril, this strategy is straightforward, fast, and exceptional for estimation of each Drug. The mobile fluid phase has been composed through using.05M sodium perchlorate and acetonitrile in the fixation proportion of 70:30 (v/v) and it is comprising heptane's sulphonic acid .1%, the consistent stream pace ie flow rate of 1µg/mL has been kept up for the examination at a pH 3.2 The drugs have been isolated on a 150-4.6 mm i.D., 5µm molecule, Cosmosil C18 column. UV location turned onto λmax at 210 nm. The methodology gets set up for all validation parameters. Accuracy linearity and precision were in the concentration of 30–70 µg/mL of Losartan and 1.75–3.25 µg/mL for Ramipril.

Keywords

Ramipril Hydrochloride; Losartan Potassium; RP-HPLC system;

Introduction

Losartan potassium is an angiotensin II receptor antagonist used for the remedy of hypertension. Ramipril is another angiotensin-converting enzyme-inhibiting, an antihypertensive drug. The structures of those drugs are proven in Figure 1. A mixture of 50 mg Losartan potassium, 2.5 mg Ramipril, mostly very broadly used for the remedy of hypertension however a literature search found out that no HPLC technique is available for simultaneous RP-HPLC dedication of these drugs in preparations. An HPLC method became therefore advanced for evaluation of Losartan potassium and Ramipril combined dosage forms [2–6]. The approach defined is simple, rapid, specific, and accurate.

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ORIGINAL ARTICLE

Enhancement of Dissolution of Fenofibrate Using Complexation with Hydroxy Propyl β-Cyclodextrin

Hidroksi Propil β-Siklodekstrin ile Kompleksasyon Kullanılarak Fenofibratın Çözünmesinin Arttırılması

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ABSTRACT

Objectives: The aim of the present study was to enhance the dissolution rate of fenofibrate using complexation with hydroxy propyl β-cyclodextrin (HPβCD).

Materials and Methods: The phase solubility behavior of fenofibrate was studied in various concentrations of (HPβCD) aq. solution at 37°C. The solubility of fenofibrate increased with an increase in the amount of HPβCD aq. solution. Gibbs free energy $(\Delta G^{\circ})_{tr}$ values were all negative. Complexes of fenofibrate with HPβCD were prepared in 1:1 ratio by kneading and coprecipitation. These complexes were evaluated by dissolution studies, fourier transform infrared (FTIR) spectroscopy, and differential scanning calorimetry (DSC) studies.

Results: The complexation of fenofibrate with HPβCD exhibited an enhanced dissolution rate. The mean dissolution time of fenofibrate decreased significantly upon complexation. FTIR studies showed the formation of intermolecular hydrogen bonding between fenofibrate and HPβCD. DSC studies indicated a loss in crystalline state of fenofibrate in complexes.

Conclusion: Complexation with HPβCD can be used as a useful tool for the enhancement of dissolution of fenofibrate.

Key words: Fenofibrate, hydroxy propyl β-cyclodextrin, solubility, Gibbs free energy, dissolution rate

ÖZ

Amaç: Bu çalışmanın amacı, hidroksi propil β-siklodekstrin (HPβCD) ile kompleksasyon kullanarak fenofibratın çözünme hızını arttırmaktı.

Gereç ve Yöntemler: Fenofibratın faz çözünürlük davranışları (HPβCD) çeşitli konsantrasyonlardaki sulu çözeltisinde, 37°C'de çalışıldı. Fenofibratın çözünürlüğü, artan miktarda HPβCD'nin sulu çözeltisi ile arttı. Gibbs serbest enerji $(\Delta G^{\circ})_{tr}$ değerlerinin hepsi negatifti. HPβCD ile fenofibrat kompleksleri, 1:1 oranında yoğurma ve kopresipitasyon ile hazırlandı. Bu kompleksler, çözünme çalışmaları, fourier dönüşümü kızılötesi spektroskopisi (FTIR) ve diferansiyel tarama kalorimetrisi (DSC) çalışmaları ile değerlendirildi.

Bulgular: Fenofibratın HPβCD ile kompleksasyonu, gelişmiş bir çözünme hızı sergiledi. Fenofibratın ortalama çözünme süresi, kompleksasyon üzerine önemli ölçüde azaldı. FTIR çalışmaları fenofibrat ve HPβCD arasında moleküller arası hidrojen bağlanmasının oluşumunu göstermiştir. DSC çalışmaları komplekslerde kristalin fenofibrat durumunda bir kayıp olduğunu gösterdi.

Sonuç: HPβCD ile kompleksasyon, fenofibratın çözünmesinin arttırılması için yararlı bir araç olarak kullanılabilir.

Anahtar kelimeler: Fenofibrat, hidroksi propil β-siklodekstrin, çözünürlük, Gibbs serbest enerjisi, çözünme hızı

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Development and Biopharmaceutical Characterization of BCS Class II Drug – Naproxen by Two Way Complexation Solid Dispersion Technique

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Abstract: The objective of this study was to increase the solubility and bioavailability of Naproxen (NP) by fabricating ternary solid dispersion (tSDs) with water soluble polymer PEG 6000 and crospovidone. tSDs were prepared and optimized by 3^2 full factorial design with PEG 6000 level (X1) and CP level (X2) as independent variables and percent drug release (D80, (Y)) as dependent variable. The optimized tSDs were evaluated for their physicochemical properties which confirmed the formation of tSDs (DSC), SEM suggested smooth surface and compact structures. PXRD revels that drug was still present in crystalline form and was not molecularly dispersed in the complex especially in non-homogeneous part of the tSDs. The optimized tSDs revels that Dissolution rate (Y) was significantly affected by independent variable PEG 6000 (X1) while CP (X2) was insignificant. The transparent characteristics of tSDs was observed as a result of lowered Tg temperature gives higher dissolution rate up to 97.70 % for optimized formulation (F9). The pharmacokinetic study in Han Wistar rats showed that the tSDs had the greatest effect on oral bioavailability of NP *in vivo* test showed that NP (tSDs) presented significantly larger $AUC_{0\text{-}t}$, which was 1.09 folds more than that of marketed formulation. C_{max} of NP (tSDs) also increased from 120 µg/ml to 146 µg/ml compared to that of marketed formulations and generated shortened T_{max} of (1.0 ± 0.416) h, compared to marketed dosage form (2.0 ± 0.456) h.

Key words: Solid dispersion, glass transition temperature, ternary solid dispersion, level optimization, & pharmacokinetics

Introduction

Systemic availability of drug depends on the two important steps. These two steps determine the rate and extend of drug absorption, so called as Rate Limiting Steps. i. e. Drug dissolution and Drug permeation [1]. Drug dissolution is always depends on the solubility of that particular drug which is hydrophobic, poorly aqueous soluble drug like NP, falls under the category of BCS class II drug [2]. The solid dispersion technique for water-insoluble drugs developed by Chiou and Reigelman provides an efficient method to improve the dissolution rate of a drug. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material [3]. Methods used to obtain solid dispersions affects the drugs crystallinity as Mooter *et al.*, revealed that with a 20/80 w/w Itraconazole/Inutec SP1 extrudate (solid solution) a dissolution of 100% could be obtained after 30 min. The same composition prepared by spray drying; however, gave rise to a dissolution of only 50% [4]. The presence of different proportions of PEG systematically lowers the degree of complexed drug NP with β-CD due to competing equilibria gives rise to ternary solid dispersions [5]. The solid dispersions and ternary complexes formed exhibits increased dissolution behaviour as result of metastable amorphous material formed which in turn cooled, it usually crystallizes below the melting temperature, (Tm). When cooling rate is sufficiently fast, the liquid fails to crystallize, and a super cooled state is attained. Further cooling to below the glass transition temperature (Tg) causes the system to fall out of structural equilibrium. Since this state is not physically stable, structural changes occur over time to achieve a more energetically favoured state leads to less dissolution rate [6]. Solid dispersions of PEG6000 and Loperamide prepared by spray drying showed deteriorated dissolution rate on storage at high temperature (40°C and 0% RH) and in conditions of higher relative humidity (25°C and 52% RH) resulting in

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Anti-Cancer Agents in Medicinal Chemistry, 2019, *19*, 000-000

RESEARCH ARTICLE

Synthesis, Biological Investigation and Docking Study of Novel Chromen Derivatives as Anti-Cancer Agents

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ARTICLE HISTORY

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Abstract: ***Background*:** According to the latest global cancer data, cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. Among that female breast cancer ranks as the fifth leading cause of death (627000 deaths, 6.6%). The main causative factor involved in breast cancer development and progression is the Estrogen Receptor (ER) which is the essential target for anti-cancer drug discovery. Since millennia ER-α has been considered as an oncology mark for the treatment of breast cancer.

***Methods*:** A series of novel 6-methyl-3-(3-oxo-1-phenyl-3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propyl)-2H-chromen-2-one was designed, synthesized and screened for their anti-breast cancer activity against estrogen receptor-positive MCF-7, ZR-75-1 and negative MDA-MB-435 human breast cancer cell lines. Estrogen level of all the potent cytotoxic compounds were measured on day 30 of intoxication was compared with the control and N-methyl-N-nitrosourea (MNU) group. The docking study was performed to predict binding orientation towards the estrogen receptor-α.

***Results*:** Among the synthesized compounds C-3, C-5 and C-15 were showing potent cytotoxicity against estrogen receptor-positive MCF-7. The potent cytotoxic compounds C-3, C-5 and C-15 were further evaluated for *in vivo* anti-cancer activity by MNU induced mammary carcinoma in female sprague-dawley rats. The *in vivo* anti-cancer activity result shows that the compound C-5 has protuberant affinity towards estrogen receptor as standard TAM (Tamoxifen). The docking of the synthesized chromen derivatives showed interaction modes comparable to that of the co-crystallized ligands.

***Conclusion*:** The designed class has very promising starting point for the development and further improvement in anti-breast cancer class of drugs.

Keywords: Breast cancer, SERMs, chalcone, docking, novel chromene derivatives, anti-cancer agents.

1. INTRODUCTION

Initiation of malignant tumor results in the formation of abnormal cells of the breast consequently leading to mammary carcinoma [1]. The line of treatment includes the most day-to- day approach as surgery, radiation, chemotherapy, hormone therapy, targeted therapy or bone-directed therapy [2]. Among the mentioned treatment, the prominently used therapy is chemotherapy which works by killing the cells, causing the tumor to shrink [3].

In the era of advanced biological processes which involve the vast development in cancer, still there is an urge to improve and implement new and effective molecules which may help out to bring the disease state in control. Craving and exploring towards the effective approaches came into existence of isolation and evaluation of phyto-constituents of natural origin for developing new chemotherapeutic agents [4]. Presently, there is a vast scientific and commercial attention for the discovery of potent, safe and selective breast cancer drugs [5]. The significance of natural products for drug discovery has been striking. Natural anticancer pharmacophores play a major role in sensitizing the tumor cells toward apoptosis [6]. Till date, a number of natural products have been isolated from plants, among which Chalcone (belonging to flavonoid class) exemplifies the most curious class of biologically active compounds. As naturally occurring and synthetic Chalcone exhibits anti-cancer activity, it ultimately turns out to be a major part of concern [7].

As stated, the flavonoid class of natural products exhibits miscellaneous pharmacological properties among which are included Chalcone and Coumarin. The two classes of flavonoids differ in structural moiety as Coumarin (a bicyclic heterocyclic compound) contains benzene and 2-pyrone rings, whereas Chalcone contains two aromatic rings connected by α, β-unsaturated carbonyl group [8, 9]. The synthetic Chalcone-Coumarin derivatives have notable cytotoxic activity against various cancer cells. There is a need for new potent anticancer agents which show more selectivity towards cancerous cells and lack of toxicity [10]. As far as steroidal hormones are concerned viz., estrogen and progesterone play a vital role in sexual differentiation and fertility. The mechanism of action involves binding to a specific nuclear receptor within the cell: Estrogen Receptor (ER) and Progesterone Receptor (PR) which are considered as prognostic factors for mammary carcinoma [11]. Approximately 70% of human mammary tumors express both receptors [12, 13].

Thus with all the observed facts and measures of key structural features, it can be stated that the Chalcone-Coumarin derivative may prove helpful for targeting breast cancer cells. This has made us inspired to synthesize novel similarities of medicinal value which may discover hybrid pharmacophores as a new class of anticancer agents (Fig. **1**), capable of targeting breast cancer cells.

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Current Drug Discovery Technologies, **2019,** *16,* **00-00**

REVIEW ARTICLE

Targeting Small Molecule Tyrosine Kinases by Polyphenols: New Move Towards Anti-tumor Drug Discovery

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Abstract: ***Background*****:** Cancer is a complex disease involving genetic and epigenetic alteration that allows cells to escape normal homeostasis. Kinases play a crucial role in signaling pathways that regulate cell functions. Deregulation of kinases leads to a variety of pathological changes, activating cancer cell proliferation and metastases. The molecular mechanism of cancer is complex and the dysregulation of tyrosine kinases like Anaplastic Lymphoma Kinase (ALK), Bcr-Abl (Fusion gene found in patient with Chronic Myelogenous Leukemia (CML), JAK (Janus Activated Kinase), Src Family Kinases (SFKs), ALK (Anaplastic lymphoma Kinase), c-MET (Mesenchymal- Epithelial Transition), EGFR (Epidermal Growth Factor receptor), PDGFR (Platelet-Derived Growth Factor Receptor), RET (Rearranged during Transfection) and VEGFR (Vascular Endothelial Growth Factor Receptor) plays major role in the process of carcinogenesis. Recently, kinase inhibitors have overcome many problems of traditional cancer chemotherapy as they effectively separate out normal, non-cancer cells as well as rapidly multiplying cancer cells.

Methods**:** Electronic databases were searched to explore the small molecule tyrosine kinases by polyphenols with the help of docking study (Glide-7.6 program interfaced with Maestro-v11.3 of Schrödinger 2017) to show the binding energies of polyphenols inhibitor with different tyrosine kinases in order to differentiate between the targets.

Results**:** From the literature survey, it was observed that the number of polyphenols derived from natural sources alters the expression and signaling cascade of tyrosine kinase in various tumor models. Therefore, the development of polyphenols as a tyrosine kinase inhibitor against targeted proteins is regarded as an upcoming trend for chemoprevention.

Conclusion**:** In this review, we have discussed the role of polyphenols as chemoreceptive which will help in future for the development and discovery of novel semisynthetic anticancer agents coupled with polyphenols.

Keywords: Tyrosine kinase, Polyphenols, Docking analysis.

1. INTRODUCTION

Cancer is a complex disease which involves genetic and epigenetic alterations that allow cells to escape normal homeostatic [1]. Signaling pathways play a vital role in higher-level cellular processes, like apoptosis, proliferation and development. Modification in signaling pathways can be fuel for cancer progression as it is intimately involved in cell growth, cell division and cell death [2]. Another most common path in cancer development and progression is mutation in number of genes. Mutated genes are frequently found in different human cancers followed by activation thus cellular abnormality leading to cancer initiation [3]. Tyrosine kinases are the main mediators of the signaling pathway and play vital roles in different biological processes. Normally these signaling pathways avoid deregulated proliferation towards apoptotic stimuli. Recent studies have shown the involvement of tyrosine kinases in the pathogenesis of cancer. In cancer, these signaling cascades are genetically and epigenetically altered. As a result, abnormal enhanced signaling gives these enzymes a leading oncoprotein status, ensuing in the faulty of signaling networks [4].

2. BIOACTIVE NATURAL PRODUCTS FROM PLANTS

Natural Products, particularly plants, have multiple biological functions and are used for the treatment of various diseases in developed and developing countries from ancient

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A Facile Synthesis of Substituted 2-(5-(Benzylthio)-1,3,4-oxadiazol-2-yl) pyrazine Using Microwave Irradiation and Conventional Method with Antioxidant and Anticancer Activities

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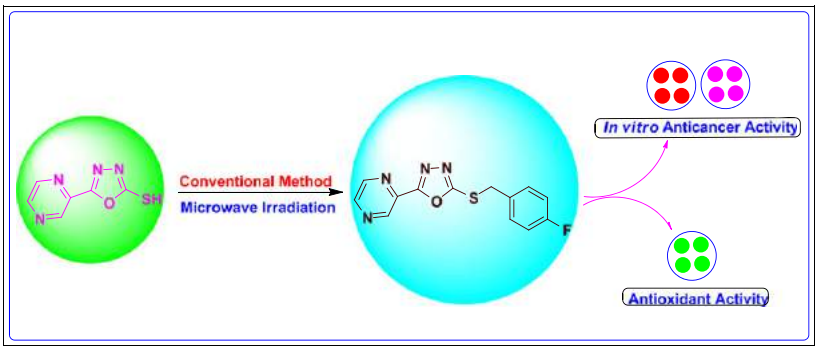

A series of novel substituted 2-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)pyrazine derivatives (**6a**–**n**) were synthesized under microwave irradiation and conventional conditions with less reaction time with good to excellent yields. All the synthesized compounds were screened for antioxidant and anticancer activities. Out of the 14 prepared derivatives, compounds **6f** and **6m** were most potent and active with antioxidant and anticancer activities, respectively. Also, the developed technique was simple, easy, and less time consuming.

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INTRODUCTION

Oxadiazole is a lead moiety in the designing of potent bioactive molecules [1]. The oxadiazole scaffold is a central part of biologically active compounds with various applications and pharmacological properties like antibacterial [2], antifungal [3], antitubercular [4], insecticidal [5], anticonvulsant [6], anticancer [7], antiviral [8], anti-inflammatory [9], antidiabetic [10], and immunosuppressive [11]. The 1,3,4-oxadiazole ring system has been identified as the main core of many bioactive molecules. For the discovery of new lead structures in drug discovery, based on high throughput screening, synthetic methodologies are required that deliver highly diverse derivatives in a timely manner. Under these circumstances, microwave-assisted chemistry appears to be a promising synthetic method [12]. Utility of microwave irradiation [13–15] to carry out organic reaction has now become a regular feature. The main benefits of performing the reaction under microwave conditions are the significant rate enhancements and the higher product yields with minimum time requirement. Here, we wish to report the development and implementation of the methodologies allowing for the synthesis of some novel 2-[(4-fluorobenzyl)thio-5-(pyrazin-2-yl)1,3,4-oxadiazole substituted derivatives. The oxadiazole has been known for over 50 years, so there have been several attempts to design antimicrobial and anticancer agents based on this heterocycle [16–18]. 1,3,4-Oxadiazole heterocycles are very good bioisosteres of amides and esters and can contribute substantially to increasing pharmacological activity by participating in hydrogen-bonding interactions with receptors [19].

In continuation of our work [20–22], on the synthesis of bioactive compounds, we have synthesized some 1,3,4-oxadiazole analogues. The synthetic protocols employed for the synthesis of oxadiazole derivatives **3** and **4** are presented in Schemes 1, 2, and 3, respectively.

RESULTS AND DISCUSSION

The first part of the study was aimed at optimizing the reaction conditions. The screening of model reaction of 2-[(4-fluorobenzyl)thio-5-(pyrazin-2-yl)1,3,4-oxadiazole **6a** (Scheme 2; Table 1) was performed. We have developed

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New *N*-phenylacetamide-incorporated 1,2,3-triazoles: [Et_3NH][OAc]-mediated efficient synthesis and biological evaluation†

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A facile, highly efficient, and greener method for the synthesis of new 1,4-disubstituted-1,2,3-triazoles was conducted using [Et_3NH][OAc] as a medium by the implementation of ultrasound irradiation *via* click chemistry, affording excellent yields. The present synthetic method exhibited numerous advantages such as mild reaction conditions, excellent product yields, minimal chemical waste, operational simplicity, shorter reaction time, and a wide range of substrate scope. The synthesized compounds were further evaluated for *in vitro* antifungal activity against five fungal strains, and some of the compounds displayed equivalent or greater potency than the standard drug. A molecular docking study against the modelled three-dimensional structure of cytochrome P450 lanosterol 14α-demethylase was also performed to understand the binding affinity and binding interactions of the enzyme. Furthermore, the synthesized compounds were evaluated for DPPH radical scavenging activity and antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain.

1. Introduction

1,2,3-Triazole, a five-membered heterocyclic ring system, is a very well-known biologically active pharmacophore constructed by the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, which is popular as a click chemistry reaction.[1] Over the last decade, 1,2,3-triazole has become one of the key structural motifs and is used in numerous fields including polymer chemistry,[2] material science,[3] and drug discovery.[4] 1,2,3-triazole-based molecules display various biological activities such as anti-fungal,[5,6] anti-bacterial,[6] anti-tubercular,[7] anti-inflammatory,[8] anti-allergic,[9] anti-HIV,[10] anti-cancer,[11] and anti-phytopathogenic.[12] Some marketed drugs have the 1,2,3-triazole unit in their structure, and these include Cefatrizine (a broad-spectrum antibiotic), Tazobactam (an antibiotic), and Carboxyamidotriazole (CAI) (a calcium channel blocker) (Fig. 1).

Azole drugs have broad-spectrum activities against most yeasts and filamentous fungi and are mostly used in antifungal chemotherapy.[13] Some well-known antifungal agents including fluconazole, voriconazole, ravuconazole, and itraconazole contain a 1,2,4-triazole ring in their structure, as shown in Fig. 2. However, their clinical uses have been restricted by their relatively high risk of toxicity, pharmacokinetic deficiencies, emergence of drug resistance, and undesirable side effects. These antifungal drugs inhibit CYP51, a key enzyme in the biosynthesis of ergosterol, through a mechanism in which the antifungal agent having a triazole scaffold is positioned perpendicular to the porphyrin plane with a ring nitrogen atom (N-4 of triazole) coordinated with a heme iron atom.[14] Over a couple of decades, the incidence of systemic fungal infections has increased due to cancer chemotherapy, organ transplantation, tuberculosis, and immunodeficiency virus (HIV) infection.[15] However, the extensive use of antifungal drugs has led to an increase in the resistance to these drugs.[16] Hence, there is an urgent need for developing new antifungal agents with effective activities, low toxicity, and minimum side effects.

Ionic liquids (ILs) are environment-friendly solvents because of their interesting properties and they can be used as alternatives to harmful organic solvents. Furthermore, they are useful in catalytic reactions[17] and organic synthesis[18] because of their

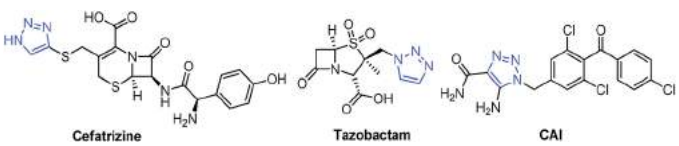

Fig. 1 Structures of drugs containing the 1,2,3-triazole unit.

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CHEMISTRY & BIOLOGY INTERFACE

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Synthesis of 1,2,3-triazole incorporated monocarbonyl curcumin analogues as potent antitubercular, antifungal and antioxidant agents

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Abstract: Curcumin is an active component of turmeric with potent therapeutic properties, but it is limited due to its poor solubility, stability and bioavailability. To enhance its efficacy, we designed a series of twelve dimeric 1,2,3-triazoles incorporated monocarbonyl curcumin analogue (**7a-l**) and evaluated for their *in vitro* antitubercular, antifungal and antioxidant activities against their respective strains. Most of the compounds shows good antitubercular as well as antioxidant activities. Among the newly synthesized series, compound **7h** was found as most potent antitubercular as well as antioxidant agent. The compound **7b**, **7i**, **7j** and **7l** were shows good antitubercular activity against *Mtb* H37Rv whereas, compound **7b**, **7i** and **7l** also shows good antioxidant activity. In support to activities, *in silico* ADME properties prediction have been also carried out in this study.

Keywords: Dimeric 1,2,3-triazoles, Monocarbonyl curcumin analogues, Antitubercular activity, Antioxidant activity, Antifungal activity.

Introduction

A “Golden Drug” from every kitchen of India is curcumin (*Curcuma longa*), commonly known as termeric. Curcumin and its analogues have been widely shows various therapeutic activities like wound healing capacity, anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, antidiabetic and treats skin diseases [1]. Owing to the potential importance of curcumin derivatives as key moieties in drug discovery, the worldwide efforts have made in the last few decades by many researchers in the synthesis and bioevaluation

EATON'S REAGENT CATALYZED SYNTHESIS, IN VITRO α-AMYLASE INHIBITORY ACTIVITY AND MOLECULAR DOCKING STUDY OF SOME SCHIFF'S BASES AS DIABETIC-II INHIBITORS

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Keywords: *α*-Amylase, Eaton's reagent, Schiff's bases, Solvent-free, Molecular docking

A series of Schiff's bases of p-tolylsulphonyl hydrazide were synthesized by using Eaton's reagent under solvent-free condition, characterized by spectroscopic data and for evaluated α-amylase inhibitory activity *in vitro*. Four among the studied compounds exhibited varying degrees of α-amylase inhibitory activity with IC_{50} values in the range of 115.48 to 169.42 µg mL^{-1}. The observed results were supported by the molecular docking study performed to understand the binding interaction of the title compounds with the active site of α-amylase enzyme. Results suggest that Schiff's bases of p-tolylsulphonyl hydrazide derivatives can act as potential antidiabetic drugs.

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INTRODUCTION

Diabetes mellitus, a metabolic disorder characterized by chronic hyperglycemia condition, has become a significantly growing disease all over the world due to changing lifestyles and increasing junk food in the diet. As per the reports of the International Diabetes Federation (IDF), approximately 366 million people have diabetes and the number may be doubled by 2030.[1] It is mainly caused by the lack of insulin, which includes increased morbidity, disability, mortality and represents a threat to the economies of all countries, especially in developing ones like India.[2] In diabetic patients, the immune system becomes weak by destroying insulin-producing cells, leading to a high level of blood glucose, which significantly increases the risk of long-term heart disease, stroke, dysfunction and kidney failure.[3]

α-Amylase is an enzyme that catalyzes the hydrolysis of carbohydrates and starch into glucose in human blood, resulting in hyperglycemic condition and eventually type-II Diabetes mellitus (T2DM). It is present in the saliva of human beings, where it begins the chemical process of digestion. Pancreas and salivary glands make α-amylase to hydrolyze dietary starch into disaccharides which are then converted by other enzymes to glucose that acts as a source of energy to the body. Inhibitors of α-amylase function by modulating the blood glucose level after a meal.[4] The ability of a drug to delay the production and absorption of glucose by inhibiting carbohydrate hydrolyzing enzymes - α-amylase and α-glucosidase is an important therapeutic approach for the development of antidiabetic drugs. Thus α-amylase functioning as a key enzyme for the digestion and absorption of starch in the blood is one of the targets in the treatment of T2DM.

Schiff's bases are the condensation products of primary amines with carbonyl compounds, named after the scientist Hugo Schiff. Schiff's bases possess imine or azomethine (–C=N–) functional group and constitute a versatile pharmacophore and reaction intermediates for the design, synthesis, and development of various bioactive lead compounds of various biological interest such as 4-thiazolidinone,[5] inorganic metal complexes[6] and azetidinones.[7] Furthermore, they are also well known to exhibit numerous biological activities such as antimicrobial,[8] antitubercular,[9] antioxidant,[10] anticonvulsant,[11] anti-inflammatory,[12] and anticancer activity.[13] They are also useful in pigments and dyes,[14] intermediates for organic synthesis,[15] polymer stabilizers[16] and corrosion inhibitors.[17]

Sulfonamide functionality is the basis of several drugs. Sulfamethoxazole (**a**) is an antibacterial sulfa drug. Acetohexamide (**b**) is a sulfonylurea used to treat diabetes mellitus. Ethoxzolamide (**c**) is a sulfonamide drug that acts on carbonic anhydrase inhibitors and widely used in the treatment of glaucoma and ulcers.[18] Mafenide (**d**), also known as sulfamylon, is a sulfonamide type medication that is used as an antibiotic. Furosemide (**e**) is used to treat fluid build-up due to heart failure, liver scarring or kidney disease and also in the treatment of high blood pressure.

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Supramolecular biomimetic catalysis by β-cyclodextrin for the synthesis of new antimicrobial chromeno[4,3-b] quinolin-isonicotinamides in water

Manisha R. Bhosle, et al. ***[full author details at the end of the article]***

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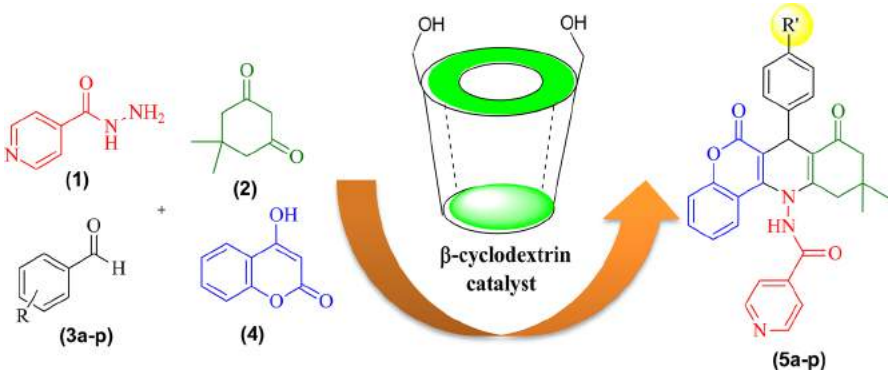
Abstract

Herein, a fast and convenient protocol for the synthesis of new isoniazid fused chromeno[4,3-b]quinolin was achieved through biomimetic catalysis by cyclodextrin in the water at 60–65 °C. The present investigation involves attractive characteristics such as the use of water as the reaction medium, one-pot conditions, short reaction periods, easy work-up/purification and reduced waste production. This method provides a green route for the synthesis of targeted scaffolds and also a wide substrate scope for several substituted aldehydes to provide good yields of the corresponding products. Furthermore, the catalyst can be easily recovered by simple filtration and reused several times without any substantial loss in activity. Our study also discloses the antimicrobial screening of new chromeno[4,3-b]quinolin-isonicotinamides against four bacterial and three fungal strains.

Graphic Abstract



Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-019-03987-x) contains supplementary material, which is available to authorized users.

Published online: 21 September 2019

HPLC METHOD DEVELOPMENT FOR DETERMINATION OF PYRAZINAMIDE AND RELATED SUBSTANCE BY USING QUALITY BY DESIGN (QBD) APPROACH

Ashish Dalal,[a] Mohammad Imran Anees,[a] Faraz Khan,[a] Mallinath Langade,[b] Firoz A. Kalam Khan,[c] Aniruddha Chabukswar[d] and Jaiprakash N. Sangshetti[a]*

Keywords: Quality by Design (QbD); HPLC; Pyrazinamide; Box-Behnken design

A robust and simplified high-performance liquid chromatography (HPLC) method was developed for the estimation of Pyrazinamide and its related substance. A systematic approach, one of the parts of QbD (quality by design) was used in suitable analytical method development. The HPLC segregation method was carried out with C-18 Column (3.9x300 mm, I. D. 10 µm), a mobile phase of phosphate buffer: acetonitrile (pH 3.0) 90:10 v/v, detected at 270 nm. Optimization to this method was done by response surface methodology by applying a three-level Box Behnken design with three center points.

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Introduction

Analytical methods contribute to the design process, manufacturing of high-quality drug products and its development pattern. Hence analytical method should be accurate and specific as well as robust. Now a day's QbD (quality by design) is applied to analytical techniques to get a reliable method to analyze the quality of the product. It also provides better regulatory compliance.[1-4] There was no method reported for the HPLC development method in a QbD environment for Pyrazinamide (PZA) drug. Hence, in this systematic HPLC method using QbD principles was outstanding in ensuring the quality of the method throughout the product lifecycle. This issue has presented a new challenge to the analytical chemistry field. A precise and applicable component of the QbD is the understanding parameters and their interaction results by a desired set of experiments.

This current study involves the development of overall science and risk-based HPLC method and subsequent validation in the analysis of active pharmaceutical constituent. QbD is a systemic process for building into a product from the final output process. QbD process means a complete understanding of the product with its related process of manufacturing, overall involvement of an investment in time and resources upfront in the discovery and development of the product. For QbD the product and process knowledge base must include an understanding of the variability of raw material, the relationship between a process and product critical quality attributes (CQA) and the association between a CQA and products clinical properties. QbD method of work deals with systematic science and depends upon product-based development and its risk factors affecting, its designing factors and techniques which should be according to ICH guidelines such as ICH Q8, Q9, and Q10. PZA is a first-line anti-tubercular agent. PZA tablets are used to treat active tuberculosis. WHO has listed this drug in the essential medicines category. PZA is applicable with a combination of other medications such as Rifampicin, Isoniazid, Streptomycin and Ethambutol. It is used in the first two months of the treatment to reduce the duration of treatment required. PZA is a potent antiuricosuric drug. It is used in hypouricemia and hyperuricosuria. It is safe in pregnancy. It is soluble in water, methanol and phosphate buffer. It possesses excellent oral absorption, metabolizing by the liver and is mainly excreted in the urine.[5] Pyrazinamide undergoes diffusion process through the mycolic acid present within this bacteria and pyrazinamidase enzyme converts to active pyrazinoic acid from pyrazinamide and binds to S1 protein attached to the ribosome and hence it shows inhibition effect for the killing of *mycobacterium tuberculosi.* In synthetic pathway[6] (Figure 1), Deamidation of PZA yields pyrazine-2-carboxylic acid. Ring oxidation is another major pathway, leading to 5-hydroxypyrazinamide, which in turn hydrolyzed to 5-hydroxypyrazinoic acid.

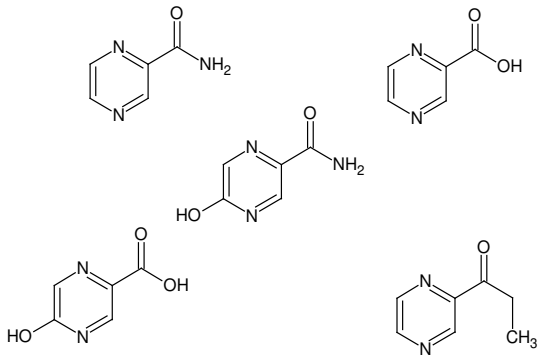

Figure 1. Pyrazinamide and its related impurities.

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Molecular docking, pharmacophore based virtual screening and molecular dynamics studies towards the identification of potential leads for the management of *H. pylori*†

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The enzyme pantothenate synthetase panC is one of the potential new antimicrobial drug targets, but it is poorly characterized in *H. pylori*. *H. pylori* infection can cause gastric cancer and the management of *H. pylori* infection is crucial in various gastric ulcers and gastric cancer. The current study describes the use of innovative drug discovery and design approaches like comparative metabolic pathway analysis (Metacyc), exploration of database of essential genes (DEG), homology modelling, pharmacophore based virtual screening, ADMET studies and molecular dynamics simulations in identifying potential lead compounds for the *H. pylori* specific panC. The top ranked virtual hits **STOCK1N-60270**, **STOCK1N-63040**, **STOCK1N-44424** and **STOCK1N-63231** can act as templates for synthesis of new *H. pylori* inhibitors and they hold a promise in the management of gastric cancers caused by *H. pylori*.

1 Introduction

The *Helicobacter pylori* infection in the patients with chronic gastritis and peptic ulcer can become the primary cause of gastric cancer.[1–5] Gastric cancer is the fourth common malignancy worldwide causing over 700 000 deaths per year. *H. pylori* is a microaerophilic, spiral-shaped Gram-negative bacterium which colonizes in the human stomach eventually causing duodenal and gastric ulcers. Broad spectrum antibacterials and antibiotics such as metronidazole, clarithromycin, levofloxacin, amoxicillin, tetracycline, furazolidone, and rifabutin are used in the treatment and management of *H. pylori* infection. Unfortunately, the efficacy of these antibiotics against *H. pylori* has weakened due to a strong resistance developed by *H. pylori* organism.[6,7] Furthermore, many factors such as the strain of *H. pylori*, the host genetic factor like polymorphism in the interleukin-1, gender, and individual's habits like smoking and their diet may aggravate the *H. pylori* infection. It is established that the colonization of the *H. pylori* with the nitro sating bacteria in the achlorhydric stomach becomes the primary cause of gastric cancer.[8] Therefore, eradication of the *H. pylori* infection and proper management and treatment of the duodenal and gastric ulcers is essential in the prevention of ensuing gastric cancer. Emergence of strong resistance is the main concern with most of the currently used broad spectrum antibacterials and antibiotics in *H. pylori* infection. Hence, design and development of the newer potential drug candidates effective against the newer targets specific for *H. pylori* may be advantageous. The enzyme pantothenate synthetase, encoded by the panC gene, catalyzes the biosynthesis of pantothenate (vitamin B5) from an adenosine triphosphate (ATP)-dependent condensation of the D-pantoate and the β-alanine in bacteria.[9] The pantothenate is a key precursor of the coenzyme A and the acyl carrier protein. Many intracellular processes such as fatty acid metabolism, cell signaling, synthesis of the polypeptides and the non-ribosomal peptides are regulated by the coenzyme A and the acyl carrier protein. Interestingly, mammals lack the pantothenate synthetase and its biosynthetic pathway and derive the pantothenate from their diet.[10] Thus, it is advantageous to target bacterium specific pantothenate

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Review article

Synthesis and biological activity of structurally diverse phthalazine derivatives: A systematic review

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A B S T R A C T

Phthalazine, a structurally and pharmacologically versatile nitrogen-containing heterocycle, has gained more attention from medicinal chemists in the design and synthesis of novel drugs owing to its pharmacological potential. In particular, phthalazine scaffold appeared as a pharmacophoric feature numerous drugs exhibiting pharmacological activities, in particular, antidiabetic, anticancer, antihypertensive, antithrombotic, anti-inflammatory, analgesic, antidepressant and antimicrobial activities. This review presents a summary of updated and detailed information on phthalazine as illustrated in both patented and non-patented literature. The reported literature have described the optimal pharmacological characteristics of phthalazine derivatives and highlighted the applicability of phthalazine, as potent scaffold in drug discovery.

1. Introduction

Phthalazine, an organic heterocyclic compound, also referred to as benzopyridazine or benzo-orthodiazine.[1–3] Phthalazine-1(2*H*)-one and 2,3-dihydrophthalazin-1,4-dione constitute two important functionalized forms of the phthalazines moiety. Extensive research on its chemical properties has revealed that introducing structural versatility improves its effectiveness with regard to numerous biological activities such as anticancer,[4–26] anticonvulsant,[27–31] antihypertensive,[32–34,36a] cardiotonic,[35] antidiabetic,[26,39–41] analgesic,[38,42] antipsychotic,[43] antimicrobial,[26,44] antithrombotic,[45] vasorelaxant,[26,46] anti-inflammatory,[26,47–53] antitrypanosomal,[54] antileishmanial,[55] asthma,[60] chronic obstructive pulmonary disorder,[60] to name a few. Phthalazine containing agents, specifically, inhibitors of poly-[ADP-ribose] polymerase (PARP),[4–9,56–59] phosphodiesterase (PDE)[48–53,60,61] and aldose reductase (AR)[40,41] have exhibited excellent enzyme inhibitory activities. Phthalazines has gained great importance owing to its antitumor activity in blood cancer, breast cancer, colon cancer, lung cancer and renal cancer. Numerous drug molecules are available in the market containing phthalazine as a pharmacophore and also in clinical development to elucidate the utility of phthalazine as a core molecule.

There are few reviews available in the literature which covers either chemistry or biological utility of phthalazine and their analogs. However, the reviews reported are not covering complete literature of chemistry and biology of phthalazine analogs. This is the first comprehensive review with an updated and detailed overview of phthalazine, covering the patented and non-patented literature of the last three decades.

2. Synthetic strategies

The considerable efforts of scientists have led to the development of various strategies to synthesize several derivatives of phthalazine.[9,15,37,62–81] Some of which are outlined in the schemes below

2.1. Synthesis of phthalazinones

In 2003, Mogilaiah et al. introduced novel strategy using solid state organic reaction[62] (SSOR) in the synthesis of phthalazinone **3** by condensing acid hydrazides **2** with phthalic anhydride **1** using *p*-toluene sulphonic acid (*p*TSA) as depicted in Scheme 1. The reaction is simple, straightforward, and quicker without yielding side products.

2.2. Synthesis of substituted triazolo phthalazine

In 2004, Carling et al. reported the synthesis of triazolo phthalazine

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New *N*-phenylacetamide-incorporated 1,2,3-triazoles: [Et_3NH][OAc]-mediated efficient synthesis and biological evaluation†

Satish V. Akolkar,[a] Amol A. Nagargoje,[a] Vagolu S. Krishna,[b] Dharmarajan Sriram,[b] Jaiprakash N. Sangshetti,[c] Manoj Damale[d] and Bapurao B. Shingate*[a]

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A facile, highly efficient, and greener method for the synthesis of new 1,4-disubstituted-1,2,3-triazoles was conducted using [Et_3NH][OAc] as a medium by the implementation of ultrasound irradiation *via* click chemistry, affording excellent yields. The present synthetic method exhibited numerous advantages such as mild reaction conditions, excellent product yields, minimal chemical waste, operational simplicity, shorter reaction time, and a wide range of substrate scope. The synthesized compounds were further evaluated for *in vitro* antifungal activity against five fungal strains, and some of the compounds displayed equivalent or greater potency than the standard drug. A molecular docking study against the modelled three-dimensional structure of cytochrome P450 lanosterol 14α-demethylase was also performed to understand the binding affinity and binding interactions of the enzyme. Furthermore, the synthesized compounds were evaluated for DPPH radical scavenging activity and antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain.

1. Introduction

1,2,3-Triazole, a five-membered heterocyclic ring system, is a very well-known biologically active pharmacophore constructed by the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, which is popular as a click chemistry reaction.[1] Over the last decade, 1,2,3-triazole has become one of the key structural motifs and is used in numerous fields including polymer chemistry,[2] material science,[3] and drug discovery.[4] 1,2,3-triazole-based molecules display various biological activities such as anti-fungal,[5,6] anti-bacterial,[6] anti-tubercular,[7] anti-inflammatory,[8] anti-allergic,[9] anti-HIV,[10] anti-cancer,[11] and anti-phytopathogenic.[12] Some marketed drugs have the 1,2,3-triazole unit in their structure, and these include Cefatrizine (a broad-spectrum antibiotic), Tazobactam (an antibiotic), and Carboxyamidotriazole (CAI) (a calcium channel blocker) (Fig. 1).

Azole drugs have broad-spectrum activities against most yeasts and filamentous fungi and are mostly used in antifungal chemotherapy.[13] Some well-known antifungal agents including fluconazole, voriconazole, ravuconazole, and itraconazole contain a 1,2,4-triazole ring in their structure, as shown in Fig. 2. However, their clinical uses have been restricted by their relatively high risk of toxicity, pharmacokinetic deficiencies, emergence of drug resistance, and undesirable side effects. These antifungal drugs inhibit CYP51, a key enzyme in the biosynthesis of ergosterol, through a mechanism in which the antifungal agent having a triazole scaffold is positioned perpendicular to the porphyrin plane with a ring nitrogen atom (N-4 of triazole) coordinated with a heme iron atom.[14] Over a couple of decades, the incidence of systemic fungal infections has increased due to cancer chemotherapy, organ transplantation, tuberculosis, and immunodeficiency virus (HIV) infection.[15] However, the extensive use of antifungal drugs has led to an increase in the resistance to these drugs.[16] Hence, there is an urgent need for developing new antifungal agents with effective activities, low toxicity, and minimum side effects.

Ionic liquids (ILs) are environment-friendly solvents because of their interesting properties and they can be used as alternatives to harmful organic solvents. Furthermore, they are useful in catalytic reactions[17] and organic synthesis[18] because of their

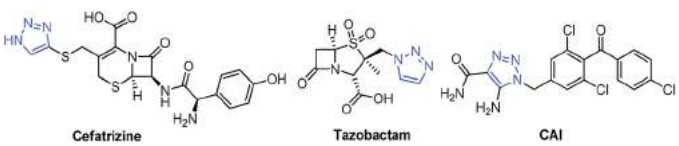

Fig. 1 Structures of drugs containing the 1,2,3-triazole unit.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra03425k

Design and Synthesis of New Aryloxy-linked Dimeric 1,2,3-Triazoles *via* Click Chemistry Approach: Biological Evaluation and Molecular Docking Study

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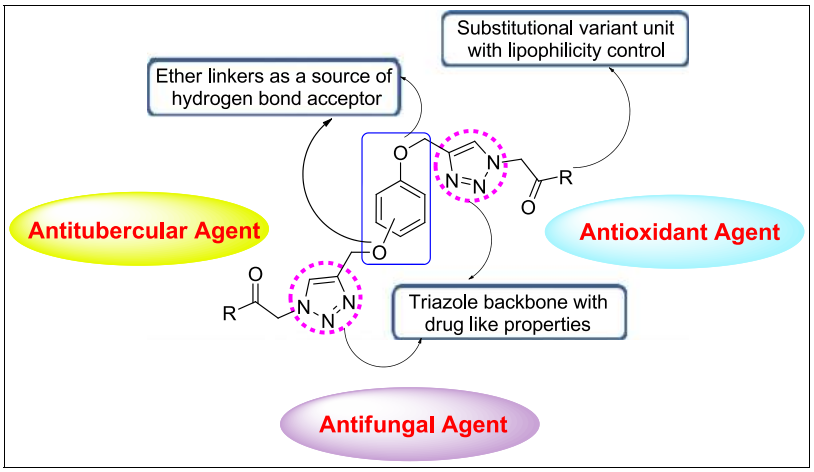

A quest for more potent new antitubercular agents has prompted to design and synthesize aryloxy-linked dimeric 1,2,3-triazoles (**4a**–**j**), from azides (**2a-e**) and bis(prop-2-yn-1-yloxy)benzene (**3a**–**b**) on 1,3-dipolar cycloaddition reaction *via* copper (I)-catalyzed click chemistry approach with good to better yields. The titled compounds (**4a**–**j**) were designed using molecular hybridization approach by assembling various bio-active pharmacophoric fragments in a single molecular framework. All the synthesized compounds have been screened for their *in vitro* antitubercular, antifungal, and antioxidant activities against their respective strains. Among them, **4h** and **4i** show the highest antifungal activity, whereas compounds **4h**, **4i**, and **4j** have revealed promising antitubercular activity against their respective strains. In addition to this, most of the synthesized compounds were found as potent antifungal and antioxidant agents. A significant network of bonded and non-bonded interactions stabilized these molecules into the active site of fungal CYP51 that is realized from the obtained well-placed docking poses and the associated thermodynamic interactions with the enzyme. The synthesized compounds have also been analyzed for absorption, distribution, metabolism, and excretion properties.

INTRODUCTION

Twin drug synthesis is one of the famous classical approaches of a promising rational drug designing [1]. There are two types of twin drugs on the basis of combining two similar or dissimilar moieties known as "identical" and "non-identical" twin drugs, respectively [2]. The identical twin drugs are obtained from dimerization of active pharmacophoric groups and possesses the C_2 symmetry in its structural motif [3]. The main aim of this synthetic approach is to obtain more potent and more selective dimeric drug as compared with monomer. It is very useful when the targeted protein exists with two binding sites [4]. Literature survey also reveals that dimeric compound shows better bioactivities than monomers [5]. Keeping these facts, many researchers focused on the synthesis and bioevaluation of dimeric molecules as shown in Figure 1 [6].

Nowadays, azole class of compounds gain more attention to researchers, especially 1,2,3-triazoles as they

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Ultrasound assisted rapid synthesis, biological evaluation, and molecular docking study of new 1,2,3-triazolyl pyrano[2,3-*c*]pyrazoles as antifungal and antioxidant agent

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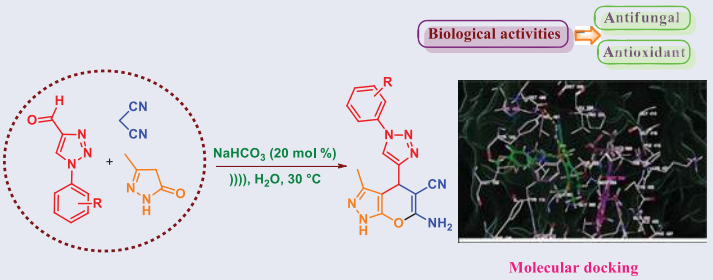
ABSTRACT

In search of new generation of triazole based antifungal agents, synthesis of series of new 1,2,3-triazolyl pyrano[2,3-*c*]pyrazoles under ultrasonic irradiation using $NaHCO_3$ has been reported. The bioevaluation results indicate that, the compounds **7c**, **7d**, **7e**, **7f**, and **7i** displayed excellent antifungal activity with lower MIC $\leq$ 25 μg/mL. Most of the compounds from the series showed potent antioxidant activity with a lower IC_{50} value in the range 09.39 ± 0.42–14.97 ± 0.24 μg/mL, in comparison to butylated hydroxyl toluene (BHT). Molecular docking studies against potential target sterol 14α-demethylase (CYP51) was also performed and showed excellent binding affinity with the target enzyme. Moreover, *in silico* ADME study shows that the derivatives could serve as drug like molecules for further drug development in clinical research.

GRAPHICAL ABSTRACT



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KEYWORDS
Antifungal activity; molecular docking study; multicomponent reactions; pyrano[2,3-*c*]pyrazole; 1,2,3-triazole

Introduction

Over the past few decades, invasive fungal infections among the immunocompromised and critically ill patients are growing rapidly and is becoming a leading cause of

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Supplemental data for this article is available online at on the publisher's website.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

Helminthicidal and Larvicidal Potentials of Biogenic Silver Nanoparticles Synthesized from Medicinal Plant *Momordica charantia*

Authors: Shelar, Amruta; Sangshetti, Jaiprakash; Chakraborti, Shampa; Singh, Ajay V.; Patil, Rajendra; Gosavi, Suresh
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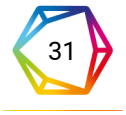

Abstract | References | Citations | Supplementary Data

Background: The drug formulations used to control mosquito vectors and helminth infections have resulted in the development of resistance, and negative impact on non-target organisms and environment.

Objective: Plant-mediated synthesis of silver nanoparticles (P-AgNPs) using aqueous fruit peel extract of M. charantia, applications of P-AgNPs for helminthicidal activity against Indian earthworms (P. posthuma) and larvicidal activity against larvae of mosquito A. albopictus and A. aegypti.

Methods: Aqueous fruit peel extract of Momordica charantia was used to reduce silver ions to silver nanoparticles (P-AgNPs). UV-Visible (UV-Vis) Spectroscopy, X-ray diffraction, Fourier Transform Infrared Spectroscopy and Transmission Electron Microscopy characterize synthesized P-AgNPs. The motility and survival rate of the worms were recorded for the helminthicidal activity. Percent mortality of larvae of A. albopictus and A. aegypti was recorded for larvicidal activity.

Results: The UV-Vis absorption spectrum of P-AgNPs showed a strong surface plasmon absorption band in the visible region with a maximum absorption at 445 nm indicating the synthesis of silver nanoparticles by the addition of aqueous fruit peel extract. The XRD spectrum of P-AgNPs showed Bragg's reflection peaks 2 value characteristics for the Face-Centered Cubic (FCC) structure of silver. The sharp absorption peak in FTIR at 1659 cm-1 assigned to C=O stretching vibration in carbonyl compounds represents terpenoids, flavonoids and polyphenols in the corona of PAgNPs; a 2 mg/mL of P-AgNPs. The concentration aqueous extract and P-AgNPs showed complete death of worms (the morphological alteration/coiling of body). A 20 ppm concentration of PAgNPs showed 85% mortality in larvae of Ae. albopictus and Ae. aegypti. P-AgNPs were nontoxic at low concentrations.

Conclusion: The aqueous extracts played a dual role as reducing and capping agent during the biosynthesis of AgNPs as per FTIR and XRD results. The surface reactivity facilitated by biomolecule corona attached to silver nanoparticles can further help to functionalize AgNPs in various pharmaceuticals, biomedicals, and environmental applications.

Keywords: Helminths; biomolecules; corona; momordica; mosquitoes; silver nanoparticles
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ORIGINAL ARTICLE

Quantitative Assessment of Tactile Allodynia and Protective Effects of flavonoids of *Ficus carica* Lam. Leaves in Diabetic Neuropathy

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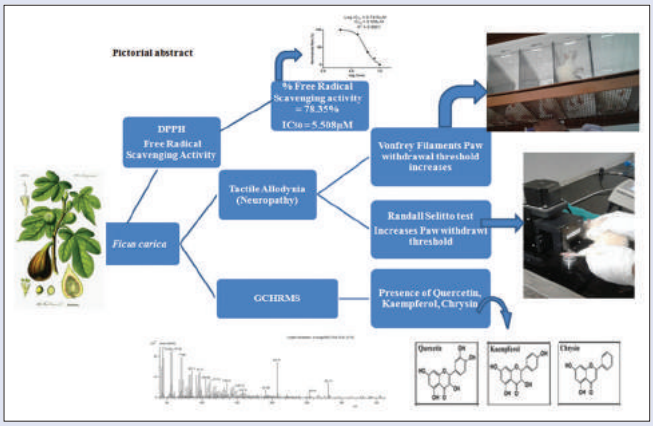
ABSTRACT

Background: Flavonoids, a group of polyphenols responsible for protective role against many diseased conditions, provide antioxidant activity which is the reason for their medicinal properties. Tactile allodynia is a behavioral biomarker of neuropathy that is well estimated by von Frey filaments and Randall–Selitto test. **Objective:** *Ficus carica* Lam. leaves were studied for the conformation of flavonoids in ethyl acetate fraction of methanolic extract (FCEA) using GC-HRMS for the identification of flavonoids. It was analyzed for antioxidant activity by *in vitro* free radical scavenging activity, performed using 2,2-diphenyl-1-picrylhydrazyl (DPPH) followed by blood glucose-level estimation, evaluation of neuropathic pain, and kidney and liver function tests in diabetic rats. **Materials and Methods:** The shade-dried leaves of *F. carica* Lam. were extracted with methanol and after that fractionated using ethyl acetate (FCEA). The characterization of FCEA was established using GC-HRMS. *In vitro* free radical scavenging activity was performed using DPPH assay. Diabetes was induced using streptozotocin (40 mg/kg/intraperitoneally), and effects of FCEA were studied on blood glucose level, neuropathy markers, and liver and kidney functions of diabetic rats. **Results:** GC-HRMS results highlighted the presence of quercetin, kaempferol, and chrysin in FCEA with free radical scavenging activity of 78.35% and IC_{50} value of 5.508 μM. FCEA reduces glucose levels and also shows protective effects in case of diabetic neuropathy as it increases the threshold of withdrawal latency in tactile allodynia and also decreases the serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, blood urea nitrogen, and creatinine levels. **Conclusion:** The protective effects of FCEA against diabetic neuropathy, hepatoprotective and nephroprotective effects might be due to strong antioxidant property of important flavonoids present which is confirmed in the study.

Key words: Chrysin, diabetic neuropathy, kaempferol, quercetin, Randall Selitto, von Frey

SUMMARY

- The research work shows the presence of quercetin, kaempferol, and chrysin in *Ficus carica* Lam. leaves; along with this, it has depicted *in vitro* free radical scavenging activity by 2,2-diphenyl-1-picrylhydrazyl assay method. After quantitative assessment of tactile allodynia, this plant sample has proven protective effects in diabetic neuropathy, and these effects were compared with surgical model of neuropathy by von Frey filaments and Randall–Selitto test.



Abbreviations used: BSTFA: N, O-Bis (trimethylsilyl) trifluoroacetamide; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FCEA: Ethyl acetate fraction from methanolic extract of leaves of *Ficus carica* Lam.; GC-HRMS: Gas chromatography–high-resolution mass spectrometry.

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INTRODUCTION

Polyphenolic substances are ubiquitously found chemical constituents in a variety of plants having medicinal properties.[1-4] A large number of plants contain flavonoids; they further consist of flavones, flavonols, isoflavonoids, anthocyanidins, and chalcones.[2,3] It has a protective role in carcinogenesis,[4,5] inflammation,[4,5] atherosclerosis,[4] thrombosis,[4] diabetes, and cardiovascular diseases[5] and has activities such as antiviral,[4,5] antimicrobial,[4] antihepatotoxic,[4] antiosteoporotic,[4,6] antiulcer,[4] immunomodulatory,[4] antiproliferative,[4,6] and apoptotic[4] as a result of their antioxidant actions.[4-6] In the last few years, gas chromatography–mass spectrometry (GC-MS) has established as a firm platform for analysis of plant's secondary metabolites and phytoconstituents. It is a hyphenated system, a compatible technique

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ARTICLE

Synthesis and evaluation of pyrazole-incorporated monocarbonyl curcumin analogues as antiproliferative and antioxidant agents

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A series of pyrazole-incorporated monocarbonyl analogues of curcumin were synthesized via Clasien–Schimidt-type condensation and subsequently screened for in vitro antiproliferative and antioxidant activity. The analogues **4c, 5d, 5e, 5g, 6e,** and **6f** showed potential activity against the MDA-MB-231 cell line. The synthesized analogues were also screened for their antioxidant activity. Compounds **5a**, **5e**, **6d,** and **6f** exhibit comparable radical scavenging activity with respect to the standard drug ascorbic acid. Furthermore, a molecular docking study has been conducted for **5d** and **5g** and suggests that these compounds have a potential to become lead molecules in drug discovery and process.

KEYWORDS

antioxidant activity, Antiproliferative activity, molecular docking, Monocarbonyl curcumin analogues

1 | INTRODUCTION

Curcuma longa, a perennial herb of the family *Zingiberaceae,* has been used extensively as an essential spice and traditional medicine in India and China since ancient times.[1] Curcumin is obtained from turmeric, which is yellow-colored powder derived from the rhizomes of *Curcuma longa.* Curcuminoid (Figure 1) exhibits a broad spectrum of pharmacological activities like antimalerial,[2] antioxidant,[3] anti-HIV,[4] anti-inflammatory,[5] anticancer,[6] anti-Parkinson,[7] anti-Alzheimer's,[8] anti-angiogenesis,[9] and free radical-scavenging activity.[10] The clinical usefulness of curcumin is restricted due to its poor oral absorption, low oral bioavailability, and poor pharmacokinetic profile.[11] It is believed that the presence of β-diketone moiety and the active methylene group is responsible for poor oral absorption, weak pharmacokinetics, and instability of curcumin under physiological conditions.[12]

In recent years, efforts have been devoted to the development of structurally modified curcumin analogues/derivatives.[13] Monocarbonyl analogue of curcumin is one of the classes of structurally modified curcuminoids obtained by removing β-diketone moiety and active methylene group from curcumin.[14,15] Monocarbonyl analogues of curcumin (MAC) shows potential antibacterial,[16a] anti-inflammatory,[16b] antioxidant,[16c] anticancer,[16d] antiparasitic,[16e] antileishmanial,[16f] Alzheimer's disease,[16g] HIV-1 IN-LEDGF/p75 interaction,[16h] topoisomerase II alpha inhibitors,[16i] antiobesity,[16j] anti-invasive chemotypes,[16k] lipoxygenase and proinflammatory cytokines,[16l] and anti-tubulin activities.[16m] It is reported that some of the monocarbonyl analogues of curcumin not only have better stability and antitumor activity in vitro but also have a better pharmacokinetic profile in vivo.[17]

Cancer is the leading cause of death worldwide next to cardiovascular disease. World cancer reports demonstrate that millions of deaths occurred due to cancer, and new cases of various cancers are expected to rise by about 70% over the next two decades. It was also observed that more than 60% of world's new annual cases of cancer occur in Asia, Africa, and Central and South America.[18] Hence, keeping in view the seriousness of cancer, the development of novel therapeutic agents against cancer has been a focus for

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Medicinal Chemistry & Drug Discovery

Identification of Promising Biofilm Inhibitory and Cytotoxic Quinazolin-4-one Derivatives: Synthesis, Evaluation, Molecular Docking and ADMET Studies

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A library of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**5a-k**) were synthesized in good yield by using 1-Ethyl-3-Methylimidazolium hydrogen sulphate (10 mol%) as a catalyst and were evaluated for their anti-biofilm, antimicrobial and cytotoxicity potential. Among the synthesized compounds, 2-(4-(1H-1,2,4-triazol-1-yl)phenyl)-2,3-dihydroquinazolin-4(1H)-one (**5d**) and 2,3-dihydro-2-(2,4,6-trimethoxyphenyl) quinazolin-4(1H)-one (**5j**) displayed better anti-biofilm activity than fluconazole (IC_{50} = 40 μM) with IC_{50} values less than 30 μM. Compound **5d** also appeared to be fungicidal against *C. Albicans* having MIC = 33.5 μg/ml comparable with standard fluconazole (50 μg/ml). All the synthesized compounds were also evaluated for cytotoxic activity by using MTT assay against HeLa, A-549 and MDA-MB-231 cell lines. The compound **5d** was found to be more potent against MDA-MB-231 and A549 cell lines (IC_{50} = 11 ± 2 μM and 34 ± 8 μM respectively) than 5-fluorouracil (IC_{50} = 19 ± 3 μM and 51 ± 5 μM respectively). The compounds substituted with 6-methyl-4-oxo-4H-chromen-3-yl (**5a**), biphenyl (**5c**) and 2-hydroxy-5-bromophenyl (**5e**) were also found to be more potent against MDA-MB-231 cell lines (IC_{50} = 13 ± 3 – 14 ± 4 μM) than 5-fluorouracil. Molecular docking simulations were also carried out using secreted aspartyl protease (SAP5), pepA enzyme of *C. albicans* for biofilm inhibition and EGFR tyrosine kinase for cyto-toxicity studies. The study reveals that the compounds **5d and 5e** can serve as an important lead moiety for biofilm inhibition and cyto-toxicity against MDA-MB-231 and A549 cancer cell-lines indicating their potential in the treatment of tougher fungal infections and breast and lung cancer.

Introduction

Currently, the treatment of microbial infection suffers a major disadvantage due to continuous emergence of multi-drug resistant microorganisms.[1] In such a situation, easily manageable microbial infections turn into a life-threatening event and miserable failure of currently marketed antimicrobial drugs.[2] Symbiotic association of microbial colonies of a same or different strain of microorganisms leads to the formation of biofilms, which further worsens the problem of multi drug resistance.[3] Biofilms are conglomerated mass formed by the association of microbial cells which is protected by the self-synthesized extra polymeric substance (EPS).[4] Biofilms help microorganisms to protect themselves, to confer resistance against antibiotics and toxins and to evade through the bloodstream to other locations. This turns infection into a chronic and difficult to cure stage.[5] *Candida albicans* is a fungal species that take advantage of causing infection in an immune compromised patient.[6,7] The major cause of mortality in hospitalized patients is due to opportunistic *C. Albicans* infections evaded to the bloodstream.[8] *C. Albicans* also give rise to biofilm formation making most of the current antifungal drugs ineffective.[9]

Cancer also poses a major health threat to the human population due to the limited efficacy of current anticancer

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A Facile Synthesis of Substituted 2-(5-(Benzylthio)-1,3,4-oxadiazol-2-yl) pyrazine Using Microwave Irradiation and Conventional Method with Antioxidant and Anticancer Activities

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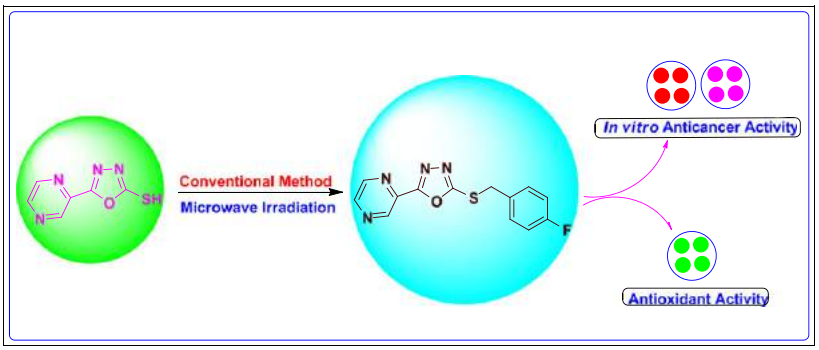

A series of novel substituted 2-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)pyrazine derivatives (**6a**–**n**) were synthesized under microwave irradiation and conventional conditions with less reaction time with good to excellent yields. All the synthesized compounds were screened for antioxidant and anticancer activities. Out of the 14 prepared derivatives, compounds **6f** and **6m** were most potent and active with antioxidant and anticancer activities, respectively. Also, the developed technique was simple, easy, and less time consuming.

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INTRODUCTION

Oxadiazole is a lead moiety in the designing of potent bioactive molecules [1]. The oxadiazole scaffold is a central part of biologically active compounds with various applications and pharmacological properties like antibacterial [2], antifungal [3], antitubercular [4], insecticidal [5], anticonvulsant [6], anticancer [7], antiviral [8], anti-inflammatory [9], antidiabetic [10], and immunosuppressive [11]. The 1,3,4-oxadiazole ring system has been identified as the main core of many bioactive molecules. For the discovery of new lead structures in drug discovery, based on high throughput screening, synthetic methodologies are required that deliver highly diverse derivatives in a timely manner. Under these circumstances, microwave-assisted chemistry appears to be a promising synthetic method [12]. Utility of microwave irradiation [13–15] to carry out organic reaction has now become a regular feature. The main benefits of performing the reaction under microwave conditions are the significant rate enhancements and the higher product yields with minimum time requirement. Here, we wish to report the development and implementation of the methodologies allowing for the synthesis of some novel 2-[(4-fluorobenzyl)thio-5-(pyrazin-2-yl)1,3,4-oxadiazole substituted derivatives. The oxadiazole has been known for over 50 years, so there have been several attempts to design antimicrobial and anticancer agents based on this heterocycle [16–18]. 1,3,4-Oxadiazole heterocycles are very good bioisosteres of amides and esters and can contribute substantially to increasing pharmacological activity by participating in hydrogen-bonding interactions with receptors [19].

In continuation of our work [20–22], on the synthesis of bioactive compounds, we have synthesized some 1,3,4-oxadiazole analogues. The synthetic protocols employed for the synthesis of oxadiazole derivatives **3** and **4** are presented in Schemes 1, 2, and 3, respectively.

RESULTS AND DISCUSSION

The first part of the study was aimed at optimizing the reaction conditions. The screening of model reaction of 2-[(4-fluorobenzyl)thio-5-(pyrazin-2-yl)1,3,4-oxadiazole **6a** (Scheme 2; Table 1) was performed. We have developed

POLYCYCLIC AROMATIC COMPOUNDS
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ChCl:2ZnCl2 Catalyzed Efficient Synthesis of New Sulfonyl Decahydroacridine-1,8-Diones via One-Pot Multicomponent Reactions to Discover Potent Antimicrobial Agents

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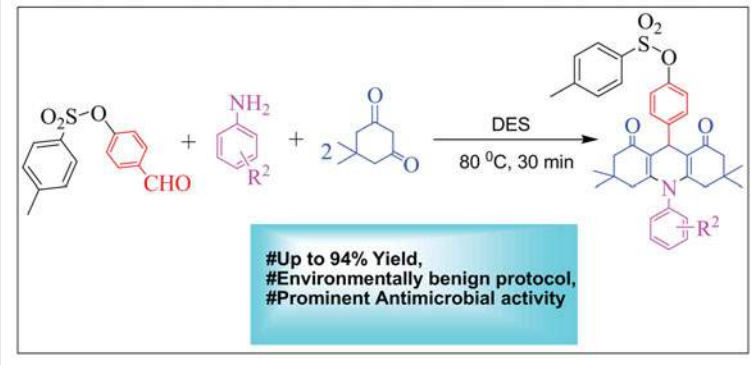
ABSTRACT

A library of new sulfonyl decahydroacridine-1,8-diones has been efficiently synthesized by the one-pot three-component reactions of 4-(*p*-tolyl sulfonoxy) benzaldehyde, dimedone, and amines in choline chloride-based deep eutectic mixture. Pure target compounds are obtained in very good to excellent yields over short reaction times using straightforward work-up procedure. The synthesized heterocyclic decahydroacridine-1,8-diones were investigated for their *in vitro* antimicrobial activity. The minimum inhibitory concentration was determined for the test compounds as well as for reference standards. Compounds **4f**, **4m**, **4n,** and **4o** have shown good antibacterial activity whereas compounds **4a**, **4c**, **4g**, **4j**, and **4r** have displayed better antifungal activity.

GRAPHICAL ABSTRACT



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KEYWORDS
ChCl:2ZnCl2; deep eutectic solvent; multicomponent reactions; decahydroacridine-1,8-diones; antimicrobial agents

Introduction

Acridinedione derivatives, a class of interesting heterocyclic compounds,[1] exhibit antiviral,[2] antibacterial,[3] anti-nociceptive,[4] anti-inflammatory,[5] and anticancer[6] activities. A great number of acridinedione compounds have been synthesized and clinically used as anthelmintic, antimalarial agents as well as they show efficiency in photodynamic therapy.[7] The acridine ring system is an ideal framework for medicinal chemist to embellish with a diversity of functional groups.

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In Vitro Hydrogen peroxide Scavenging Activity of Royal Jelly

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Abstract

During normal cellular metabolicpathway the reactive oxygen species (ROS) like hydroxyl radicals, superoxide anion, hydrogen peroxide and nitric oxide, generated which produce oxidative damage to cells and tissues. The peroxyl radical attacks membrane protein and enzymes causing alteration in the structure and function of the membrane, mutations and cell death. Present investigation aims to detect the inhibitory activity of royal jelly against hydrogen peroxide assay was performed by Ruch et al method. Result of the study showed larger concentration of water dissolved royal jelly exhibit a significant inhibition of hydrogen peroxide radicals as ascorbic acid.it was concluded that Presence of certain antioxidant compounds such as flavonoids and phenolic compounds in royal jelly make it scavenger to inhibit a free hydrogen peroxide radicals. Thus it can be used as a dietary substance for reducing the oxidative stress.

Keywords: hydrogen peroxide, royal jelly, flavonoids,phenolic compounds.

Introduction

Royal Jelly, is a creamy product secreted by the hypo pharyngeal glands in the head of the young nurse worker bees primarily for developing and maintaining the queen bee. [1]. it is a yellowish-white, acidic secretion, with a pungent odor and taste. Royal jelly is considered as a richest diet of nature because of its unique composition. It containing the all five nutritive and building materials (proteins, fats, carbohydrates, vitamins and minerals) [2]. Previous studies showed that RJ has anti-microbial effects [3], suppression of allergic reactions, lowering the amount of blood cholesterol [4], preventing cell damage in cancer and HIV patients, as well as wound healing and growth acceleration. The RJ has a wide variety of unique health benefits: it enhances the immune system, promotes wound treatment, has antitumor/anticancer properties, lowers cholesterol levels, increases fat metabolism, and regulates blood sugar levels being a powerful antioxidant [2]. The action of RJ on the cell level was investigated on the genetic material proving that its disturbance was returned into a normal condition by the using of RJ [5].

The present study was carried out to determine the free hydrogen per oxide radical scavenging activity of royal jelly.

Materials and method

1.1.Preparation of Royal Jelly and ascorbic acid

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Research Article Open Access

Development and Biopharmaceutical Characterization of BCS Class II Drug – Naproxen by Two Way Complexation Solid Dispersion Technique

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Abstract: The objective of this study was to increase the solubility and bioavailability of Naproxen (NP) by fabricating ternary solid dispersion (tSDs) with water soluble polymer PEG 6000 and crospovidone. tSDs were prepared and optimized by 3^2 full factorial design with PEG 6000 level (X1) and CP level (X2) as independent variables and percent drug release (D80, (Y)) as dependent variable. The optimized tSDs were evaluated for their physicochemical properties which confirmed the formation of tSDs (DSC), SEM suggested smooth surface and compact structures. PXRD revels that drug was still present in crystalline form and was not molecularly dispersed in the complex especially in non-homogeneous part of the tSDs. The optimized tSDs revels that Dissolution rate (Y) was significantly affected by independent variable PEG 6000 (X1) while CP (X2) was insignificant. The transparent characteristics of tSDs was observed as a result of lowered Tg temperature gives higher dissolution rate up to 97.70 % for optimized formulation (F9). The pharmacokinetic study in Han Wistar rats showed that the tSDs had the greatest effect on oral bioavailability of NP *in vivo* test showed that NP (tSDs) presented significantly larger $AUC_{0\text{-}t}$, which was 1.09 folds more than that of marketed formulation. C_{max} of NP (tSDs) also increased from 120 µg/ml to 146 µg/ml compared to that of marketed formulations and generated shortened T_{max} of (1.0 ± 0.416) h, compared to marketed dosage form (2.0 ± 0.456) h.

Key words: Solid dispersion, glass transition temperature, ternary solid dispersion, level optimization, & pharmacokinetics

Introduction

Systemic availability of drug depends on the two important steps. These two steps determine the rate and extend of drug absorption, so called as Rate Limiting Steps. i. e. Drug dissolution and Drug permeation [1]. Drug dissolution is always depends on the solubility of that particular drug which is hydrophobic, poorly aqueous soluble drug like NP, falls under the category of BCS class II drug [2]. The solid dispersion technique for water-insoluble drugs developed by Chiou and Reigelman provides an efficient method to improve the dissolution rate of a drug. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material [3]. Methods used to obtain solid dispersions affects the drugs crystallinity as Mooter *et al.*, revealed that with a 20/80 w/w Itraconazole/Inutec SP1 extrudate (solid solution) a dissolution of 100% could be obtained after 30 min. The same composition prepared by spray drying; however, gave rise to a dissolution of only 50% [4]. The presence of different proportions of PEG systematically lowers the degree of complexed drug NP with β-CD due to competing equilibria gives rise to ternary solid dispersions [5]. The solid dispersions and ternary complexes formed exhibits increased dissolution behaviour as result of metastable amorphous material formed which in turn cooled, it usually crystallizes below the melting temperature, (Tm). When cooling rate is sufficiently fast, the liquid fails to crystallize, and a super cooled state is attained. Further cooling to below the glass transition temperature (Tg) causes the system to fall out of structural equilibrium. Since this state is not physically stable, structural changes occur over time to achieve a more energetically favoured state leads to less dissolution rate [6]. Solid dispersions of PEG6000 and Loperamide prepared by spray drying showed deteriorated dissolution rate on storage at high temperature (40°C and 0% RH) and in conditions of higher relative humidity (25°C and 52% RH) resulting in

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Quality by Design Based RP-HPLC for Simultaneous Estimation of Aspirin and Prasugrel HCL in Marketed Formulation

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Abstract:- Considering todays regulatory requirement for the development of an analytical method, a reversed phase high performance liquid chromatography method for simultaneous estimation of aspirin and prasugrel HCl in capsule dosage form has been optimized by analytical quality by design approach. Unlike the regular approach, this study began with the understanding of the objective profile of the quality product, the objective analytical profile and the risk assessment for the method variables that affect the response of the method. A liquid chromatography system equipped with a waters C_{18} column (150×3.9 mm, 5 µm), a isocratic delivery system (pump) and photodiode array detector were used to develop the method. The optimized method was achieved at 0.7 ml/min flow rate of using mobile phase of 1% Phosphoric acid buffer and Acetonitrile at 20:80(v/v), pH was adjusted to 3.5 with tri ethylene amine. To plan and analyses the experimental observations and obtain quadratic process model Design Expert software Version 11 was used. The process model was used for predicting solution for resolution. The optimized working condition was then validated according to ICH guidelines for linearity, LOD, LOQ, specificity.

Keywords:- *Quality by Design, Plackett-Burman, Box Behnken, HPLC, Aspirin, Prasugrel HCl.*

I. INTRODUCTION

Quality means fitness for the intended use.[1] Presently the pharmaceutical industry is adopting the QbD concept to improve the robustness of manufacturing processes and to facilitate continuous improvement strategies, to shape and improve product quality and manufacturing productivity. As per ICH Q8 (R2) quality by design is defined as *""A systematic approach to development that starts with predefined goals and focuses on understanding products and processes and controlling processes, based on sound and quality risk management."* [2] .

Aspirin is chemically 2-(acetyloxy) benzoic acid is cyclo oxygenase inhibitor and inhibits platelet aggregation while Prasugrel is [5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-6,7-dihydro-4H-thieno[3,2-c]pyridin-2-yl] acetate, is a member of the class of thienopyridines that inhibit the ADP receptor that induces platelet aggregation. Both agents act by binding irreversibly to P2Y12 receptors. Prasugrel acts more rapidly, consistently and to a greater extent in combination with aspirin.[5-6] Structure of Aspirin and Prasugrel are given as fig.1 and 2.

Literature survey revealed that few analytical methods such as RP-HPLC, LC-MS, UV and HPTLC have been reported for simultaneous estimation of Aspirin and Prasugrel HCl. QbD based RP- HPLC for simultaneous estimation of Aspirin and Prasugrel HCl in the marketed formulation has not been reported till date.[8-15] Hence the objective was to develop a simple, rapid, cost effective, sensitive, accurate, and precise RP-HPLC method for simultaneous estimation of Aspirin and Prasugrel HCl which was optimized by design of experiment software version 11. This work describes a simple, accurate, sensitive, accurate and validated method of simultaneous estimation of aspirin and prasugrel hydrochloride in the marketed formulation.

II. MATERIALS AND METHODS

- *Chemicals and Reagents:*

Bulk drugs Prasugrel HCl was obtained as a gift sample from MYLAN and Aspirin from ACROS ORGANICS. Acetonitrile, o-Phosphoric acid, Tri-ethylene amine were obtain from Merck and Milli-Q water of HPLC grade was used for the analysis.

- *Stock and Standard solution:*

75mg of Aspirin and 10 mg of Prasugrel HCl were weighed accurately and transferred to 100ml volumetric flask to it 50 ml of 1% o- phosphoric acid buffer and acetonitrile (50:50 v/v) was added, sonication for 10 minutes then the volume was made to the mark. This gives the standard stock solution having concentration of 750µg/ml of Aspirin and 100 µg/ml of Prasugrel HCl.

- *Preparation of Calibration Curve:*

Stock solution was prepared by dissolving 10mg of Aspirin and Prasugrel HCl in 100ml volumetric flask, 50

Publications of 2018

RESEARCH ARTICLE

Effects of Formulation Parameters on the Characteristics of Biodegradable Microspheres of Goserelin Acetate

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Abstract

Aim: The purpose of this study was to develop biodegradable microspheres controlling drug delivery for treatment of prostate and breast cancer. The effects of formulation parameters on the characteristics of microspheres were studied. **Material and Methods**: Emulsification/extraction method was used to prepare goserelin acetate controlled-release poly(D, L-lactide-co-glycolide) (PLGA)-based biodegradable microspheres. Microspheres were formulated and characterized in terms of encapsulation efficiency, particle size distribution, surface morphology, and drug release profile. **Results and Discussion**: Preparative variables such as concentrations of stabilizer, drug–polymer ratio, stirring rate, and the ratio of internal to external phases were found to be important factors for the preparation of goserelin acetate-loaded PLGA microspheres. These changes were also reflected in drug release profile. **Conclusion**: The *in vitro* goserelin acetate release study from PLGA microspheres proved that the present microspheres had the properties of an ideal controlled release formulation for anticancer therapy.

Key words: Breast cancer, Goserelin acetate, Microspheres, poly(D, L-lactide-co-glycolide), Prostate cancer

INTRODUCTION

Controlled release drug delivery systems are being developed to address many of the difficulties associated with traditional methods of administration. The development of novel technologies in the area of drug discovery such as genetic engineering, combinatorial chemistry, and high-throughput screening leads to numbers of drug candidates with high therapeutic potentials. However, majority of them have poor oral absorption or a short biological half-life. The emerging of these complex active ingredients has drawn considerable attention on development of novel techniques to deliver them in an effective and efficient way. Parenteral controlled release of drugs represents one of such approach. Single-dose administration of these systems can maintain the drug in the desired therapeutic range for days, weeks, months, and for some products, even years.[1]

One of the technological resources used to improve the performance of drugs at the site of action is the use of therapeutic systems prepared using biodegradable polymers. Biodegradable polymers show increasing importance in the development of sustained release drug delivery system. Biodegradable polyanhydrides and polyesters are useful materials for controlled drug delivery. They have hydrophobic backbones with hydrolytically labile anhydrides and/or esters that may hydrolyze to dicarboxylic acids and hydroxy acid monomers when placed in an aqueous medium. Fatty acids are suitable candidates for the preparation of biodegradable polymers because they are natural body components and are hydrophobic and thus may retain an encapsulated drug for longer periods when used as drug carriers.[2]

Biodegradable polymers are useful material for controlled release drug delivery system such as disks, rods, pellets, or microparticles that encapsulate drug and control release rates for extended period. Such systems offer several potential

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ORIGINAL ARTICLE

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Development and validation of analytical method by RP-HPLC estimation of Goserelin acetate in biodegradable microspheres

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ABSTRACT

A simple, rapid, accurate and sensitive method was developed for quantitative analysis of Goserelin acetate in biodegradable microspheres formulation using reversed-phase high-performance liquid chromatography (RP-HPLC). The analysis is carried out using a reversed-phase C18 column with UV-Vis detection at 220nm. The isocratic mobile phase was phosphate buffer (pH7.4): acetonitrile in the ratio of 70:30 v/v at a flow rate of 1mL/min and column temperature maintained at 35°C. The developed method was validated according to the International Conference on Harmonisation (ICH) guideline with respect to system suitability, accuracy, precision, specificity, linearity and robustness. The linearity in the range of 2.5-90µg/mL presents a correlation of coefficient 0.999. The presence of components of the microspheres did not interfere in the results of the analysis. The method showed adequate precision, with a relative standard deviation (RSD) ≤ 2.0. The method was found to be suitable for routine quality control assay for encapsulated Goserelin acetate in biodegradable microspheres formulation was developed and validated.

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INTRODUCTION

Gonadotropin-releasing hormone (GnRH) analogues now offer the possibility of a medical castration, which reversible compared with the definitive castration produced by surgery or radiation. These analogues are a class of compound widely used in human medicine to treat prostate cancer, endometriosis and breast cancer. GnRH analogues are closely related to the naturally occurring decapeptide that is produced in the hypothalamus (Jean-Pierre G *et al.,* 1992).

The modification of the peptide at residues 6 and 10 leads to highly potent agonists with a marked and prolonged effect compared to the natural hormone (Bajusz S *et al.,* 1988).

Continuous administration of agonist analogues in supraphysiologic doses produces a decrease of pituitary luteinizing hormone-releasing factor (LHRH) receptors (receptor downregulation), which leads to inhibition of gonadotrophin synthesis and release and subsequently inhibits ovarian hormone production (Bambino TH *et al.,* 1980).

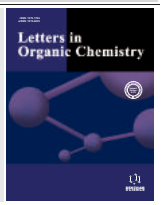
Goserelin acetate is a luteinizing hormone-releasing hormone agonist (LHRHa). It is a synthetic analogue of gonadotropin-releasing hormone or luteinizing hormone-releasing hormone. Initial or intermittent administration of Goserelin acetate stimulates the release of gonadotropins, pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH), from the anterior pituitary (Anderson J *et al.,* 2008, Miller K *et al.,* 2009 and Kaufmann M *et al.,* 1989).

Long term extended use of Goserelin acetate is associated with an early phase of increased LH and

Letters in Organic Chemistry, 2018, *15*, 32-38

RESEARCH ARTICLE

A Simple and Efficient Supramolecular Chemistry Approach for Synthesis of Bis(indolyl)methanes Using Aqueous β-Cyclodextrin as Green Promoter Host



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ARTICLE HISTORY

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Abstract: ***Background***: In the recent years, various bis-heterocyclic compounds are reported for their varied biological activities. Bis(indolyl)methanes and its derivatives are commonly present in over 3000 natural isolates and reported for its broad spectrum of biological activities. Though, there are so many methods reported for the synthesis of bis(indolyl)methanes, there is a need to develop a green and eco-friendly synthetic protocol which in turn is important for economic and synthetic point of view.

Method: The supramolecular chemistry approach was efficiently used for the synthesis of bis(indolyl)methane derivatives **3(a-o)** by the condensation reaction of indole **1** (2.0 mmol) and substituted aldehydes **2(a-o)** (1.0 mmol) at 60°C using β-cyclodextrin in water. The progress of the reaction was monitored by TLC using ethyl acetate:hexane (7:3) as a mobile phase. The identity and purity of the products were confirmed by MASS, ^{1}H NMR, and ^{13}C NMR.

Results: This report describes supramolecular synthesis of bis(indolyl)methanes **3(a-o)** using β-cyclodextrin (1.0 mol%) in water at 60°C. The synthesized compounds **3(a–o)** were obtained in excellent yields (80-92 %) in less reaction time (20-40 min). The hydrophobic binding of β-cyclodextrin with one of the reactants is explained by ^{1}H NMR. The rate of the reaction is accelerated if electron withdrawing groups like Cl and F are present on the aromatic ring.

Conclusion: We have efficiently synthesized bis(indolyl)methanes **3(a–o)** *via* three-component one-pot condensation reaction of indole with substituted aldehydes using β-cyclodextrin as a supramolecular catalyst in aqueous medium. β-cyclodextrin is biodegradable, recoverable and purely environmentally benign. This method has several advantages over existing catalytic protocols as it has simple and green experimental procedures, use of green reaction media (water), lower reaction time, high reaction rate and avoids cumbersome work-up.

Keywords: Supramolecular chemistry, β-cyclodextrin, water, bis(indolyl)methanes, one-pot reaction, green promoter.

1. INTRODUCTION

Over the past decades, considerable interest was developed in the synthesis and pharmacological activities of various bis-heterocyclic compounds [1]. Bis(indolyl)methanes and its derivatives have been of great importance in medicinal chemistry due to its broad spectrum of biological activities [2]. Bis(indolyl)methanes are commonly present in over 3000 natural isolates including terrestrial and marine origin (marine sponges) [3, 4]. Some bioactive metabolites which possess bisindole as active pharmacophore are Chondriamide A and C [5], Vibrindole A [6], Dendridine A [7], and Lynamicin A, B, C, D, and E [8] (Fig. **1**). Consequently, a number of methods have been reported for the synthesis of bis(indolyl)methanes in synthetic chemistry [9-11]. Recently, some new methods for synthesis of bis(indolyl)methanes were also reported such as AgOTf [12], silica-supported-3-(triethoxysilyl)propane-1-ammonium chloride [13], ionic liquids includes triethyl ammonium dihydrogen phosphate [14] and phase transfer catalyst such as acidic tetrabutylammonium hydrogen sulfate (TBAHS) [15], surfactants as iodine-sodium dodecylsulfate (SDS) [16] and aqueous β-cyclodextrin in sulphuric acid [17]. However, there is need to develop a very powerful green and eco-friendly synthetic protocol which in turn is important for economic and synthetic point of view.

Recently, remarkable advances in supramolecular catalysis have gained a great importance in the field of synthetic organic chemistry [18]. Supramolecular chemistry involves

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Synthesis, Biological Evaluation and Computational Study of New Quinoline Hybrids as Antitubercular Agent

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Background: Tuberculosis is global health threat caused by infectious bacillus called Mycobacterium tuberculosis. To develop newer antitubercular agents against bacterial resistance, we have designed new quinoline derivatives 6a-6f and 7a-7f by molecular hybridization approach and evaluated for antitubercular, antioxidant and cytotoxicity studies along with molecular docking study.

Methods: The designed molecules were synthesized by multi-step synthetic protocol and structures of compounds were confirmed by NMR, Mass and Elemental analysis. The synthesized derivatives were screened for antitubercular activity against Mycobacterium tuberculosis using Microplate Alamar Blue Assay (MABA). The antioxidant activity and cytotoxicity were also evaluated using 1,1-Dipheny-1-picrylhydrazyl (DPPH) radical scavenging and Sulforhodamine B (SRB) assay, respectively. The molecular docking studies were performed in Glide v5.6 (Schrodinger).

Results: Among the synthesized derivatives, the compounds 6d and 7d displayed promising antitubercular activity, with MIC value of 18.27 and 15.00 μM respectively and are relatively nontoxic to HeLa cell line. The

Anticancer Agents Med Chem. 2018;18(7):1009-1015. doi: 10.2174/1871520618666171129153655.

Design, Synthesis and Anti-breast Cancer Activity of Some Novel Substituted Isoxazoles as Anti-breast Cancer Agent

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PMID: 29189180 DOI: 10.2174/1871520618666171129153655

Abstract

Methods: A novel series of isoxazole (S21-S30) derivatives were designed, synthesized and screened for their anticancer activity against estrogen receptor-positive MCF-7 and negative MDA-MB-435 breast cancer cell lines. The synthesized derivative has the ability to inhibit the growth of the human breast cancer cell line at low concentrations. In vivo anticancer activity was performed on virgin female sprague dawley rats.

Results: The result shows that compound S23 has more selectivity and marked estrogen modulator activity than the standard tamoxifen.

Keywords: Chalcone; S21-S30; breast cancer; estrogen receptor; isoxazole; tamoxifen..

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ORIGINAL ARTICLE

Ameliorative Effect of Quercetin and Rutin via Modulation of Hypothalamic–Pituitary–Adrenal Axis and Regulation of Fasting Glucose in Chronic Stress-Induced Prediabetes

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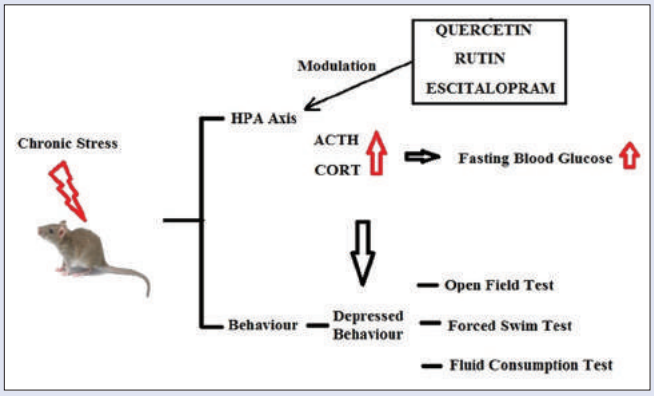
ABSTRACT

Background: Quercetin (QUE) and Rutin (RUT) have nutritive and medicinal values. On the other hand, there are no reports of scientific assessment of its hypothalamo–pituitary–adrenal (HPA) axis modulation in the treatment of prediabetes (DM). **Aim:** The current study was designed to investigate the modulatory effects of QUE, RUT, and escitalopram (ESC) as antidepressants on HPA axis in chronic stress-induced pre-DM in rats. **Materials and Methods:** The experimental protocol was of 5 weeks. Chronic unpredictable mild stress (CUMS) was used as a model of depression to induce pre-DM in rats. The treatment was started at the end of 4th week. After 5th week, the plasma adrenocorticotropic hormone (ACTH), serum corticosterone (CORT), fasting blood glucose (FBG), and behavioral parameters were evaluated. **Results:** Oral administration of QUE (50 mg/kg), RUT (50 mg/kg), and ESC (2.5 mg/kg) to stressed control alleviated HPA axis-associated parameters (ACTH and CORT) and significantly decreased the FBG. Besides this, the depressive effects induced by CUMS were significantly improved as evident from results indicating a promising antidepressant activity. Moreover, submaximal dose of QUE (25 mg/kg) and RUT (25 mg/kg) enhanced the antidepressant activity of ESC (1 mg/kg, p.o.), which suggests that they may act through the HPA axis. **Conclusion:** Current results suggest that chronic stress in rats causes dysregulation of the HPA axis which leads to diabetic-like condition, i.e., "pre-DM." It is possible that QUE, RUT, and ESC may be able to suppress the HPA axis response which could be beneficial for the treatment of stressed diabetic patients.

Key words: Antidepressants, chronic unpredictable mild stress, depression, diabetes, hypothalamo–pituitary–adrenal axis

SUMMARY

- The present study aims to reveal and establish the modulatory effects of quercetin, rutin, and escitalopram as antidepressants on hypothalamo–pituitary–adrenal axis in chronic stress-induced prediabetes in rats.



Abbreviations used: QUE: Quercetin; RUT: Rutin; HPA: Hypothalamic–Pituitary–Adrenal Axis; CUMS: Chronic unpredictable mild stress; ACTH: Adrenocorticotropic hormone; CORT: Corticosterone; FBG: Fasting Blood Glucose; ESC: Escitalopram; FST: Fasting Blood Glucose.

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INTRODUCTION

Stress is a term used in behavioral research that indicates "a physical, chemical, or emotional factor to which an individual fails to make a satisfactory adaptation" and it varies from person to person.[1] When the hypothalamus senses stimuli, produces general adaptation syndrome and stimuli are called stressors.[2] It has been well established that stress gives rise to the pathogenesis of a variety of diseases, including psychiatric disorders, endocrine disorders, immune suppression, sexual and cognitive dysfunctions, peptic ulcer, hypertension and heart diseases, ulcerative colitis, anxiety, and depression.[3,4]

A number of clinical studies have given evidence that depression is associated with hyperactivity of the hypothalamo–pituitary–adrenal (HPA) axis.[5] Antidepressant drug treatment normalizes the hyperactivity of the HPA axis with clinical recovery on or after depression.

Chronic stress in animals results in elevated adrenocorticotropic hormone (ACTH) and glucocorticoid levels in plasma and elevated production of corticotropin-releasing hormone (CRH) in the hypothalamic paraventricular nucleus.[6] The increased CRH secretion due to impaired negative feedback to the increment of cortisol is associated with depression.[7] A clear relationship of stress has been established for depression and DM. It may lead to deterioration of glycemic control through the neuroendocrine system in which the

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PHARMACOLOGY

Azithromycin in Combination with Ceftriaxone Reduces Systemic Inflammation and Provides Survival Benefit in a Murine Model of Polymicrobial Sepsis

Anasuya Patel,[a,b] Jiji Joseph,[b] Hariharan Periasamy,[b] Santosh Mokale[a]

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ABSTRACT Sepsis is a life-threatening systemic inflammatory condition triggered as a result of an excessive host immune response to infection. In the past, immunomodulators have demonstrated a protective effect in sepsis. Azithromycin (a macrolide antibiotic) has immunomodulatory activity and was therefore evaluated in combination with ceftriaxone in a clinically relevant murine model of sepsis induced by cecal ligation and puncture (CLP). First, mice underwent CLP and 3 h later were administered the vehicle or a subprotective dose of ceftriaxone (100 mg/kg of body weight subcutaneously) alone or in combination with an immunomodulatory dose of azithromycin (100 mg/kg intraperitoneally). Survival was monitored for 5 days. In order to assess the immunomodulatory activity, parameters such as plasma and lung cytokine (interleukin-6 [IL-6], IL-1β, tumor necrosis factor alpha) concentrations, the plasma glutathione (GSH) concentration, plasma and lung myeloperoxidase (MPO) concentrations, body temperature, blood glucose concentration, and total white blood cell count, along with the bacterial load in blood, peritoneal lavage fluid, and lung homogenate, were measured 18 h after CLP challenge. Azithromycin in the presence of ceftriaxone significantly improved the survival of CLP-challenged mice. Further, the combination attenuated the elevated levels of inflammatory cytokines and MPO in plasma and lung tissue and increased the body temperature and blood glucose and GSH concentrations, which were otherwise markedly decreased in CLP-challenged mice. Ceftriaxone produced a significant reduction in the bacterial load, while coadministration of azithromycin did not produce a further reduction. Therefore, the survival benefit offered by azithromycin was due to immunomodulation and not its antibacterial action. The findings of this study indicate that azithromycin, in conjunction with appropriate antibacterial agents, could provide clinical benefits in sepsis.

KEYWORDS polymicrobial sepsis, cytokines, survival, bacterial count

Sepsis is characterized by life-threatening organ dysfunction, in which the proinflammatory cytokines released by host immune cells in response to infection play a major role in pathogenesis (1, 2). In septic patients, there is an imbalance of proinflammatory/anti-inflammatory and oxidant/antioxidant mechanisms, resulting in the uncontrolled production of proinflammatory cytokines (e.g., interleukin-1β [IL-1β], IL-6, and tumor necrosis factor alpha [TNF-α]), oxidative enzymes (e.g., myeloperoxidase [MPO]), and free oxygen species that induce oxidative stress, inflammation, and direct mitochondrial damage, precipitating to organ dysfunction (3, 4, 5). Despite recent advances in our understanding of the pathophysiological mechanism of sepsis and improved antimicrobial therapy, the rate of mortality from sepsis remains frustratingly high (6). Unfortunately, many of the therapeutic options for the management of sepsis proposed over the years have either failed to meet their initial expectations or re-

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SOLUBILITY ENHANCEMENT OF OFLOXACIN BY MIXED SOLVENCY APPROACH

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(Received 12 August 2016) (Accepted 25 May 2018)

ABSTRACT

In current study we attempted mixed solvency approach for solubility enhancement of poorly water soluble drug, ofloxacin. Various hydrotropic agents including sodium benzoate, urea, sodium citrate, sodium acetate, niaciniamide, Lignocaine hydrochloride, PEG6000, PEG-400 were evaluated under study for enhancing solubility of drug. Further effect of various blends of these hydrotropic agents on solubility of ofloxacin was studied. Aqueous injection of ofloxacin was prepared and evaluated for its antimicrobial effectiveness and stability. It was found that mixed solvency approach is useful in solubility enhancement of ofloxacin without affecting its antimicrobial properties.

Keywords: Ofloxacin, hydrotropy, mixed solvency, solubility.

INTRODUCTION

The low solubility of new chemical entities is a major issue in drug development and discovery. Compounds with insufficient solubility have a higher risk of attrition and higher costs in drug development. Studies showed that 75% of the drug development candidates had low solubility and belonged to Biopharmaceutical Classification System (BCS) classes II and IV[1]. Poor bioavailability limits the performance of drug as it may require much higher doses than strictly required from a pharmacologic view point. This can induce important side effects or create problems related to the cost of treatment. Poor bioavailability may also oblige the formulator to choose the injection route instead of the oral route. For good oral bioavailability, drug must be soluble in gastro-intestinal fluids i.e. aqueous soluble and also possess permeability properties for good membrane diffusion in order to reach the bloodstream[2].

For parenteral administration of the drug solubility may be altered by use of cosolvents or by alteration pH of solution. The optimum amount of cosovelnt is required for solubility enhancement which should have minimum toxicity[3-4]. The use of non aqueous solvents at higher concentrations may be required to enhance solubility of semipolar drugs[5]. Hydrotropy is one of the several technologies utilized to enhance the aqueous solubilities of poorly water-soluble drugs. The term "hydrotropy" has been used to designate the increase in aqueous solubility of various poorly water-soluble compounds due to the presence of a large amount of additives. Concentrated aqueous hydrotropic solutions of urea, nicotinamide, sodium benzoate, sodium salicylate, sodium acetate, and sodium citrate have been observed to improve the aqueous solubility of many poorly water-soluble drugs[6-8]. It was demonstrated that the synergistic solubilizing capacity of two or more hydrotropes when used together which is called as mixed-hydrotropy approach. This approach has been applied to analyze the poorly water-soluble drug, aceclofenac, titrimetrically. Their research revealed application of hydrotropy in titrimetric and spectrophotometric estimations of a large number of poorly water-soluble drugs precluding the use of organic solvents[9-11]. Its potential to improve solubility was reported in literature[12].

Ofloxacin is a second generation fluoroquinolone antimicrobial with a 6-fluoro substituent and 7-piperazinyl substituent on the quinolone ring structure. Ofloxacin have broad spectrum activity against a wide range of Gram-positive and Gram-negative organisms and proved useful against micro-organisms that are resistant to other antimicrobial agents. Ofloxacin inhibits DNA gyrase which leads to promotion of double strand DNA breakage in susceptible organisms leading to bactericidal effects. Ofloxacin is slightly soluble in water[13].

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Original Article

FORMULATION AND EVALUATION OF MOISTURIZING CREAM CONTAINING SUNFLOWER WAX

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ABSTRACT

Objective: The main objective of the present investigation was to design, prepare and evaluate moisturizing cream using sunflower wax.

Methods: In the present work 3^2 full factorial design was applied to study the effect of varying concentration of independent variables stearic acid (X1) and sunflower wax (X2) on dependent variables viscosity and spreadability. All of the prepared formulations of moisturizing cream were evaluated for its physicochemical parameters. Further, the optimized formulation and selected commercial moisturizer compared and evaluated for its physicochemical parameters like pH, particle size, spreadability, viscosity and *in vitro* occlusivity test.

Results: Nine different formulations of the moisturizing cream were prepared and all the findings obtained were within the prescribed limit. When compared to the prototype formulation of cream, the formulation MF5 showed good viscosity, *in vitro* occlusivity and spreadability. From the nine different formulations, MF5 containing 2 % stearic acid and 2 % sunflower was chosen as the optimized formula. Optimization was done on the basis of *in vitro* occlusivity studies and physicochemical parameters.

Conclusion: The results obtained in this research work clearly showed a promising potential of moisturizing cream containing a specific ratio of stearic acid and sunflower wax as emulsifiers. Thus it can be concluded that sunflower wax is incorporated in the moisturizing cream, to avail of its cosmetic benefits.

Keywords: Moisturizing cream, Sunflower wax, *In vitro* occlusivity, Spreadability

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INTRODUCTION

The appearance and function of the skin are maintained by an important balance between the water content of the stratum corneum and skin surface lipids [1-2]. The skin represents the most superficial layer of the body, and so it is constantly exposed to different environmental stimuli [3]. Exposure to external factors as well as endogenous factors may disrupt this balance [4-6]. In addition, frequent use of soaps, detergents and topical irritants such as alcohol and hot water can remove the skin surface lipids [7]. Disruption of skin barrier led to the various type of skin problems most common condition is a loss of water content which leads to dryness of skin such as roughness, scaling, cracks, redness and an uncomfortable feeling of tightness, sometimes with itching and stinging [8]. Treatment with moisturizer aims at maintaining skin integrity and well-being by providing a healthy appearance of the individual. Numbers of moisturizers are available under the label of natural, safe, organic, herbal while the basic properties of humectancy, occlusivity and emolliency are consistent across all moisturizers [9]. Most of the available moisturizers use synthetic adhesives, emulsifiers, perfuming agents, pigments, surfactants and thickeners to form the base. There is extensive need to replace toxic synthetic agent from the base using natural agents [10-11].

Waxes from both animal and plant origin are esters of high molecular weight monohydroxy alcohols and high molecular weight carboxylic acids [12]. They are chemically different from fats and oils, from hydrocarbons or paraffin waxes and from synthetic polyether waxes such as carbowax. Carnauba wax, bees wax, candelilla wax are the natural waxes commonly used in cosmetic and pharmaceutical products. Sunflower wax is a hard, white crystalline, high melting point vegetable wax and is Ecocert certified [13-14]. It largely contains ceryl cerotate. It is also economical as compared to imported carnauba wax. It helps to thicken the formulation by providing a rigid structural network of wax crystals, improving oil binding, emolliency, film formation and lubricity. Sunflower wax can be a useful replacement for the carnauba, candelilla or mineral waxes particularly in lipsticks, mascara, balms, creams, lotions and other oil based formulations [15-16]. Therefore, an attempt has been made in the present study to utilize sunflower wax substituting stearic acid with functional benefits. Our endeavour has been to formulate moisturizer with sunflower wax to evaluate its efficacy and safety parameters as compare to available commercial moisturizer.

MATERIALS AND METHODS

Materials

The sunflower wax was obtained as a gift sample from M/s. Mahesh India, Mumbai. Stearic acid, lanoline, glycerin, liquid paraffin, glyceryl monostearate, isopropyl myristate, triethanolamine and borax were used of analytical grade.

Methods

Preparation of moisturizing cream

In the preliminary stages of these studies, the objective was to manufacture a moisturizing cream formulation extemporaneously that showed no visible signs of physical instability such as cracking, creaming, phase inversion and/or bleeding of the cream base from the container. Physical instability was evaluated immediately after manufacture and then twenty-four (24) hours after manufacture and storage at room temperature (25 °C). Initial formulation development was undertaken on batches of only 25 g and any formulation that showed signs of physical instability immediately and/or after twenty-four (24) hours of storage at room temperature (25 °C) was considered unsuitable and therefore not considered for further investigation. The formulation for the prototype moisturizing cream based on triethanolamine stearate as shown in table 1. Moisturizing cream formulation were developed from a prototype moisturizing

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Research Article Open Access

Solid Self-Microemulsifying Drug Delivery System (SMEDDS) of Primaquine: Bio-distribution and Enhanced Liver Uptake

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Abstract

Aim: The present research work was aimed at developing a self-microemulsifying drug delivery system (SMEDDS) of Primaquine (PQ) with increased liver uptake and hence enhanced antimalarial efficacy against the liver stages of *Plasmodium vivax*.

Materials and methods: SMEDDS was formulated using generally regarded as safe (GRAS) excipients and adsorbed on Aerosil 200. The optimized SMEDDS were characterized for various physicochemical parameters. Pharmacodynamic efficacy in murine model was evaluated using Peter's Four Day Suppresive Test. Biodistribution studies were carried out using flow cytometry.

Results: The adsorbed SMEDDS showed a particle size of 75 nm and exhibited enhanced antimalarial efficacy as compared to marketed formulations. Biodistribution studies revealed enhanced uptake in the liver.

Conclusion: Preliminary studies in lower animals indicated the potential of SMEDDS to enhance the uptake of PQ at its site of action i.e. liver.

Keywords: Pharmacodynamic efficacy; Biodistribution; Liver uptake; SMEDDS; Primaquine

Introduction

Malaria is a major cause of illness and death in children and adults, especially in tropical countries. The situation has recently become even more serious due to the increase in resistance to the drugs normally used to combat the parasites that cause the disease. In humans, malaria is caused by five distinct species of the blood borne Apicomplexan parasite *Plasmodium: P. vivax, P. falciparum, P. malariae, P. Ovale and P. knowelsi* [1]. *P. vivax* and *P. ovale* persist in the liver in the form of hypnozoites for years and can cause an erythrocytic infection upon reactivation [2,3]. Primaquine (PQ), an 8-aminoquinoline drug, has been an important antimalarial agent for over 40 years because of its unique effectiveness against exoerythrocytic forms of both *P. vivax* and *P. ovale* [4,5]. PQ is useful to fight malaria on three different fronts: (i) primary prophylaxis against all species of malaria, (ii) presumptive antirelapse therapy (terminal prophylaxis) for persons extensively exposed to *P. vivax* or *P. ovale*, (iii) radical cure in individuals infected with *P. vivax* or *P. ovale*. In endemic regions, PQ is used as a gametocytocide to prevent the transmission of the infection from the human host to the mosquitoes, thus blocking the spread of the disease. It is the only anti-malarial effective in treating the liver stages of the parasite [6]. However PQ is characterized by dose-limiting side effects like acute hemolytic anemia in patients with G6PD deficiency, methanoglobenemia, leukocytopenia, leukocytosis, GI disturbances and abdominal cramps [7,8]. Further, PQ is also characterized by low plasma half-life (5.6 h) and is subject to first-pass metabolism, which requires frequent administration and amplifies its adverse effects [9]. In view of its crucial role in antimalarial chemotherapy, it is important to reduce the adverse effects of PQ. To improve the therapeutic efficacy of the drug and diminish its toxicity, many researchers have attempted to encapsulate PQ into drug delivery systems, such as liposomes, microspheres, and nanoparticles, or to conjugate PQ to protein carriers to modify its toxicity profile [10]. Targeting PQ to its site of action, i.e., the liver is likely to reduce the therapeutic dose and result in a toxicity reduction. However, PQ is advised not to be administered parenterally because of the risk of marked hypotension. Thus the oral route is preferable for PQ administration. Targeting via oral route is made possible by using a nanoparticulate system that mimics natural lipoproteins with regards to the intestinal absorption and distribution [1].

SMEDDS is defined as isotropic mixture of oil, surfactant, cosurfactant, and drug that rapidly forms o/w microemulsion when exposed to aqueous media under conditions of gentle agitation or digestive motility that is encountered in GI tract. SMEDDS presents the drug in nanosized droplets offering large interfacial area for drug diffusion [11]. SMEDDS can be easily scaled up and are commercially feasible. They can also be converted to solid dosage forms and filled in hard gelatin capsules and show improved physical stability upon long term storage due to their anhydrous nature [12]. Self-microemulsifying system of PQ would be an efficient, and convenient and more likely to have higher patient compliance. Hence, the feasibility of SMEDDS as a strategy for improving the delivery of PQ was evaluated. PQ free base, which exists in liquid state at room and physiologic temperature, served as an oily phase of the microemulsions in the present investigation.

Materials and Methods

Chemicals

Primaquine Diphosphate was a generous gift from Ipca Laboratories Limited, Mumbai. Cremophor EL (PEG - 35 Castor oil), Cremophor RH 40 (Polyoxyl 40 Hydrogenated Castor Oil), Solutol HS

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Review article

A review on treatment of Human Immunodeficiency Virus (HIV) by Naturopathy

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Keywords: HIV, AIDS, Immuno-suppression Syndrome.

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Abstract

Acquired immunodeficiency syndrome is a clinical syndrome that is the result of infection with human immune deficiency virus which causes profound immunosuppression. Current therapies are available for symptomatic treatment of AIDS is quite expensive. Herbal medicines can be developed as a safe, effective and economical alternative. Herbal medications provide sensible means for the treatment of AIDS. The herbal medicines which are used for the treatment of AIDS are kalmegh, asparagus, Indian gooseberry, Ashoka, etc. Many compounds of plants origin inhibit HIV during the various stage of the HIV life cycle, these include several alkaloids carbohydrates, coumarin, lignin, and proteins. These candidates have the potential to come up as the drug for treatment for HIV infection. So, the purpose of this article is to identify herbs and there active constituents having activity against human immune-deficiency virus with an objective of providing an effective method for preventing the transmission and the treatment of this disease.

Introduction

Acquired immune-deficiency syndrome (AIDS) is a scientific condition that is the result of infection with human immunodeficiency virus (HIV), which causes superficial immune clamp down. It is a serious, life aggressive health problem since the first case was recognized in 1981 and is the most quickly increasing disease of the era. Since the widespread began, more than 60 million people have been infected with the virus and HIV/AIDS is now leading to the death. According to the recent report of WHO and "UNAIDS" at the end of 2004, a predictable 40 million people (37.2 million adults and 2.2 million children) were living with HIV worldwide out of which about 22 million had died [1]. The most pretentious is sub-Saharan Africa, where 3.1 million expired in 2004. By the end of 2004, the total figure of people living with HIV/AIDS in the region has reached 25.4 million. Further 540000 people are predictable to have died of AIDS in 2004. The range of HIV in India has been miscellaneous, with much of India having a low rate of infection and the widespread being most extreme in the southern states. The disease usually occurs in stages from a latent stage with initial symptoms such by means of temperature, wooziness, paleness, also joint pain, rashes and widespread lymphadenopathy tailed by way of the asymptomatic latency period. In the middle stage symptoms such as fever, weight loss, night sweats, diarrhea, thrust, skin lesion and depression are common. Herbal drugs offer balanced means for the action of many illnesses. In Europe, herbal treatment has been considered as the most popular complementary medicine used by HIV infected individuals [2]. HIV goes to a distinct class of viruses called retrovirus. The normal Human immunodeficiency virus (HIV), the virus actual responsible for AIDS, is around 0.000031 inches (120Å) long and has an RNA core. The ribonucleotide particle is encapsulated by a capsid made up of a capsid protein (CA), p24. The capsid environment also contains other viral proteins such as intergrase and reverse transcriptase. It also covers a wide variety of additional macromolecules derived from the cell including tRNAlys3, which serves as a primer for reverse transcription [3]. The major HIV protein associated with envelope is gp120/41, these functions as the viral attachment proteins.

Types of HIV

Two major types of HIV have been identified as follows [4]:
HIV-1: It is the basis of the international wide spread and is most usually mentioned to as HIV. It is an extremely adaptable virus, which transforms readily. There are many dissimilar straining of HIV-1, which can be categorized according to groups and subtypes; M and O.

Synthesis and Antibacterial Activities of Novel Sulphonamide Containing 1, 3-diarylpyrazolyl Amides

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Abstract | References | Citations | Supplementary Data

Background: Infectious diseases are the leaders among the challenging drug targets because of the multi-drug resist antimicrobial pathogens and continuous rise in the emerging infections from known and unknown sources. Though there is an availability of a large number of antibiotics and chemotherapeutics for medical use, the emerging resistance drives it for the search of new classes of antimicrobial agents. In the present study, a series of novel amides (5a-j) containing 1, 3-diaryl pyrazoles were synthesized, characterized and evaluated for their anti-bacterial properties against gram - positive organisms (B. subtilis) and gram - negative organisms (E. coli).

Method: The evaluation of the synthesized compounds (5a-j) for antibacterial activity was carried out by standard literature procedure using agar diffusion method by finding the zone of inhibition of the drug sample against the standard drugs. The organisms employed in vitro testing of the compounds were Escherichia coli (Gram Negative) and Bacillus subtilis (Gram Positive). All the cultures were maintained on Nutrient agar (Microbiology) grade, Hi Media medium by periodic sub culturing. Ciprofloxacin was used as reference compound for antibacterial activity. The compounds were tested at a concentration of a 50 µg/ml and 100 µg/ml and were prepared in Dimethylsulphoxide. Obtained zone of inhibition at tested concentrations was recorded. Minimum inhibitory concentrations (MIC) assay of two superior molecules 5e and 5f was done according to CLSI standard protocol. Ciprofloxacin was used as a standard drug. The minimum inhibitory concentrations (MIC) values were determined.

Results: The structures of these novel compounds were confirmed by 1H NMR, ES-MS and elemental analysis. Ciprofloxacin was used as standard reference compound. In the initial inhibitory study at 100 µg/ml, compounds 5e (12 ± 0.816) and 5f (17 ± 0.816) demonstrated comparable zone of inhibition with ciprofloxacin (20.66 ± 0.942) in E. coli strain, while for B. subtilis, at 100µg/ml, compounds 5e (25.66 ± 0.942) and 5f (26.33 ± 0.942) were found to be equipotent as compared to standard ciprofloxacin (27.66 ± 0.471). Hence 5e and 5f were tested for their MIC values (µg/ml) using E. coli and B. subtilis bacterial strains. To summarize, 5e (MIC = 8µg/ml for E. coli and MIC = 4 µg/ml for B. subtilis) and 5f (MIC = 16 µg/ml for E. coli and MIC = 8 µg/ml for B. subtilis) showed better MIC values than the standard Ciprofloxacin (MIC = 20 µg/ml for E. coli and MIC = 12 µg/ml for B. subtilis).

Conclusion: We have discovered a series of 1, 3 diaryl pyrazolyl amides, and preliminary bioassay results imply that some of the compounds displayed moderate antibacterial activities against various bacterial species. Two promising compounds 5e and 5f exhibited superior MIC (µg/ml) values in vitro when compared with standard drug. Compounds 5e and 5f were the new findings from this research work and it will be studied further in near future.

Keywords: 1, 3-diaryl pyrazole; 4-Hydrazino-benzenesulfonamide; MIC; anti-bacterial activities; sulfonamide

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More about this publication?

Anti-inflammatory Exploration of Sulfonamide Containing Diaryl Pyrazoles with Promising COX-2 Selectivity and Enhanced Gastric Safety Profile

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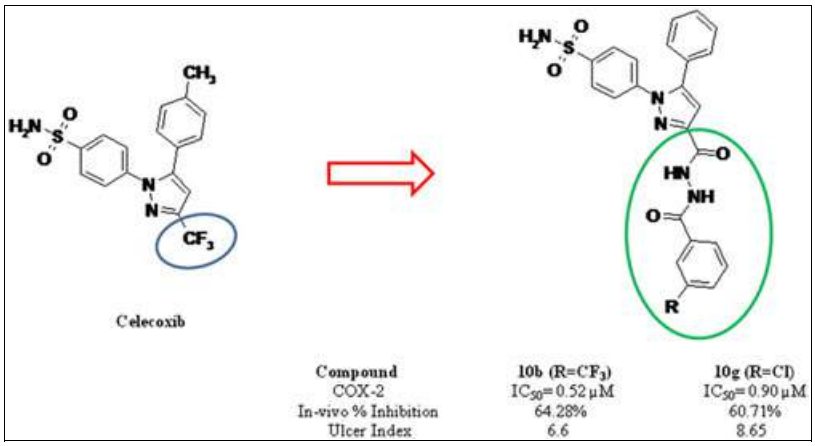

Novel sulfonamide containing diaryl pyrazoles were synthesized and were subsequently tested for their *in vitro* cyclooxygenase inhibitory assay. Compounds that showed promising *in vitro* COX-2 IC_{50} values and selectivity indices were then evaluated for their *in vivo* anti-inflammatory inhibition assay using standard carrageenan-induced rat paw edema method. Two promising inhibitors were evaluated for ulcerogenic liability. X-ray crystal structure of COX-2 was taken from PDB entry COX-2 (3LN1) having a resolution of 2.80 Å (Angstroms). Structural preparations for docking studies were accomplished using protein preparation wizard in Maestro 9.0. Compound **10b** displayed reasonable COX-2 inhibition (COX-2 IC_{50} = 0.52 µM) and COX-2 selectivity index (SI = 10.73) when compared with celecoxib (COX-2 IC_{50} = 0.78 µM) and (SI = 9.51). *In vivo* anti-inflammatory studies demonstrated 64.28% inhibition for **10b** in comparison with the 57.14% for that of celecoxib itself. The results of ulcerogenic liability were also found comparable with standard celecoxib. Molecular docking studies revealed that all the designed molecules showed good interactions with receptor active site with glide scores in the range −13.130 to −10.624.

INTRODUCTION

Fast and effective relief of pain and inflammation in the human being is continued to be a major task for the medicinal chemist. Non-steroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for the alleviation of pain and inflammation associated with a number of pathological conditions [1]. NSAIDs bestow their effect by inhibiting the catalytic activity of cyclooxygenase (COX), which results in a blockage of the formation of prostaglandins (PGs) and thromboxane (TXs) [2,3]. The cyclooxygenase exists as two distinct isoforms (COX-1 and COX-2) [4]. The maintenance of physiological functions such as protection of gastric mucosa, vascular homeostasis, and platelet aggregation is governed by the constitutively expressed COX-1 isoform as organization enzyme while the upregulation of the COX-2 is observed in acute and chronic inflammation [5,6]. Thus, inhibition of COX-2 accounts for the anti-inflammatory effects of NSAIDs, whereas interruption of COX-1 leads to gastrointestinal toxicity ranging from ulcers to perforation and bleeding [7]. Time-honored non-selective NSAIDs such as indomethacin, ibuprofen, and aspirin interact with both forms (COX-1 and COX-2), accounting for their anti-inflammatory activity in addition to their pronounced side effects, resulting from the inhibition of gastroprotective PGs synthesized through COX-1 pathway [8]. Hence, a number of selective COX-2 inhibitors such as celecoxib I, rofecoxib II, and valdecoxib III (coxibs) have been developed and approved for marketing by virtue of their fewer gastrointestinal side effects compared with traditional NSAIDs (Fig. 1). Celecoxib, in the 1,5-diarylpyrazole class of compound, was the first launched selective COX-2 inhibitor with

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Phytochemical analysis of *Canna indica* L. roots and rhizomes extract

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ABSTRACT

Canna indica L. (Cannaceae) roots and rhizomes were reported to possess various biological properties like antimicrobial, anthelmintic potential and HIV-1 reverse transcriptase inhibition. In our previous studies, they showed antidiabetic activity on normal rats and rats co-addicted with caffeine and nicotine. In the pursuit of the phytochemical/s responsible for these biological activities, present study was aimed at phytochemical evaluation of hydroalcoholic extract (HAE) of *C. indica* L. roots and rhizomes; including preliminary screening, thin layer chromatography, H^1-NMR and HR-LC/MS-MS analysis. After preliminary detection of flavonoids, tannins and sterols, HAE was tested for presence of β-sitosterol using TLC. H^1-NMR spectrum of HAE revealed the presence of around 761 deshielded protons corresponding to different polar compounds. HR-LC/MS-MS analysis carried out at both positive and negative ion mode, indicated the presence of more than 90 compounds including short fragment of peptide. As per METLIN database, predicted major phytochemicals were 3′-hydroxytrimethoprim, 3,7-epoxycaryophyllan-6-one, swietenine, typhasterol, hexacosanedioic acid and 3β, 6α,7α-trihydroxy-5β-cholan-24-oic acid few of which, are biologically active.

1. Introduction

Crude plant extracts are the complex mixture of different biologically active secondary metabolites. Their rapid and accurate identification and quantification is thereby very crucial in phytochemical analysis. Recently developed advanced instrumental techniques like chromatographic separation under high pressure (HPLC) hyphenated with mass fragmentation (MS) of separated compounds and their Nuclear Magnetic Resonance (NMR) spectrum made this phytochemical investigation possible.

Canna indica L. (Cannaceae) (Fig. 1) is an ornamental, perennial herb; native of tropical regions of America but also found in other tropical countries of world [3]; widely used as a folklore medicine with beneficial effects in, hepatitis, infection, rheumatism [5]. Roots and rhizomes of *C. indica* L. are thick, cylindrical and creamy white or pinkish in colour. Roots are about 2–5 mm in diameter with numerous root hairs. Rhizomes may be sympodial, stoloniferous or tuberous. Secondary lateral roots are also present [1]Its roots and rhizomes were shown to exhibit variety of pharmacological activities. Woradulayapinij et al. 2005 [24] demonstrated inhibitory activity on HIV-1 reverse transcriptase; Nirmal et al. 2007 [19] proved anthelmintic potential of *C. indica* roots and rhizomes while Gaur et al. 2014 [8] reported *C. indica* L roots to have antimicrobial activity against bacteria. A decoction of the root with fermented rice is used in the treatment of gonorrhea and amenorrhea [13]. In our previous research articles [15,16] we reported antidiabetic activity of hydroalcoholic extract in normal rats as well as rats co-addicted with caffeine and nicotine. Since few decades, it has been used in constructed wetland for removal of organic pollutants, nitrogen, phosphorous and heavy metals [18,6].

Considering the wide uses of *C. indica* L. roots and rhizomes, the present research work is an attempt to explore phyto-compounds present in *Canna indica* L. roots and rhizomes probably responsible for different pharmacological activities exhibited and thereby therapeutic uses attributed to them.

2. Materials and methods

2.1. Collection of plant material and extraction

The plant *C. indica* L. was identified and collected from the valley of Pawana River, Pimpri-Chinchwad region of Pune, India and then authenticated from Western Regional Centre- Botanical Survey of India, Pune (Voucher Specimen No. SK01). Plant material was washed under tap water and allowed to dry in shade. Dried material was then pulverised to powder. About 50 gm of powder was then extracted with 300 ml of mixture of ethanol and water (1:1) using Soxhlet apparatus.

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, biological evaluation and docking study of some novel isoxazole clubbed 1,3,4-oxadiazoles derivatives

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Abstract

A novel series of isoxazole clubbed 1,3,4-oxadiazole derivatives have been synthesized by reaction of 5-(3-fluoro-4-methoxyphenyl) isoxazole-3-carbohydrazide with different substituted benzoic/pyridinyl/indolyl acids in phosphorous oxychloride, characterized by IR, ^{1}H NMR, ^{13}C NMR, MS analytical data and evaluated for their antimicrobial as well as antitubercular activity. Antibacterial activity of compounds **5e**, **5g**, **5h**, **5j** and **5l** were found to be good against *E. coli, P. aeruginosa, S. aureus* and *S. pyogenes* as compared to standard Ampicillin. Compound **5b** and **5i** were found to be active antitubercular agents against *M. tuberculosis* H37Rv. Antibacterial and antitubercular activity was supported by molecular docking to gain insights of the mode of inhibition of MurD ligase enzyme.

Keywords Isoxazole · 1,3,4-oxadiazole · Antimicrobial · Antitubercular activity · Molecular docking

Introduction

Antimicrobial resistance is the major concern to public health, especially in communicable diseases like tuberculosis (TB). The alarming increase in the reports of multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XRD-TB) clearly signifies this concern (Global action plan on antimicrobial resistance—WHO 2015). In the year 2015 nearly two million people succumbed to TB and over 6.1 million people were reported with TB. As per these estimates approximately 33% of world's population is under the threat of *Mycobacterium tuberculosis* (Global tuberculosis report—WHO 2016; Tuberculosis fact sheet—WHO 2017). In view of this, the resolution was passed by WHO in 2015 to intensify the research and innovations in TB therapeutics and to adopt imperishable development goals (End TB strategy 2015). To fulfil these development goals, there is an immense need of new, potent, antimicrobial and antimycobacterial agents. The synthesis of novel antimicrobial and antimycobacterial agents, especially targeting the novel bacterial protein targets, is certainly an attractive strategy in fulfilling these development goals. The synthesis of fluorine-containing compounds is pertinent in such task because such compounds have significant biological activity due to their lipophilicity and metabolic stability. The 4-methoxy-3-fluorophenyl is a useful pharmacophore fragment moiety having widespread therapeutic properties such as antimicrobial (Raundal et al. 2015, 2016), antitumor (Li and Guo-Yuan 2013), anticancer (Tang 2004), antioxidant, analgesic (Shyma et al. 2014) and also a key fragment moiety of anti-inflammatory drug Deracoxib. Azoles on the other hand are the lipophilic heterocyclic compounds with favourable pharmacokinetic property and exhibit the promising antitubercular activity (Kini et al. 2009; Andreani et al. 2001). The 1,3,4-oxadiazole derivatives play a key role in the field of medicinal chemistry, especially as antimicrobial (Chandrakantha et al. 2010; Kumar et al. 2010;

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Biological Chemistry & Chemical Biology

Synthesis, Antimicrobial Evaluation and Docking Study of Some Pyrazole Bearing [1,2,4]Triazolo[3,4-b][1,3,4] thiadiazole Derivatives

Ramesh M. Shingare,[a] Yogesh S. Patil,[a] Jaiprakash N. Sangshetti,[b] Manoj G. Damale,[c] Dhanji P. Rajani,[d] and Balaji R. Madje*[a]

A novel series of pyrazole bearing[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole derivatives (**6a-l**) such as 3-(5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-3-yl)-6-(2-methoxyphenyl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole were synthesized by cyclo-condensation of 4-amino-5-[5-(3-fluoro-4-methoxy-phenyl)-1*H*-pyrazol-3-yl]-4*H*-[1,2,4]triazole-3-thiol (**5**) with substituted benzoic/pyridinyl acids in phosphorus oxychloride giving good yields and purity. IR, ^{1}H NMR, ^{13}C NMR and LCMS/MS spectroscopy were used to characterise all the synthesized compounds. All the new derivatives were appraised for their antimicrobial activity, antifungal assay against *C. Albicans, A. Niger* and *A. Clavatus* along with Nystatin and Griseofulvin as standard drug and antibacterial assay against *E. Coli, P. Aeruginosa, S. Aureus, S. Pyogenus* along with Ampicillin as standard drug. Compounds (**6b**) and (**6j**) displayed excellent antifungal activity whereas compound (**6d**) and (**6e**) displayed excellent antibacterial activity. Molecular modelling and adsorption, distribution, metabolism and excretion-toxicity (ADMET) prediction data clearly shows that 1,2,4-triazolo[3,4-b][1,3,4] thiadiazole derivatives (**6a-l**) have potential to explore in the drug discovery pipeline as antifungal agents.

Introduction

Being azoles, both 1,2,4-triazoles and 1,3,4-thiadiazole individually have their own importance in the field of medicinal chemistry, agriculture as well as industrial applications. Triazolo-thiadiazole, fused product of 1,2,4-triazole and 1,3,4-thiadiazole are renowned heterocycles due to their versatile therapeutical applications such as antimicrobial,[1–3,8] anti-inflammatory, analgesic,[4–8] antibacterial,[9–11] anti-oxidant,[8,10,11] antifungal,[11–15] anticancer,[16] anthelmintic,[17] anti-HIV,[18] antitumor[18–20] and anti-tubercular.[21] Triazolo-thiadiazole derivatives reported to possess the CNS stimulant properties[22] and anti-hyperglycemic activity.[23] These molecules also reported with the strong cytotoxicity.[24–26] Presence of electron withdrawing groups such as chloro, chloro-fluoro and electron releasing groups like OH, -OCH_3 attached to triazolo-thiadiazole ring has a significant effect on antimicrobial activity.[27]

In view of the reported literature and as part of our research work on synthesis and biological screening of some novel heterocyclic compounds containing azole moiety,[28] We thought to develop fused heterocyclic scaffolds of 1,2,4-triazole and thiadiazole containing both electron withdrawing groups like chloro or fluoro as well as electron releasing groups like -OCH_3, So herein we report synthesis and antimicrobial activity of 6-substituted-3-[5-(3-fluoro-4-methoxy-phenyl)-1*H*-pyrazol-3-yl]-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives **(6a-l)**.

Results and Discussion

The synthetic route used to synthesize the proposed scaffolds is outlined in Scheme 1. Starting from 4-methoxy-3-fluoro-acetophenone (**1**), we have synthesized intermediates (**2-4**) as per the reported process[29,30] and the synthesized intermediates were compared with the reported data. Pyrazole carbohydrazide (**4**) was processed with carbon disulfide and ethanolic potassium hydroxide under reflux condition for 6 h, completion of reaction was monitored by TLC and obtained corresponding dithiocarbazinate potassium salt was in-situ processed for the next step. In which above salt was reacted with hydrazine hydrate at reflux temperature for 12 h to gives corresponding derivative (**5**) with good yield. Formation of compound (**5**) confirmed by mean of IR, ^{1}H NMR, and MS analysis. Further structure related studies[31,32] described thiol-thione tautomeric equilibrium of heterocyclic thione derivatives. Typically, IR spectra shows two absorption bands at 3360–3250 cm^{-1}, indicate presence of NH_2 and SH groups along with this two other absorption bands at 1633–1513 cm^{-1} indicates the -C=N vibrations, which confirm formation of triazole ring. ^{1}H NMR

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β-Cyclodextrin catalyzed one-pot four component auspicious protocol for synthesis of spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-trione as a potential antimicrobial agent

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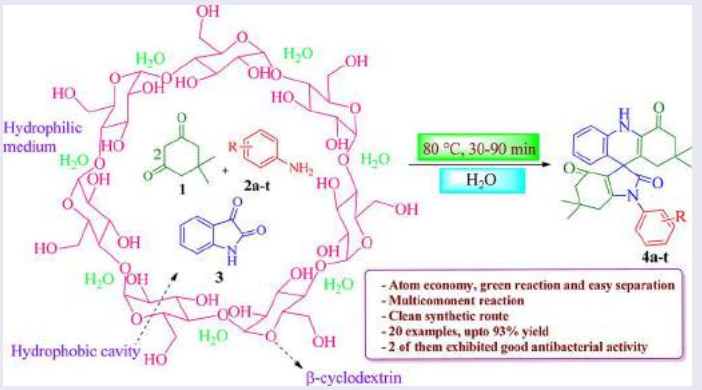
ABSTRACT

We have developed an perceptive and facile approach for the synthesis of new spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-trione derivatives (**4a–t**) by one-pot four component condensation involving two equivalence of dimedone (**1**), substituted anilines (**2a–t**), and isatin (**3**) catalyzed by β-cyclodextrin in water within short reaction time at 80 °C in good to excellent yields. We believe that this novel procedure may open the door for the easy generation of new and bioactive spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-triones. The most exciting feature of this methodology is its mechanism involving the unusual ring opening of an isatin moiety followed by recyclization. Synthesized compounds were evaluated for their antimicrobial activities against four bacteria and three fungi. All the spirooxindole derivatives exhibited significant antibacterial activity against bacteria and fungi. Among 20 compounds screened, compound (**4i**) and (**4h**) was found to be more active against tested bacterial strain.

GRAPHICAL ABSTRACT



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Antimicrobial activity; β-cyclodextrin; multicomponent reaction; spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-trione; supramolecular catalyst

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data (Spectroscopic characterizations of the compounds) can be accessed on the publisher's website.

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β-CD-catalyzed multicomponent domino reaction: synthesis, characterization, in silico molecular docking and biological evaluation of pyrano[2,3-*d*]-pyrimidinone derivatives

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Abstract Simple and green synthetic procedures constitute an important goal in organic synthesis. The combination of multicomponent reactions (MCRs) and unconventional solvents has become a new research direction, which enables simultaneous growth of both MCRs and green solvents toward ideal organic synthesis. In this paper, we have summarized recent results of MCRs obtained in unconventional media using water and β-cyclodextrin, as supramolecular catalyst, for the synthesis of pyrano[2,3-*d*]-pyrimidinone (**4a–q**) derivatives. The compounds were evaluated for their in vitro antimicrobial activity. Among the synthesized compounds, compounds **4h**, **4m** and **4p** exhibited higher antimicrobial activity than ciprofloxacin used as the reference drug. Most of the synthesized compounds have good to excellent antimicrobial activity. Furthermore, \ molecular docking study was performed to help understand binding interactions of the most active analogs with C_{30} carotenoid dehydrosqualene synthase enzyme.

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ORIGINAL ARTICLE

Structural insights of dipeptidyl peptidase-IV inhibitors through molecular dynamics-guided receptor-dependent 4D-QSAR studies

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Abstract

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are promising antidiabetic agents. Currently, several DPP-IV inhibitors have been approved for therapeutic use in diabetes mellitus. Receptor-dependent 4D-QSAR is comparatively a new approach which uses molecular dynamics simulations to generate conformational ensemble profiles of compounds representing a dynamic state of compounds at a target's binding site. This work describes a receptor-dependent 4D-QSAR study on triazolopiperazine derivatives. QSARINS multiple linear regression method was adopted to generate 4D-QSAR models. A model with 9 variables was found to have better predictive accuracy with $R^2 = 0.692$, Q^2 (leave-one-out) = 0.592 and R^2 predicted = 0.597. The location of these 9 variables at the binding site of DPP-IV revealed the importance of the residues Val711, Tyr662, Tyr666, Val202, Asp200 and Thr199 in making critical interactions with DPP-IV inhibitors. The study of these critical interactions revealed the structural features required in DPP-IV inhibitors. Thus, in this study the importance of a halogen substituent on a phenyl ring, the extent of substitution on the triazolopiperazine ring, the presence of an ionizable amino group and the presence of a hydrophobic substituent that can bind deeper in binding pocket of DPP-IV were revealed.

Keywords Diabetes · DPP-IV · 4D QSAR · Molecular dynamics · Sitagliptin

Introduction

Type-2 diabetes mellitus is a disorder manifested due to the progressive decline in insulin activity usually followed by pancreatic β-cell dysfunction resulting in lower level of insulin. In the biosynthesis of insulin, incretin hormones like glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) play a major role in stimulation of insulin biosynthesis, insulin secretion, and glucose-dependent inhibition of glucagon release [1,2].

Dipeptidyl peptidase-IV (DPP-IV) is a transmembrane glycoprotein, with serine protease activity that cleaves X-proline dipeptides from the N-terminus of GLP-1 and GIP [3,4]. Inhibition of DPP-IV leads to increased levels of physiologically active GLP-1, which in turn contributes to normalizing elevated glucose levels [5]. Sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin and teneligliptin are approved DPP-IV inhibitors for clinical use in the management of type-2 diabetes [6,7].

Rational drug design, a process to find more active molecules or lead compounds, mostly relies on the information of how ligands bind at the binding site of their target enzyme and which residues participate in binding [8]. Typically, the binding site is established by including residues that are within 5 Å distance from a ligand's heavy atoms (non-hydrogen atoms). The binding pocket of the Cdk5-p25 complex (cyclin-dependent kinase-5 with its activator p25) where ATP binds was defined by such criteria [9] and later used in identifying the functional domains or binding pockets of target proteins [10–13]. A triazolopiperazine derivative, sitagliptin, was approved worldwide as first-in-class DPP-

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LQTA-R: A new 3D-QSAR methodology applied to a set of DGAT1 inhibitors

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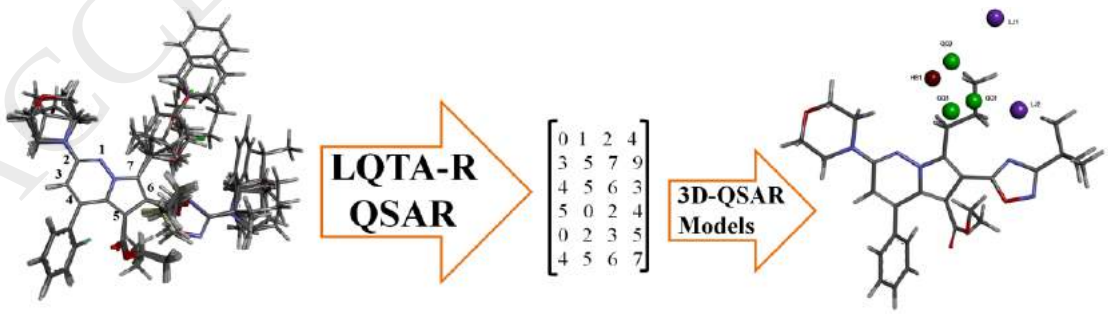
Graphical abstract



Highlights:

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Synthesis and biological evaluation of novel triazole-biscoumarin conjugates as potential antitubercular and anti-oxidant agents

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Abstract The synthesis of a new series of triazole-biscoumarin conjugates by using a molecular hybridization approach is described. The newly synthesized compounds **6a–k** were evaluated for their in vitro antitubercular activity against active and dormant *Mtb* H37Ra and anti-oxidant activity against DPPH radical scavenging. Molecular docking simulations for the antitubercular activity showed that the conjugates **6a–k** bind in the pocket of the DprE1 enzyme. Most of the conjugates displayed good antitubercular activity against both the active and dormant *Mtb* H37Ra strain. The compound **6h** displayed very good antitubercular activity against dormant *Mtb* H37Ra with an IC_{50} value of 1.44 μg/mL. Most of the synthesized conjugates exhibit excellent anti-oxidant activity with an IC_{50} of less than the standard BHT. Compound **6b** is the most active among all the conjugates with an IC_{50} value of 08.17 ± 0.11 μg/mL. The molecular docking study shows good agreement between the observed antitubercular activity and the binding affinity.

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Chemistry SELECT Full Papers

Medicinal Chemistry & Drug Discovery

Synthesis of Novel α-Aminophosphonate Derivatives, Biological Evaluation as Potent Antiproliferative Agents and Molecular Docking

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A series of novel fluorine containing α-aminophosphonate derivatives (**4a–4q**) were synthesized in excellent yield and high purity. All these novel Fluorinated α-aminophosphonate compounds were screened for antiproliferative and apoptosis activity on human non small cell lung carcinoma cells (A549) and human skin melanoma cells (SK-MEL-2). Compounds **4a**, **4b**, **4c**, **4f**, **4i**, **4j** and **4m** were found to be more active antiproliferative agent against A549 and SK-MEL-2 cells with IC_{50} value 0.22 to 1.25 μM. Molecular docking study related to binding affinity and binding mode analysis showed that synthesized compounds had potential to inhibit human Topoisomerase IIa enzyme system. Flow cytometric study showed some of these derivatives also induced cell apoptosis and arrest cell cycle at G1 and at G_2/M phase. Overall, this study provides future perspective of lead candidate for the future anticancer drug discovery initiatives.

Introduction

Cancer is second leading cause of mortality worldwide,[1] in last two decades this disease has been the main cause of the death. WHO reports approximately 14 million new cancer cases were found, among which 8.8 million cancer patients died and 32.6 million people are affected from disease in 2012. The number is expected to rise up to 14 million to 22 million in the year 2030.[2,3] Aminophosphonates, known as phosphorus analogues of amino acids, have received much more attention due to diverse applications in medicine. They play a vital role in antibody generation.[4] Recently, α-amino phosphonates are proved to posses potent biological activities, such as selective inhibitors of tyrosine kinase,[5] cytotoxic to cancer cells,[6,7,8] antibacterial,[9] antifungal,[10] antitumor and antiproliferative agents,[11–14] enzyme inhibitors,[15,16] antiviral,[17] and plant growth regulators.[18]

Fluorinated α-amino acids and their derivatives such as α-(fluoromethyl)-substituted α-amino acids have employed as selective inhibitor of pyridoxal phosphate dependent enzymes. The probe of fluorine containing aromatic and aliphatic compounds exhibit a significant medicinal value in pharmaceutical industries.[19–21] An incorporation of -CF_3 group at α-position of a cyclic α-amino acid enhances the biological properties of peptides.[22] Due to wide medicinal applications of fluorinated α-aminophosphonates compounds they show significant biological activity and two major review focus on fluorinated α-aminophosphonates compound.[23,24] Several methods are reported for the synthesis of α-aminophosphonates. More commonly used methods include hydrophosphonylation of pregenerated imines or *in situ* generated imines by nucleophilic addition to phosphonate ester in various catalysis such as $InCl_3$,[25] $TaCl_5{\cdot}SiO_2$,[26] $Mg(ClO_4)_2$,[27] $LiClO_4$,[28a–d] $AlCl_3$,[29] lanthanide triflates,[30] montmorillonite clay-MW,[31] CF_3COOH,[32] sulfamic acid,[33] $BF_3{\cdot}Et_2O$,[34] $ZrOCl_2$,[35] TiO_2,[36] $LaCl_3$,[37] ethyl ammonium nitrate,[38] and $Cd(ClO_4)$.[39] Recently, reported used solvate ionic liquids $[G_4(Li)]TFSI$.[40] To overcome the problems of longer reaction time, use of toxic metal catalysts and tedious workup, a new method has been developed for the synthesis of α-aminophosphonates.

Herein, report an efficient method for the synthesis of novel bis-CF_3-containing α-aminophosphonates using lanthanum chloride as a catalyst *via* solvent free condensation of substituted aromatics aldehyde, amine and diethyl phosphite (Scheme-1). Furthermore, these α-aminophosphonate derivatives were screened for antiproliferative activity on human cancer cell lines (SK-MEL-2 and A549 cells).

These compounds were found active against Human non small cell lung carcinoma cells (A549 cell) and Human skin melanoma cells (SK-MEL-2). Apoptotic activity of these compounds was evaluated by early apoptotic markers in compound

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Synthesis, biological evaluations and computational studies of *N*-(3-(-2-(7-Chloroquinolin-2-yl)vinyl) benzylidene)anilines as fungal biofilm inhibitors

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ABSTRACT

In the present investigation, new chloroquinoline derivatives bearing vinyl benzylidene aniline substituents at 2nd position were synthesized and screed for biofilm inhibitory, antifungal and antibacterial activity. The result of biofilm inhibition of *C. albicans* suggested that compounds **5j** (IC_{50} value= 51.2 μM) and **5a** (IC_{50} value= 66.2 μM) possess promising antibiofilm inhibition when compared with the standard antifungal drug fluconazole (IC_{50}= 40.0 μM). Two compounds **5a** (MIC= 94.2 μg/mL) and **5f** (MIC= 98.8 μg/mL) also exhibited good antifungal activity comparable to standard drug fluconazole (MIC= 50.0 μg/mL). The antibacterial screening against four strains of bacteria *viz. E. coli, P. aeruginosa, B. subtilis, and S. aureus* suggested their potential antibacterial activity and especially all the compounds except **5g** were found more active than the standard drug ciprofloxacin against *B. subtilis.* To further gain insights into the possible mechanism of these compounds in biofilm inhibition through the agglutinin like protein (Als), molecular docking and molecular dynamics simulation studies were carried out. Molecular

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Chemistry SELECT Full Papers

Biological Chemistry & Chemical Biology

Design, Synthesis and Molecular Docking Studies of Novel Triazole-Chromene Conjugates as Antitubercular, Antioxidant and Antifungal Agents

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A green and efficient protocol has been developed for the synthesis of novel 1,2,3-triazole-chromene conjugates (**7a-j**) *via* ultrasound assisted and $NaHCO_3$ catalyzed for the first time. Structures of all the new conjugates were deduced by various spectroscopic techniques. The newly synthesized triazole-chromene conjugates were evaluated for their in vitro antitubercular activity against *Mycobacterium tuberculosis* (MTB) H37Rv strain. The conjugates **7f** and **7h** were found to be most active with MIC value 12.5 μg/mL. Furthermore, all the conjugates were screened for their antioxidant activity and are highly active (IC_{50} = 7.05-14 μg/mL) than the reference drug BHT (16.47 μg/mL). The triazole-chromene conjugates were also screened for their in vitro antifungal activity and some of the conjugates **7a**, **7b**, **7d**, **7e**, **7f** and **7i** were exhibited potent activity (MIC = 6.25-25 μg/mL) than the reference drug Miconazole. Docking studies showed significant binding affinity in the active site of *Mycobacterium tuberculosis* DprE1 enzyme.

1. Introduction

In recent years, click chemistry has been emerged as powerful tool for the synthesis of various biologically active molecules.[1] The concept of "click chemistry" was first coined by Sharpless and coworkers.[2] The copper catalysed azide-alkyne cycloaddition (CuAAC) is the most popular example of click chemistry and widely used for the synthesis of triazoles. In particular, 1,2,3-triazoles are the important class of nitrogen heterocycles in drug discovery which can act as bioisostere and linker. The 1,2,3-triazole based compounds possess wide range of biological activities such as antimicrobial,[3a] antifungal,[3b] anticancer,[3c] antidibetic,[3c] anti-HIV[3d] and antimalarial activity.[3e] There are several drugs in the market that have 1,2,3-triazole moiety such as Cefatrizine and Tazobactam and many more are in the different phases of clinical trials, For instance, Carboxyamidotriazole (CAI) and *tert*-butyldimethylsilylspiroaminooxathioledioxide (TSAO) (Figure 1).[4] The emerging trend in the designing of biocompatible drugs as a new class of antitubercular agents includes triazole linked fatty acid,[5a] nitrofuran based 1,2,3-triazoles,[5b] pyrazole-1,2,3-triazole hybrids,[5c] aryloxy linked coumarinyl triazoles[5d] and triazolyl xanthenones.[5e] Recently, many researchers has been reported the triazole incorporated analogues as antitubercular agent (Figure 2).[6]

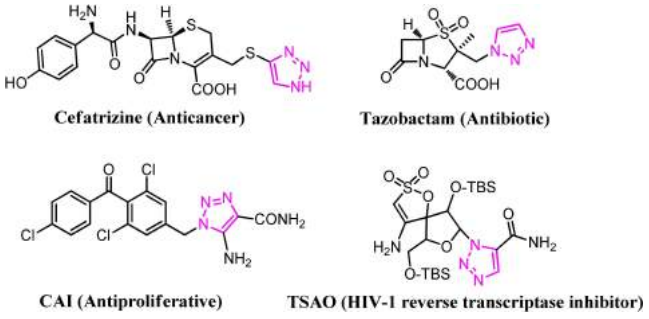

Figure 1. 1,2,3-Triazole based potential drug molecules.

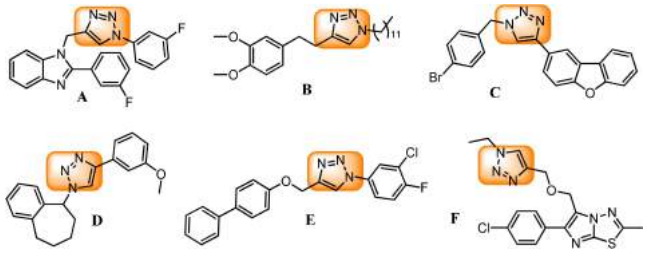

Figure 2. Triazole based antitubercular agents.

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Biological Chemistry & Chemical Biology

Design, Synthesis and Biological Screening of Novel 1,3,4-Oxadiazoles as Antitubercular Agents

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A series of novel 2,5-disubstitued 1,3,4-oxadiazole derivatives bearing 2,2-dimethyl-2,3-dihydrobenzofuran scaffold has been synthesized and screened for antitubercular activity. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C-NMR and Mass spectral study. The in vitro antitubercular activity of the synthesized compounds was evaluated against *Mycobacterium tuberculosis* H_{37}Ra(ATCC 25177) strain. Among the synthesized compounds, four compound displayed good antitubercular activity IC_{50} values in low micro-gram range (< 10 μg/mL). The antitubercular data suggested that growth inhibition MTB can be imparted by the introduction of a 4-trifluoromethyl phenyl acetylene substituent. Specificity of these compounds was checked by screening them for their anti-bacterial activity against four bacterial strains (Gram-negative strains: *E. coli, S. aureus;* Gram-positive strains: *P. aeruginosa and B. subtilis).* None of the compound displayed antibacterial activity against any of the seleted strain. Molecular docking studies were carried out on InhA (FabI/ENR) which shows that the synthesized compounds bind at the catalytic site in a most favourable manner suggesting their potential as anti-mycobacterial agents. The research presented here was found to be adventitious for the development of new therapeutic agents against *Mycobacterium* infection.

1. Introduction

Nowadays, a threat of infectious diseases is a serious problem in developing and most populated countries due to adoption of modified genotype by parasite to develop resistance against drug candidates. The continuing problem of the multidrug resistance (MDR) diseases can cause great damage to society as well as economical slowdown of the countries.[1,2] Moreover, nosocomial infections are caused by resistance of *Acinetobacter baumannii* to drugs like aminoglycoside, cefetime, fluoroquinolone and most of the antibiotics.[3,4] One of this is tuberculosis infection, which continued a measure cause of morbidity and mortality all over the world.[5] The TB-infected person generally develops clinical pulmonary tuberculosis which lead to three million annual death approximately.[6,7] Although, there is extreme rise in the use of enormous therapeutic agents as driving force against tuberculosis, the first line drugs such as isoniazid, streptomycin ethambutol, rifampicin, pyrazilnamid etc. have become insensitive against *Mycobacterium tuberculosis* strain.[8-11] The most of the available anti-tubercular drugs are ineffective to treat mutant strains like MDR,[12-14] XDR,[15,16] and TDR.[17] In addition, the available treatment of tuberculosis requires long term treatment (6-9 months of DOTS strategy), adverse drug reactions and cases of Drug-Drug interactions. It has been found that the multidrug-resistant TB (MDR-TB) and extremely drug-resistant tuberculosis (XDR-TB) does not respond to the standard treatments available. Hence, there is dire need to recognize new chemical entity with appreciable mode of action against *Mycobacterium tuberculosis* infection.

The derivatives of 1,3,4-oxadiazole are known to possesses broad spectrum of bioactivities and good bioisosters of amide and ester functionalities.[18] It displayed interesting H-bond acceptor properties and improved lipophilicity profile as well as favorable ADME properties.[19] The 1,3,4-oxadiazole derivatives such as **A**, **B** are good anti-TB agents (MIC: 0.78 and 0.68 μg/mL),[20,21] Raltegravir (**C**) was used to be antiretroviral drug[22] and zibotentan (**D**) was found to be potent anticancer agent[23] (Figure 1).

Furthermore, 1,3,4-oxadiazole derivatives exhibits diverse biological profile such as anti-HIV,[24] antimalarial,[25] analgesic,[26] anti-inflammatory[27] anticonvulsant,[28a] antitubercular,[28(b-c)] and as lipid per oxidation inhibition properties.[29] Interestingly, the constrained analogue of isopropyl phenyl ether such as 2,2-dimethyl-2,3-dihydrobenzofuran has been found as core of 5-HT3 antagonist zatosetron (**E**)[30] and serotonin 2C agonist (**G**)[31] (Figure 2).

By knowing the biocompatibility of 1,3,4-oxadiazole and 2,2-di-methyl-2,3-dihydrobenzofuran core, herein we have

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Efficient siRNA delivery using osmotically active and biodegradable poly(ester amine)

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Abstract

Biodegradable and hyperbranched poly(ester amine) (PEA) was prepared by reaction of glycerol dimethacrylate (GDM) with low molecular weight polyethylenimine (LMW-PEI) by Michael addition reaction. This novel gene carrier showed excellent physicochemical properties and relatively low cytotoxicity compared with PEI 25K. It showed excellent transfection efficiency and siRNA delivery. The higher silencing efficiency of PEAs could be attributed to the synergistic effect arising from hyperosmotic glycerol and proton sponge active PEI residues in the PEA backbone.

Keywords: Poly (ester amine), hyperosmotic effect, proton sponge effect, siRNA delivery.

Introduction

Enormous research is being performed to better understand the mechanism of RNA interference (RNAi) in mammalian cells, making *in vivo* therapeutic applications of RNAi increasingly likely to emerge soon. However, systemic application of virally delivered siRNA duplexes and related RNAi products are unlikely to be viable in the near future, due to host immune responses upon repeated delivery and ineffective tumor targeting. Various groups reported non-viral systemic delivery approaches by high-volume tail vein injection or high pressure-injection of nucleic acids. However, these methods lacked the suitability and showed unacceptability in routine clinical applications in humans [1-3]. Numerous systemic administrations of siRNA to mice have been reported using naked siRNA[4, 5], plasmids expressing short hairpin RNA[6, 7] lipid- formulated siRNA [8] or polycation formulated siRNA [9-11]. There are several reports describing the *in vivo* success with the siRNA by direct delivery of naked siRNA. However, naked siRNA requires chemical stabilization for *in vivo* use [4, 12]. Like single stranded antisense agents, naked siRNAs have also non-specific biodistribution [13] which requires larger doses and repeated doses for efficacy [4]. Thus the principal challenge that remains in achieving the broadest application of RNAi therapeutics is the hurdle of delivery.

Among the several approaches for delivery of RNAi therapeutics, lipids and polymer-based nanoparticle approaches are the most widely used for the systemic delivery of siRNA *in vivo*. Although the complexity of these strategies is a key developmental challenge, they represent a promising potential approach for the development of RNAi therapeutics. With the current formulation and delivery approaches for siRNA, polymeric carriers have immense capability and therapeutic potential. Despite much recent progress, new chemistry and delivery approaches are greatly needed to systemically silence disease-causing genes in a tissue specific manner with high efficiencies and at clinically achievable [14]. To date, various cationic polymers showed their potential as a successful gene carrier owing to their versatility in chemical structure. Dynamic polyconjugates[15], cyclodextrin-based nanoparticles [16], atelocollagen (protease treated collagen) [17], chitosan [18, 19] as the various polymeric approaches have been investigated broadly as siRNA carrier because they can successfully self-assemble and condense with siRNA into the structures small enough to enter the cells through endocytosis. PEI also showed remarkable success in delivering siRNA, however, its cytotoxicity owing to its non-degradability hindered its use and gave the birth of development of biodegradable polymers [11, 20-25].

Poly(ester amine)s (PEAs) synthesized by Michael addition reaction via conjugate addition of amines to acrylate resulted in biodegradable esters [26]. The biodegradable PEAs easily undergo hydrolysis of their ester backbone leading to formation of low molecular weight bis(β-amino acids) and diol moieties which are less toxic than their parent polymers [27]. Our group has developed several biodegradable gene carriers based on LMW PEI with poly(ethylene glycol) (PEG) [28], polycaprolactone [29], poloxamer [30], glycerol dimethacrylate (GDM) [31]. All these PEAs successfully transfected pDNA and showed excellent gene expression than PEI *in vitro* and *in vivo*. We therefore, investigated siRNA delivery ability of some

molecules

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New 2-Oxoindolin Phosphonates as Novel Agents to Treat Cancer: A Green Synthesis and Molecular Modeling

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Abstract: The work reports the facile synthesis of novel α-aminophosphonate derivatives coupled with indole-2,3-dione moieties, namely the diethyl(substituted phenyl/heteroaryl) (2-(2-oxoindolin-3-ylidene)hydrazinyl)methylphosphonates derivatives **4**(**a**–**n**). One-pot three component Kabachnik-Fields reactions were used to synthesize these derivatives. The reaction was carried out at room temperature by stirring in presence of ceric ammonium nitrate (CAN) as a green catalyst. The structures of the synthesized compounds were established by spectral studies. The synthesized derivatives **4**(**a**–**n**) were evaluated for their in vitro anticancer activity against six human cancer cell lines by the SRB assay method. The cancer cell lines used in this research work are SK-MEL-2 (melanoma), MCF-7 (breast cancer), IMR-32 (neuroblastoma) MG-63 (human osteosarcoma), HT-29 (human colon cancer) and Hep-G2 (human hepatoma). All the synthesized derivatives inhibited the cell proliferation. Importantly, all the target compounds showed no cytotoxicity towards normal tissue cells (GI_{50} > 250 μM). A docking study was performed to predict the mode of action. Docking results indicate that the compounds have good binding with the enzyme tyrosine kinase as well as with microtubules, which makes them dual inhibitors. The result of in-silico bioavailability studies suggests that the compounds from the present series have good oral drug-like properties and are non-toxic in nature. In vivo acute oral toxicity study results indicate that the compounds can be considered safe, and therefore could be developed in the future as good anticancer agents or as leads for the design and synthesis of novel anticancer agents.

Keywords: indole-2,3-dione; α-aminophosphonates; in-vitro anticancer activity; ceric ammonium nitrate; docking

1. Introduction

The number of patients dying across the globe because of cancer and the non-availability of effective, non-toxic anticancer drugs in the present drug market continues to increase. Consequently, preventing this fatal disease is more challenging and hence the invention of novel anticancer agents is of paramount significance.

During carcinogenesis, an angiogenic switch occurs and several angiogenic growth factors stimulate their receptor tyrosine kinases (RTKs) to initiate multiple pro-angiogenic events [1].

molecules

MDPI

Article

Ultrasound Assisted Synthesis of 4-(Benzyloxy)-*N*-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl) Benzamide as Challenging Anti-Tubercular Scaffold

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Abstract: A series of ten novel derivatives of 4-(benzyloxy)-*N*-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) benzamide **6a–j** were synthesized in good yield from the key compound 4-(benzyloxy)-*N*′-(substituted benzylidene) benzo hydrazide, called Schiff 's bases **5a–j**, by Staudinger reaction ([2 + 2] ketene-imine cycloaddition reaction) with chloro acetyl chloride in the presence of catalyst tri ethylamine and solvent dimethyl formamide (DMF), by using ultra-sonication as one of the green chemistry tools. All the synthesised compounds were evaluated for *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* (MTB) and most of them showed promising activity with an IC_{50} value of less than 1 μg/mL. To establish the safety, all the synthesized compounds were further tested for cytotoxicity against the human cancer cell line HeLa and all **6a–j** compounds were found to be non-cytotoxic in nature. The molecular docking study was carried out with essential enzyme InhA (FabI/ENR) of *Mycobacterium* responsible for cell wall synthesis which suggests that **6a** and **6e** are the most active derivatives of the series. The theoretical evaluation of cell permeability based on Lipinski's rule of five has helped to rationalize the biological results and hence the synthesized azetidinone derivatives **6a–j** were also analyzed for physicochemical evaluation that is, absorption, distribution, metabolism, excretion, and toxicity (*ADMET*) properties and the results showed that all the derivatives could comply with essential features required for a potential lead in the anti-tubercular drug discovery process.

Keywords: green chemistry; ultra-sonication; azetidinone; anti-tubercular screening; cytotoxicity study; molecular docking; ADMET study

1. Introduction

Tuberculosis (TB) is one of the life threating disease caused by *Mycobacterium tuberculosis* (*MTB*), which has shown advanced mechanisms to evade host defense. Decades after the discovery of *MTB*, TB remains a major cause of morbidity and mortality in many developing countries. The

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A rapid and green method for expedient multicomponent synthesis of N-substituted decahydroacridine-1,8-diones as potential antimicrobial agents

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Abstract

An efficient, green, high yielding, and quick method for the synthesis of N-substituted decahydroacridine-1,8-diones was achieved by multicomponent reaction between various aromatic aldehydes (**1a–q**), dimedone (**2**), and various aromatic amines (**2a–d**) using ChCl:Urea deep eutectic solvent as a recyclable organocatalyst and medium. The reaction conditions are relatively mild and do not require additional metals, acid catalysts, or organic solvents. The mild reaction conditions, experimental simplicity, straightforward purification procedures, excellent yields with short reaction times, as well as the application of green chemistry principles, are the advantages of this methodology. This simple ammonium deep eutectic solvent, easily synthesized from choline chloride and urea, is relatively inexpensive and biodegradable, making it applicable for industrial use. The deep eutectic solvent was easily separated and reused without loss of activity, and thus provides a good alternative. The synthesized 10-(substituted phenyl)-9-(substitutedphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-diones (**4a–l**) were screened for their in vitro antimicrobial activity against four bacterial Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and three fungal strains (*Candida albicans*, *Aspergillus niger and Aspergillus flavus*). Among them, the 9-(*N*,*N*-Dimethylphenyl)-3,3,6,6-tetramethyl-10-(3-pyridyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4f**), 10-(4-Bromophenyl)-9-(3-hydroxy-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4i**) and 9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**4k**) show good antimicrobial activity.

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Targeted Delivery of siRNA Therapeutics using Ligand Mediated Biodegradable Polymeric Nanocarriers

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Abstract | References | Citations | Supplementary Data

Background: Cancer poses a major public health issue, is linked with high mortality rates across the world, and shows a strong interplay between genetic and environmental factors. To date, common therapeutics, including chemotherapy, immunotherapy, and radiotherapy, have made significant contributions to cancer treatment, although diverse obstacles for achieving the permanent “magic bullet” cure have remained. Recently, various anticancer therapeutic agents designed to overcome the limitations of these conventional cancer treatments have received considerable attention. One of these promising and novel agents is the siRNA delivery system; however, poor cellular uptake and altered siRNA stability in physiological environments have limited its use in clinical trials. Therefore, developing the ideal siRNA delivery system with low cytotoxicity, improved siRNA stability in the body's circulation, and prevention of its rapid clearance from bodily fluids, is rapidly emerging as an innovative therapeutic strategy to combat cancer. Moreover, active targeting using ligand moieties which bind to over-expressed receptors on the surface of cancer cells would enhance the therapeutic efficiency of siRNA.

Conclusion: In this review, we provide 1) an overview of the non-viral carrier associated with siRNA delivery for cancer treatment, and 2) a description of the five major cancer-targeting ligands.

Keywords: RNA interference (RNAi); cancer therapy; chemotherapy; immunotherapy; ligand; nanocarrier

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Chemistry SELECT Full Papers

Medicinal Chemistry & Drug Discovery

Synthesis of Novel α-Aminophosphonate Derivatives, Biological Evaluation as Potent Antiproliferative Agents and Molecular Docking

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A series of novel fluorine containing α-aminophosphonate derivatives (**4a–4q**) were synthesized in excellent yield and high purity. All these novel Fluorinated α-aminophosphonate compounds were screened for antiproliferative and apoptosis activity on human non small cell lung carcinoma cells (A549) and human skin melanoma cells (SK-MEL-2). Compounds **4a**, **4b**, **4c**, **4f**, **4i**, **4j** and **4m** were found to be more active antiproliferative agent against A549 and SK-MEL-2 cells with IC_{50} value 0.22 to 1.25 μM. Molecular docking study related to binding affinity and binding mode analysis showed that synthesized compounds had potential to inhibit human Topoisomerase IIa enzyme system. Flow cytometric study showed some of these derivatives also induced cell apoptosis and arrest cell cycle at G1 and at G_2/M phase. Overall, this study provides future perspective of lead candidate for the future anticancer drug discovery initiatives.

Introduction

Cancer is second leading cause of mortality worldwide,[1] in last two decades this disease has been the main cause of the death. WHO reports approximately 14 million new cancer cases were found, among which 8.8 million cancer patients died and 32.6 million people are affected from disease in 2012. The number is expected to rise up to 14 million to 22 million in the year 2030.[2,3] Aminophosphonates, known as phosphorus analogues of amino acids, have received much more attention due to diverse applications in medicine. They play a vital role in antibody generation.[4] Recently, α-amino phosphonates are proved to posses potent biological activities, such as selective inhibitors of tyrosine kinase,[5] cytotoxic to cancer cells,[6,7,8] antibacterial,[9] antifungal,[10] antitumor and antiproliferative agents,[11–14] enzyme inhibitors,[15,16] antiviral,[17] and plant growth regulators.[18]

Fluorinated α-amino acids and their derivatives such as α-(fluoromethyl)-substituted α-amino acids have employed as selective inhibitor of pyridoxal phosphate dependent enzymes. The probe of fluorine containing aromatic and aliphatic compounds exhibit a significant medicinal value in pharmaceutical industries.[19–21] An incorporation of -CF_3 group at α-position of a cyclic α-amino acid enhances the biological properties of peptides.[22] Due to wide medicinal applications of fluorinated α-aminophosphonates compounds they show significant biological activity and two major review focus on fluorinated α-aminophosphonates compound.[23,24] Several methods are reported for the synthesis of α-aminophosphonates. More commonly used methods include hydrophosphonylation of pregenerated imines or *in situ* generated imines by nucleophilic addition to phosphonate ester in various catalysis such as $InCl_3$,[25] $TaCl_5{\cdot}SiO_2$,[26] $Mg(ClO_4)_2$,[27] $LiClO_4$,[28a–d] $AlCl_3$,[29] lanthanide triflates,[30] montmorillonite clay-MW,[31] CF_3COOH,[32] sulfamic acid,[33] $BF_3{\cdot}Et_2O$,[34] $ZrOCl_2$,[35] TiO_2,[36] $LaCl_3$,[37] ethyl ammonium nitrate,[38] and $Cd(ClO_4)$.[39] Recently, reported used solvate ionic liquids $[G_4(Li)]TFSI$.[40] To overcome the problems of longer reaction time, use of toxic metal catalysts and tedious workup, a new method has been developed for the synthesis of α-aminophosphonates.

Herein, report an efficient method for the synthesis of novel bis-CF_3-containing α-aminophosphonates using lanthanum chloride as a catalyst *via* solvent free condensation of substituted aromatics aldehyde, amine and diethyl phosphite (Scheme-1). Furthermore, these α-aminophosphonate derivatives were screened for antiproliferative activity on human cancer cell lines (SK-MEL-2 and A549 cells).

These compounds were found active against Human non small cell lung carcinoma cells (A549 cell) and Human skin melanoma cells (SK-MEL-2). Apoptotic activity of these compounds was evaluated by early apoptotic markers in compound

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Synthesis and biological evaluation of novel triazole-biscoumarin conjugates as potential antitubercular and anti-oxidant agents

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Abstract The synthesis of a new series of triazole-biscoumarin conjugates by using a molecular hybridization approach is described. The newly synthesized compounds **6a–k** were evaluated for their in vitro antitubercular activity against active and dormant *Mtb* H37Ra and anti-oxidant activity against DPPH radical scavenging. Molecular docking simulations for the antitubercular activity showed that the conjugates **6a–k** bind in the pocket of the DprE1 enzyme. Most of the conjugates displayed good antitubercular activity against both the active and dormant *Mtb* H37Ra strain. The compound **6h** displayed very good antitubercular activity against dormant *Mtb* H37Ra with an IC_{50} value of 1.44 μg/mL. Most of the synthesized conjugates exhibit excellent anti-oxidant activity with an IC_{50} of less than the standard BHT. Compound **6b** is the most active among all the conjugates with an IC_{50} value of 08.17 ± 0.11 μg/mL. The molecular docking study shows good agreement between the observed antitubercular activity and the binding affinity.

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Facile one-pot synthesis, antibacterial activity and *in silico* ADME prediction of 1-substituted-1*H*-1,2,3,4-tetrazoles

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ABSTRACT

Facile one-pot synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles **7(a-l)** were presented from various aromatic amines, triethyl orthoformate and sodium azide using silver oxide as reusable catalyst and screened for their *in vitro* antibacterial activity. Compounds **7c** (MIC range= 80.30- 184.50 µg/mL) and **7i** (MIC range= 94.60- 179.40 µg/mL) were shown potent antibacterial activity when compared with standard ampicillin (MIC range= 100.00- 250.00 µg/mL). *In silico* ADME parameters were predicted and suggest the potential of **7(a-l)** to develop oral drug like candidate.

Keywords: Tetrazoles; Silver oxide; Antibacterial activity; *In silico* studies

Ultrasound Promoted Green Synthesis, Docking Study of Indole Spliced Thiadiazole, α-amino Phosphonates as Anticancer Agents and Anti-tyrosinase Agents

Authors: Nikalje, Annapratima G.; Gawhane, Pramod A.; Tiwari, Shailee V.; Sangshetti, Jaiprakash N.; Damale, Manoj G.
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Background: Regardless of recent advances in the development of clinically authorized anticancer agents the number of deaths due to cancer is increasing day by day all over the world. The aim of this research work is to synthesis novel anticancer agents.

Method: In this work, a new series of diethyl ((1H-indole-3-yl)((5-phenyl-1,3,4-thiadiazole-2-yl)amino) methyl)phosphonate derivatives 6(a-j) were designed and synthesized in Ultrasound by green protocol using Kabachnik-Fields reaction. The structures of the synthesized compounds were confirmed by spectral analysis such as elemental analyses, IR, 1H NMR, 13C NMR, 31P NMR and mass spectra. The synthesized compounds 6(a-j) were appraised for their in vitro anticancer activity against human cancer cell lines such as SK-MEL-2 (melanoma), IMR-32 (Neuroblastoma), HT-29(Colon) and also on normal murine embryonic fibroblast NIH/3T3 by Sulforhodamine B (SRB) assay, using Adriamycin as a standard drug.

Result: The treatment of SK-MEL-2 cancer cells with 6i showed apoptosis and morphological changes like cell shrinkage, cell wall deformation and reduced number of viable cells. The synthesized derivatives were also evaluated for their anti-tyrosinase effect. Nearly all the tested derivatives have been found to be potent tyrosinase inhibitors.

Conclusion: Nearly all the compounds were tested, the docking study was performed and indicates that the compounds have good binding interactions with tyrosine kinase enzyme. Absorption, Distribution, Metabolism and Elimination (ADME) properties of the synthesized compounds were also analyzed which manifested their potentiality to thrive as good oral drug candidates.

Keywords: ADME prediction; Indole; Kabachnik-Fields reaction; docking; in-vitro anticancer activity; thiadiazole

Document Type: Research Article

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Benzene sulfonamide pyrazole thio-oxadiazole hybrid as potential antimicrobial and antitubercular agents

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Abstract To fulfil the development goals towards the synthesis of innovative, potent and highly effective antimicrobial and antimycobacterial agents, a set of benzene sulfonamide pyrazole thio-oxadiazole derivatives **(6a–6l)** have been synthesized by the reaction of 4-[5-(3-fluoro-4-methoxyphenyl)-3-(5-mercapto-1,3,4-oxadiazol-2-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide with alkyl/aryl halides, identified by IR, NMR (^{1}H, ^{13}C, ^{19}F) and MS data. Composed compounds were examined for their antimicrobial and antitubercular activity. Antibacterial activity of compounds **6c**, **6d**, **6j** and **6l** was found promising against *E. coli, P. Aeruginosa, S. Aureus* and *S. Pyogenes* as compared to standard ampicillin. Compounds **6d, 6e, 6g, 6h** and **6i** were found active against tubercular strain H37Rv. Molecular docking studies against *mycobacterium tuberculosis* β-ketoacyl-acyl carrier protein synthase A (Kas-A) was carried out which suggests a possible mode of inhibition for this target protein and the potential of synthesized compounds as antitubercular agents.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-018-3396-y) contains supplementary material, which is available to authorized users.

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ORIGINAL ARTICLE

Structural insights of dipeptidyl peptidase-IV inhibitors through molecular dynamics-guided receptor-dependent 4D-QSAR studies

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Abstract

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are promising antidiabetic agents. Currently, several DPP-IV inhibitors have been approved for therapeutic use in diabetes mellitus. Receptor-dependent 4D-QSAR is comparatively a new approach which uses molecular dynamics simulations to generate conformational ensemble profiles of compounds representing a dynamic state of compounds at a target's binding site. This work describes a receptor-dependent 4D-QSAR study on triazolopiperazine derivatives. QSARINS multiple linear regression method was adopted to generate 4D-QSAR models. A model with 9 variables was found to have better predictive accuracy with $R^2 = 0.692$, Q^2 (leave-one-out) = 0.592 and R^2 predicted = 0.597. The location of these 9 variables at the binding site of DPP-IV revealed the importance of the residues Val711, Tyr662, Tyr666, Val202, Asp200 and Thr199 in making critical interactions with DPP-IV inhibitors. The study of these critical interactions revealed the structural features required in DPP-IV inhibitors. Thus, in this study the importance of a halogen substituent on a phenyl ring, the extent of substitution on the triazolopiperazine ring, the presence of an ionizable amino group and the presence of a hydrophobic substituent that can bind deeper in binding pocket of DPP-IV were revealed.

Keywords Diabetes · DPP-IV · 4D QSAR · Molecular dynamics · Sitagliptin

Introduction

Type-2 diabetes mellitus is a disorder manifested due to the progressive decline in insulin activity usually followed by pancreatic β-cell dysfunction resulting in lower level of insulin. In the biosynthesis of insulin, incretin hormones like glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) play a major role in stimulation of insulin biosynthesis, insulin secretion, and glucose-dependent inhibition of glucagon release [1,2].

Dipeptidyl peptidase-IV (DPP-IV) is a transmembrane glycoprotein, with serine protease activity that cleaves X-proline dipeptides from the N-terminus of GLP-1 and GIP [3,4]. Inhibition of DPP-IV leads to increased levels of physiologically active GLP-1, which in turn contributes to normalizing elevated glucose levels [5]. Sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin and teneligliptin are approved DPP-IV inhibitors for clinical use in the management of type-2 diabetes [6,7].

Rational drug design, a process to find more active molecules or lead compounds, mostly relies on the information of how ligands bind at the binding site of their target enzyme and which residues participate in binding [8]. Typically, the binding site is established by including residues that are within 5 Å distance from a ligand's heavy atoms (non-hydrogen atoms). The binding pocket of the Cdk5-p25 complex (cyclin-dependent kinase-5 with its activator p25) where ATP binds was defined by such criteria [9] and later used in identifying the functional domains or binding pockets of target proteins [10–13]. A triazolopiperazine derivative, sitagliptin, was approved worldwide as first-in-class DPP-

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Ultrasound-mediated synthesis, biological evaluation, docking and in vivo acute oral toxicity study of novel indolin-2-one coupled pyrimidine derivatives

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Abstract The work reports ultrasound-mediated greener synthesis of 11 novel 3-(4-(4-chlorophenyl)-6-(substituted phenyl/heteryl)pyrimidin-2-ylimino)indolin-2-one (**7a**–**7k**) derivatives. The synthesized derivatives were evaluated for their in vitro anticancer activity against a panel of selected human cancer cell lines of breast (MCF-7), cervix (HeLa), prostate (PC-3) and lung (A-549). Among the tested compounds, **7b** exhibited most promising in vitro anticancer activity against HeLa, PC-3 and A-549 with GI_{50} value 15.38, 19.67 and 4.37 μM, respectively. The compounds (**7a**–**7k**) were also screened for induction of apoptosis and morphological changes in cancer cells at their GI_{50} concentration. The treatment of HeLa, PC-3 and A549 cancer cells with **7b** and treatment of MCF-7 cancer cells with **7h** showed apoptosis and morphological changes such as cell shrinkage, cell wall deformation and reduced number of viable cells. The compound **7b** has shown almost 5.00 times more selectivity for PC-3 cancer cell lines in comparison to the RWPE-1 normal prostate epithelial cells. Molecular docking study has been carried out, which replicates results of biological activity in cases of initial hits **7b**, **7c** and **7d,** suggesting that these compounds have a potential to become lead molecules in the drug discovery process. In silico ADMET study was performed for predicting pharmacokinetic properties and toxicity profile of the synthesized compounds and expressed good oral drug-like behaviour. An in vivo acute oral toxicity study was performed using Swiss albino mice for the most active compounds **7b** and **7c**, and results indicate that the compounds are non-toxic in nature.

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β-Cyclodextrin catalyzed one-pot four component auspicious protocol for synthesis of spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-trione as a potential antimicrobial agent

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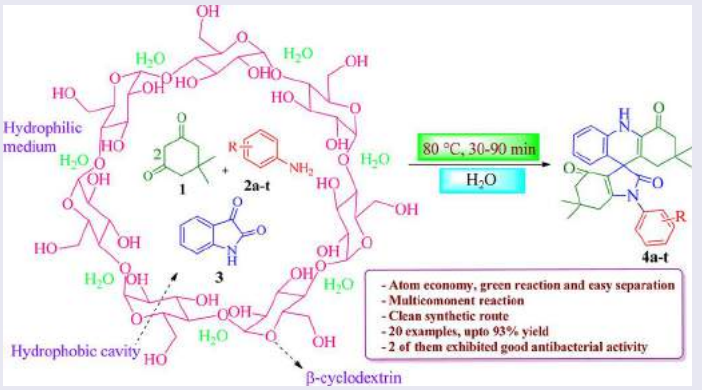
ABSTRACT

We have developed an perceptive and facile approach for the synthesis of new spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-trione derivatives (**4a–t**) by one-pot four component condensation involving two equivalence of dimedone (**1**), substituted anilines (**2a–t**), and isatin (**3**) catalyzed by β-cyclodextrin in water within short reaction time at 80 °C in good to excellent yields. We believe that this novel procedure may open the door for the easy generation of new and bioactive spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-triones. The most exciting feature of this methodology is its mechanism involving the unusual ring opening of an isatin moiety followed by recyclization. Synthesized compounds were evaluated for their antimicrobial activities against four bacteria and three fungi. All the spirooxindole derivatives exhibited significant antibacterial activity against bacteria and fungi. Among 20 compounds screened, compound (**4i**) and (**4h**) was found to be more active against tested bacterial strain.

GRAPHICAL ABSTRACT



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Antimicrobial activity; β-cyclodextrin; multicomponent reaction; spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,10H)-trione; supramolecular catalyst

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data (Spectroscopic characterizations of the compounds) can be accessed on the publisher's website.

Review Article

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A Review: Zam Zam a miracle water

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Zam Zam water,
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Abstract

This article reviews the inorganic configuration and possible health benefits of Zam Zam water. Zam Zam water is dissimilar from natural water in relationships of inorganic and radiological features. The miracle of Zam Zam is non-stop flow ever since 2000 BC. The presence of the Zam Zam well directed to the foundation of the settlement of the Makah valley. Zam Zam water reduces the thirstiness and shows potential to treat numerous diseases. Different studies have been led to discover the legendary potentials of this water; so there is a need to conduct wide spread research and to explore its healthcare welfares, inorganic profile, and technical viewpoints.

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INTRODUCTION

Zam Zam water is to be found inside the Holy Mosque at around 20 meters east of the Ka'ba in Makkah Al-Mukarramah, Saudi Arabia. The well of Zam zam is hand-excavated and is around 30.5 m deep, with an inner diameter ranging from 1.08 to 2.66 meters. Zam Zam water is dissimilar from other water in many means: major no bacteria can form at its source. Another it doesn't go mouldy nor does it alter color, taste or smell [1]. Natural growth and vegetation typically take place in most wells. This makes water indigestible owing to the growth of algae foremost to changes in taste and odor. But, in Zam Zam water well, there isn't any sign of biological growth [2]. The Chemical examination of Zam Zam water covers some inorganic components such as sodium (Na), calcium (Ca), magnesium (Mg), potassium (K), bicarbonate (HCO3), chloride (Cl), fluoride (Fl), nitrate (3– NO), sulfate (SO4), and totally dissolved salts (TDS) [3].

According to Arab historians, the Zam Zam Well has been in use for about 4000 years. The well symbols the site of a spring where Allah, in His mercy, sent the Angel Gabriel, who scraped the ground, causing the spring to appear. That was while Hajar Prophet Abraham's wife, and their infant son Ismail (PBUH) had left in her desperate look at for water, who was dying of thirsting. On discovery the spring, and fearing that it Might run out of water, Hajar enclosed it in sand and stones. The name Zam Zam creates from the phrase Zomë Zomë, meaning 'stop flowing' [4].

In 1971, the Ministry of Agriculture and Water Resources sent samples of Aabe- Zam Zam for examinations to the European laboratories to test the portability of the water. The results of the water samples verified by the European laboratories presented that Zam Zam water has a superior build that makes it beneficial water. The main change between Zam Zam water and other water was in the amount of calcium and magnesium salts, the content of these was somewhat higher in Zam Zam water, but more meaningfully, the water contains fluorides that have an in effect germicidal action. Furthermore, the comments of the European laboratories showed that the water was fit for consumption [5].

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Review article

A review on treatment of Human Immunodeficiency Virus (HIV) by Naturopathy

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Keywords: HIV, AIDS, Immuno-suppression Syndrome.

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Abstract

Acquired immunodeficiency syndrome is a clinical syndrome that is the result of infection with human immune deficiency virus which causes profound immunosuppression. Current therapies are available for symptomatic treatment of AIDS is quite expensive. Herbal medicines can be developed as a safe, effective and economical alternative. Herbal medications provide sensible means for the treatment of AIDS. The herbal medicines which are used for the treatment of AIDS are kalmegh, asparagus, Indian gooseberry, Ashoka, etc. Many compounds of plants origin inhibit HIV during the various stage of the HIV life cycle, these include several alkaloids carbohydrates, coumarin, lignin, and proteins. These candidates have the potential to come up as the drug for treatment for HIV infection. So, the purpose of this article is to identify herbs and there active constituents having activity against human immune-deficiency virus with an objective of providing an effective method for preventing the transmission and the treatment of this disease.

Introduction

Acquired immune-deficiency syndrome (AIDS) is a scientific condition that is the result of infection with human immunodeficiency virus (HIV), which causes superficial immune clamp down. It is a serious, life aggressive health problem since the first case was recognized in 1981 and is the most quickly increasing disease of the era. Since the widespread began, more than 60 million people have been infected with the virus and HIV/AIDS is now leading to the death. According to the recent report of WHO and "UNAIDS" at the end of 2004, a predictable 40 million people (37.2 million adults and 2.2 million children) were living with HIV worldwide out of which about 22 million had died [1]. The most pretentious is sub-Saharan Africa, where 3.1 million expired in 2004. By the end of 2004, the total figure of people living with HIV/AIDS in the region has reached 25.4 million. Further 540000 people are predictable to have died of AIDS in 2004. The range of HIV in India has been miscellaneous, with much of India having a low rate of infection and the widespread being most extreme in the southern states. The disease usually occurs in stages from a latent stage with initial symptoms such by means of temperature, wooziness, paleness, also joint pain, rashes and widespread lymphadenopathy tailed by way of the asymptomatic latency period. In the middle stage symptoms such as fever, weight loss, night sweats, diarrhea, thrust, skin lesion and depression are common. Herbal drugs offer balanced means for the action of many illnesses. In Europe, herbal treatment has been considered as the most popular complementary medicine used by HIV infected individuals [2]. HIV goes to a distinct class of viruses called retrovirus. The normal Human immunodeficiency virus (HIV), the virus actual responsible for AIDS, is around 0.000031 inches (120Å) long and has an RNA core. The ribonucleotide particle is encapsulated by a capsid made up of a capsid protein (CA), p24. The capsid environment also contains other viral proteins such as intergrase and reverse transcriptase. It also covers a wide variety of additional macromolecules derived from the cell including tRNAlys3, which serves as a primer for reverse transcription [3]. The major HIV protein associated with envelope is gp120/41, these functions as the viral attachment proteins.

Types of HIV

Two major types of HIV have been identified as follows [4]:
HIV-1: It is the basis of the international wide spread and is most usually mentioned to as HIV. It is an extremely adaptable virus, which transforms readily. There are many dissimilar straining of HIV-1, which can be categorized according to groups and subtypes; M and O.

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ANTIDIARRHEAL ACTIVITY OF AQUEOUS EXTRACT OF LEAVES OF FIMBRISTYLIS BISUMBELLATA

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ABSTRACT

Fimbristylis bisumbellata is a plant belonging to the family Cyperaceae. Antidiarrheal effect of aqueous leaves extract of Fimbristylis bisumbellata was evaluated in female wistar rats. A preliminary phytochemical screening of aqueous extract of leaves of Fimbristylis bisumbellata gave positive tests for tannins. Studies were carried out on in-vivo gastrointestinal motility, on castor oil induced diarrhea in rats. 200mg/kg and 400mg/kg doses were used against castor oil induced diarrhea in rats against loperamide as a standard. The extract showed decrease in number of stools within 12 hours and increase in diarrhea free period. Results obtained showed that the aqueous extract of leaves has significant Antidiarrheal activity. Present research aspects is an honest presentation of the determination of activities possessed by chemical constituents in the leaves of plant Fimbristylis bisumbellata. Significantly it shows Antidiarrheal against experimentally induced Castor oil diarrhea.

KEYWORDS: Fimbristylis bisumbellata.

INTRODUCTION

Diarrhea is defined as the passage of three or more abnormally loose or watery stools per 24 hours. However, recent change in consistency and character of the stools is more important rather than the number of stools. During the initial 2–3 months of life, infants, particularly those who are being breastfed, may normally pass as many as 8–10 semi-formed stools daily that do not constitute diarrhea. Again, a recent change in character of stools should be given

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MICROWAVE ASSISTED EXTRACTION OF TANNINS FROM HARDA

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ABSTRACT

The study was aimed to investigate the use of microwave assisted extraction (MAE) to improve the extraction efficiency of the Polyphones from crude drugs. Classical solvent extraction techniques have several limitation especially low yield and time consumption; hence the present study was designed to provide an effective alternative method of extraction which can be adopted at industrial level. In this study poly-phenol were extracted from Harda (*Terminalia chebula*) using Soxhlet and microwave apparatus, and effectiveness of the both process was evaluated by determining tannin concentration. The method selected for tannin estimation was Folien-ciocalteu method. Result of the study clearly demonstrated that microwave is better method. Study had also undertaken the task of optimization of parameters such as solvent type, microwave power, extraction time and temperature. Results had revealed that the best possible combination parameter for fast and highest extraction by this method was found to be 2 Power of microwave, 50ºC temperature, 4 min. time and alcohol as solvent.

KEYWORDS: Microwave, Soxhlet extraction, Phenolic compound, Extraction time, optimized method.

INTRODUCTION

Medicinal plants and its extracts are gaining much interest recently because their use in ethno medicine treating common disease; and tannins is one of them. Development of extracts is the major hurdle as conventional methods are having many limitations such as low yield, time consumption, excessive use of solvents, and many more[1]. Hence there is need to implement new methods of extraction for herbals to get better yield, low usage of solvent and reduction of time. The present investigation is an attempt to implement microwave extraction protocol for extraction of tannins from Harda (*Terminalia chebula* of family Combretaceae).

Microwave-assisted extraction (MAE) or simply microwave extraction is relatively recent extraction technique started in 1980. It combines microwave and traditional solvent extraction and selectively used to extract target compounds from various raw materials.[2] The method uses microwave, a high frequency radio waves (radiofrequency fields) are used primarily for TV

Research Article

Asian Journal of Biochemical and Pharmaceutical Research

Development and Evaluation of Process Analytical Technology (PAT) Tool For Functional Coating Weight Gain Determination By Pellet Characteristics Measurement

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Abstract: The present study is directed towards development of non-destructive Process Analytical Technology (PAT) enabled weight gain determination of functional coated pellets manufactured by Wurster coating. Currently, the traditional method of weight build up is being used wherein the complete batch is unloaded from the Wurster equipment and weighed. But this method is not accurate and do not produce exact weight gain results due to some of the reasons such as high static charges build up during unloading of pellets that make pellets to stick to wurster machine internally and hence lost during weighing, during dry loading of coating material when it is in powder form, some of it may not get loaded on the pellets and this (dry form of coating material) may get weighed during weighing of pellets (providing false weight gain results), if during initial loading small pellets are lost from the bag, then there are chances of excess weight build up because the initial input material weight has changed, etc; and if drug loaded pellets are fragile then there are chances of the drug eroding out in powder form from the pellets and drug may get coated with coating material and weighing of complete batch cannot give the exact weight gain obtained on the pellets.

Therefore, there is a need to develop PAT tools for weight gain estimation. In this work, we have successfully developed quantification techniques using DATA Count JR-PH and Gel Permeation Chromatography (Ethyl cellulose content estimation) for determining exact weight build up on drug layered pellets.

INTRODUCTION:

Wurster Coating: In 1959, the Wurster process was invented by Dr. Dale Wurster at University of Wisconsin. Since its invention all major companies are venturing into pellets coating in wurster. The process can be done with same ease for both aqueous and non-aqueous applications [1]. The Wurster process provides a high quality reproducible films and highly organised particle flow. The process parameters in the Fluid Beds are precisely controllable, which ensures easier optimization and reproducibility of the product quality [2]. This process is particularly suitable for a controlled release extended release formulation.

However, there are challenges associated with weight gain estimation in pellets system. The performance of the final modified release dosage form is greatly influenced by uniformity, thickness and morphology of the coating. For instance, if the coating is thinner than required, it will not control the release of drug for an anticipated predetermined duration which is required for sustained release. On the other hand if the coating is

Shelf Life Assessment of Drug Product after opening Container for the first time

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***ABSTRACT*: The continued integrity of products in multi-dose containers after the first opening is an important quality issue. The purpose of in-use stability testing is to establish a period of time during which the product in multi-dose container can be used retaining quality within an accepted specification once the container is opened.**

KEYWORDS*: *Multi-dose, container, quality in-use, stability, testing

PREFACE:

The authors of this paper suggest that any approach used to demonstrate in-use stability of medicinal products be science and risk based and that many approaches could be used with justification. A framework for the use of multiple approaches is provided in the following paper, which is intended to shade some light on how in use stability can be performed. This paper provides an approach to address the void created due to absence of regulatory guideline. The authors do not advocate that the following approaches given in this paper be the only way that in-use stability should be assessed. To the contrary, the publication of other approaches that can be used within the framework of this paper is welcomed and encouraged, and it is expected that regulators will consider all science- and risk-based approaches when setting guidance for industry. These other approaches may include various method to assess in-use stability, with justification.

INTRODUCTION:

The continued integrity of products in multidose containers after the first opening is an important quality issue. While this principle is acknowledged in various Guidelines, no specific guidance is available on defining test design and conduct of studies to be undertaken to define in-use shelf life in a uniform fashion. Therefore, this article attempts to define a framework for selection of batches, test design, test storage conditions, test parameters, test procedures etc., taking into consideration the broad range of products concerned. Stability of products is the length of time that they retain their properties and functionality while stored or handled as defined by the manufacture's specifications. During their life span products may change as they age but they are considered to be stable as long as their characteristics remain with the specifications. The change of the performance as products age is called degradation and is usually defined in terms of loss of activity or/and decrease of performance. Stability encompasses several stages of product life; i.e., time and events during transportation of products from manufacturer to the end user, the length of time that products are stored at recommended conditions without being used, time and events while products are being used. The last stage is referred to as in-use stability. The above stages may not be all inclusive and all products may not go through all of them. There are products that are designed for a single use while others are stored in containers that can be used for a period of time after it is opened.

The absence of a detailed and authoritative guideline for the human pharmaceutical sector does not assist in the design and conduct of such studies, and when manufacturers design their own studies it is by no means certain that the regulatory agencies will find the data to be completely acceptable. Furthermore, there are circumstances when the generation of data from specific in-use simulations may not add significantly to the data already generated from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (1CH)-compliant stability studies. There are also situations (e.g. when small multi-dose containers are involved) where it is difficult to conduct meaningful studies due to the limited quantities of residual product on which to perform chemical or microbiological testing.

Modified Approach for the assessment of In-use shelf life for multi dose container after first opening:

Selection of batches:

A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies. The batch number, date of manufacture and size of each batch should be stated. The container and closure of the product and, if present, the medicinal device should be equivalent to that proposed for marketing [2]. Study can also be performed by bracketing the study design on same batch i.e study should be initiated at beginning and at the end of shelf life of the product.

In use period (Design of study):

As far as possible the period to which the in use stability study is to be performed should be design in such a way that it will simulate the use of the product in practice taking into consideration the filling volume of the container and any dilution/reconstitution before

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QUALITY BY DESIGN (QbD) APPROACH TO DEVELOPMENT OF ANALYTICAL RP-HPLC METHOD FOR REGADENOSON AND BALOFLOXACIN

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ABSTRACT

Quality by design (QbD) refers to the achievement of certain predictable quality with desired and predetermined specifications. A very useful component of the QbD is the understanding of factors and their interaction effects by a desired set of experiments. The present study describes the development of a comprehensive science and risk based RP-HPLC method and subsequent validation for the analysis of Regadenoson and Balofloxacin using a quality by design approach. Experimental designs were applied for multivariate optimization of the experimental conditions of RP-HPLC method. Interaction of independent factors on the depended factor such as tailing factor was studied for both drug. Box Behenken Experimental Design was used to study response surface technique and to study in depth the effects of these independent factors. The optimized chromatographic conditions of HPLC method for regadenoson were water (0.1% o-phosphoric acid): methanol (60:40) as mobile phase, flow rate 1.2 ml/min, wavelength 247. And for Balofloxacin were flow rate 1ml/min, pH 5.7 and Phosphate buffer: Acetonitrile (70:30) as mobile phase. The optimized method condition was validated according to ICH guidelines to confirm LOD and LOQ, linearity, accuracy and precision. The proposed method can be used for routine analysis of Regadenosone and Balofloxacin in quality control laboratories.

KEYWORDS: Quality by design, Regadenoson, Balofloxacin, HPLC.

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Nootropic activity of Ethanolic extract of *Daucuscarota* Linn. Leaves in mice.

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ABSTRACT

In the present study we have evaluated the Nootropic activity of Ethanolic extract of *Daucuscarota* Linn. Leaves(EDCL)with the various doses (100,250,500mg/kg)in mice. Elevated plus Maze, Morris-Water Maze, Passive avoidance test, Object recognition test, Estimation of Acetyl cholinesterase(AchE) activity was done in mice brain. Piracetam was used as standard drug and Scopolamine was used to produce amnesia in mice. No mice showed mortality up to 5000mg/kg. On, Elevated plus Maze, EDCL shows significantly (*P<0.01*) decrease in Transfer Latency (TL) and increased in inflexion ratio (I.R) compared to vehicle treated group and antagonised effect of scopolamine. On, Morris-Water Maze, Escape Latency significantly (*P<0.01*) decreased by EDCL and piracetam treated groups in mice. On, Passive avoidance test, significant (*P<0.01*) increase in step down latency by EDCL was observed and increased occupancy in the shock free zone (SFZ) of the paradigm and also exhibited diminished preference to the preferred shock zone. The results of Object recognition test, shows EDCL and piracetamantagonises the amnestic effect of scopolamine and it spent more time exploring the novel object. EDCL shows significantly (*P<0.01*) decreased the AChE level in mice brain and hence indicates the involvement of cholinergic system in its mechanism. Thus from the results and observations it is prove that EDCL has potential anti-cholinesterase agent and it enhanced memory retention and protected against scopolamine induced amnesia in mice.

Keywords: Nootropic, *Daucuscarota*Linn. Leaves, Elevated plus maze, Morris-water maze,Acetyl cholinesterase (AchE).

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ORIGINAL ARTICLE

Ameliorative Effect of Quercetin and Rutin via Modulation of Hypothalamic–Pituitary–Adrenal Axis and Regulation of Fasting Glucose in Chronic Stress-Induced Prediabetes

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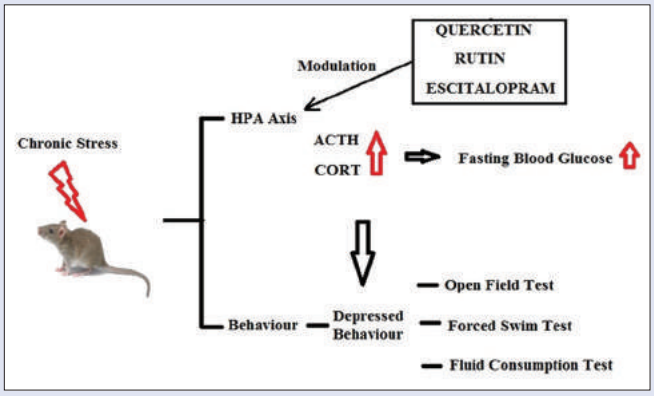
ABSTRACT

Background: Quercetin (QUE) and Rutin (RUT) have nutritive and medicinal values. On the other hand, there are no reports of scientific assessment of its hypothalamo–pituitary–adrenal (HPA) axis modulation in the treatment of prediabetes (DM). **Aim:** The current study was designed to investigate the modulatory effects of QUE, RUT, and escitalopram (ESC) as antidepressants on HPA axis in chronic stress-induced pre-DM in rats. **Materials and Methods:** The experimental protocol was of 5 weeks. Chronic unpredictable mild stress (CUMS) was used as a model of depression to induce pre-DM in rats. The treatment was started at the end of 4th week. After 5th week, the plasma adrenocorticotropic hormone (ACTH), serum corticosterone (CORT), fasting blood glucose (FBG), and behavioral parameters were evaluated. **Results:** Oral administration of QUE (50 mg/kg), RUT (50 mg/kg), and ESC (2.5 mg/kg) to stressed control alleviated HPA axis-associated parameters (ACTH and CORT) and significantly decreased the FBG. Besides this, the depressive effects induced by CUMS were significantly improved as evident from results indicating a promising antidepressant activity. Moreover, submaximal dose of QUE (25 mg/kg) and RUT (25 mg/kg) enhanced the antidepressant activity of ESC (1 mg/kg, p.o.), which suggests that they may act through the HPA axis. **Conclusion:** Current results suggest that chronic stress in rats causes dysregulation of the HPA axis which leads to diabetic-like condition, i.e., "pre-DM." It is possible that QUE, RUT, and ESC may be able to suppress the HPA axis response which could be beneficial for the treatment of stressed diabetic patients.

Key words: Antidepressants, chronic unpredictable mild stress, depression, diabetes, hypothalamo–pituitary–adrenal axis

SUMMARY

- The present study aims to reveal and establish the modulatory effects of quercetin, rutin, and escitalopram as antidepressants on hypothalamo–pituitary–adrenal axis in chronic stress-induced prediabetes in rats.



Abbreviations used: QUE: Quercetin; RUT: Rutin; HPA: Hypothalamic–Pituitary–Adrenal Axis; CUMS: Chronic unpredictable mild stress; ACTH: Adrenocorticotropic hormone; CORT: Corticosterone; FBG: Fasting Blood Glucose; ESC: Escitalopram; FST: Fasting Blood Glucose.

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INTRODUCTION

Stress is a term used in behavioral research that indicates "a physical, chemical, or emotional factor to which an individual fails to make a satisfactory adaptation" and it varies from person to person.[1] When the hypothalamus senses stimuli, produces general adaptation syndrome and stimuli are called stressors.[2] It has been well established that stress gives rise to the pathogenesis of a variety of diseases, including psychiatric disorders, endocrine disorders, immune suppression, sexual and cognitive dysfunctions, peptic ulcer, hypertension and heart diseases, ulcerative colitis, anxiety, and depression.[3,4]

A number of clinical studies have given evidence that depression is associated with hyperactivity of the hypothalamo–pituitary–adrenal (HPA) axis.[5] Antidepressant drug treatment normalizes the hyperactivity of the HPA axis with clinical recovery on or after depression.

Chronic stress in animals results in elevated adrenocorticotropic hormone (ACTH) and glucocorticoid levels in plasma and elevated production of corticotropin-releasing hormone (CRH) in the hypothalamic paraventricular nucleus.[6] The increased CRH secretion due to impaired negative feedback to the increment of cortisol is associated with depression.[7] A clear relationship of stress has been established for depression and DM. It may lead to deterioration of glycemic control through the neuroendocrine system in which the

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