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Research article

Formulation, development and optimization of gastroretentive floating pellets of febuxostat

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ABSTRACT

The aim of the study was to develop gastro retentive floating pellets of febuxostat used to treat gout condition which having low solubility and high bioavailability. The gastro retentive floating pellets of febuxostat were formulated using Gelucire 43/01 and ethyl cellulose as a sustain release polymer and microcrystalline cellulose as spheronizing agent by extrusion- spheronization technique. A 3^2 full factorial design was applied to investigate the effect of the two-independent variable, that is, ratio of Drug: Gelucire (X_1) and ratio of Drug: ethyl cellulose (X_2), on the dependent variables, Floating lag time (Y_1) and cumulative % drug release at 24th hour(Y_2). The optimized formulation (B11) exhibits a floating lag time 110.2±0.02 sec. and cumulative % drug release at 24th hour 98.8±0.02. The *in vitro* release of B1- B12 batches were found in between 98.8% and 68.9% at 24 h. Floating lag time of B1- B12 batches was found to be 62.0±0.01 s – 200.2±0.01 s. Gelucire 43/01 and ethyl cellulose had a significant effect on floating lag time and in vitro drug release. Scanning electron microscopy photomicrograph of pellets revealed that the surface was rough and the pellets were spherical shaped in nature. The in vitro release kinetics revealed zero order models are followed.

Keywords: Gelucire, Gastro retentive floating pellets, Febuxostat, Ethyl cellulose.

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INTRODUCTION

From the past four decades' oral dosage forms have been developed due to their significant therapeutic advantages for example patient compliance, ease of patient administration and flexibility in formulation [1]. Gastro retentive drug delivery system is an advanced approach for the novel drug delivery system in which the drug retained in the stomach for a prolonged period [2,3]. GRDDS is mostly appropriate for drugs that acts locally in a part of the gastrointestinal tract, drugs which are unstable in intestinal fluids, drugs having narrow absorption window and drugs that show poor solubility [4,5]. The Multiparticulate FDDS was preferred over a single-unit system due to minimum inter and intrasubject variability in drug absorption and lower possibility of dose dumping [6]. Hence pelletization of febuxostat reduce the risk of dose dumping unlike in tablet dosage form and gastroprotection solve the low solubility problem of drug as febuxostat is BCS class II drug which having low solubility and high permeability

Target serum uric acid(sUA) levels do not achieve by the patients who treated with allopurinol, due to intolerability to allopurinol doses above 300 mg and patients with renal insufficiency dose reduction are required, while treated with febuxostat, rapid and considerable reductions in sUA levels. Compared with allopurinol-treated patients, patients receiving febuxostat 40 and 80 mg were more likely to achieve sUA concentrations less than 6 mg/dl. [7,8]. Based on mentioned criteria, febuxostat is suitable candidate to treat gout condition and provide sustain release effect by preparing pellets using Gelucire and ethyl cellulose.

Febuxostat is a 2- arylthiazole derivative, BCS class II drug having high permeability and low solubility. The Febuxostat decreasing serum uric acid by inhibiting xanthine oxidase with an in vivo inhibition k_i value less than one nanomolar and it potently inhibit both the oxidized and reduced forms of xanthine oxidase [9].

Although conventional oral dosage forms are widely used for the treatment of gout, but very poor bioavailability are observed in conventional dosage forms due to hepatic first pass metabolism. Pelletization provide uniform distribution of drug.

Hence, the objective of present work is to formulate gastro retentive non-effervescent floating pellets of febuxostat using extrusion spheronization technique.

MATERIALS AND METHOD

Febuxostat was obtained as a gift sample from Spentica life science, Rajkot. Ethyl cellulose 20cps and Microcrystalline cellulose was procured from Quali Chem, Vadodara, Gelucire 43/01 procured from Gatte fosse. All the studies were carried in distilled water.

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Natural Bridged Bicyclic Peptide Macrobiomolecules from *Celosia argentea* and *Amanita phalloides*

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Abstract

Bridged peptide macrobicycles (BPMs) from natural resources belong to types of compounds that are not investigated fully in terms of their formation, pharmacological potential, and stereo- chemical properties. This division of biologically active congeners with multiple circular rings has merits over other varieties of peptide molecules. BPMs form one of the most hopeful grounds for the establishment of drugs because of their close resemblance and biocompatibility with proteins, and these bio-actives are debated as feasible, realistic tools in diverse biomedical applications. Despite huge potential, poor metabolic stability and cell permeability limit the therapeutic success of macrocyclic peptides. In this review, we have comprehensively explored major bicyclic peptides sourced from plants and mushrooms, including β^{s}-leucyl-tryptophano-histidine bridged and tryptophanocysteine bridged peptide macrobicycles. The unique structural features, structure-activity relationship, synthetic routes, bioproperties, and therapeutic potential of the natural BPMs are also discussed.

Keywords: Bridged peptides; bicycles; mushrooms; peptide synthesis; plant seeds; tubulin polymerization inhibition.

Supplementary concepts

Amanita phalloides

LinkOut - more resources

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Towards the Synthesis of a Heterocyclic Analogue of Natural Cyclooligopeptide with Improved Bio-properties

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Abstract

Aims: The present investigation is targeted towards the synthesis of a novel analogue of a natural peptide of marine origin.

Background: Marine sponges are enriched with bioactive secondary metabolites, especially circu-lar peptides. Heterocycles are established organic compounds with potential biological value. Tak-ing into consideration the bio-properties of heterocycles and marine sponge-derived natural pep-tides, an effort was made for the synthesis of a heterocyclic analogue of a natural cyclopeptide.

Objective: A heterocyclic analogue of a sponge-derived proline-containing cyclic peptide, rolloam-ide A, was synthesized by interaction of Boc-protected L-histidinyl-L-prolyl-L-valine and L-prolyl-L-leucyl-L-prolyl-L-isoleucine methyl ester and compared with synthetic rolloamide A with bioac-tivity against bacteria, fungi, and earthworms.

Methods: The synthesis of cycloheptapeptide was accomplished employing the liquid phase method. The larger peptide segment was prepared by interaction of Boc-protected L-prolyl-L-leu-cine with L-prolyl-L-isoleucine methyl ester. Similarly, the tripeptide unit was synthesized from Boc-protected L-histidinyl-L-proline with L-valine ester. The linear heptapeptide segment (7) was cyclized by utilizing pentafluorophenyl (pfp) ester, and the structure was elucidated by elemental and spectral (IR, $^{1}H/^{13}C$ NMR, MS) analysis. The peptide was also screened for diverse bioactivities such as antibacterial, antifungal, and potential against earthworms and cytotoxicity.

Results: The novel cyclooligopeptide was synthesized with 84% yield by making use of car-bodiimides. The synthesized cyclopeptide exhibited significant cytotoxicity against two cell lines. In addition, promising antifungal and antihelmintic properties were observed for newly synthesized heterocyclic peptide derivative (8) against dermatophytes and three earthworm species at 6 µg/mL and 2 mg/mL, respectively.

Conclusion: Solution-phase technique employing carbodiimide chemistry was established to be promising for synthesizing the cycloheptapeptide derivative (8), and C5H5N was proved to be a better base for heptapeptide circling when compared to N-methylmorpholine and triethylamine.

Keywords: Cyclopeptide; biopotential; cyclization; heterocycle; peptide synthesis; sponge.

Related information

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Research article

Design, synthesis and biological screening of novel heterocyclic ring derivatives as antibacterial agents

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ABSTRACT

For a long time, numerous attempts are being made by researchers to discover and develop new antimicrobial agents based on synthetic compounds and medicinal plants. These attempts were forced due to increasing rate of microbial resistance. In the present study, it has been discussed that the synthesis of various dihydropyrimidine fused with benzimidazole moiety. In which o-phenylenediamine and chloroacetic acid react in acidic medium by nucleophilic addition reaction to form 2-chloro methyl Benzimidazole. (1). The substituted Chalcone (2) was synthesized by a claisan-schmidt condensation reaction. The condensation of an aromatic aldehyde with aromatic ketone having α- hydrogen in presence of a strong base to form α,β-unsaturated ketone i.e Chalcone is form. The substituted Chalcone react with thiourea by Michael reaction. It is also called 1,4 addition reaction. In which thiourea act as nucleophile attack on 4-positon of the α,β-unsaturated ketone and keto-enol tautomerism occurs and 4-substitutedphenyl-6-substitutedphenyl-4,5-dihydropyrimidine-2- thiol . (3). Benzimidazole (1) fused with substituted dihydropyrimidine-2-thiol (3) in presence of THF and form 2-((4-substituted phenyl-6-substituted phenyl pyrimidine-2-ylthio)methyl)-1*H*-benzo[d]imidazole. (4). The synthesized compounds APUS1 – APUS21 were assigned by its spectral data (IR, NMR and mass spectra). The synthesized compounds have been tested for their antibacterial activity against Gram (+) bacteria (*S. aureus*) , (*B.subtilis*) and Gram (-) bacteria (*E.coli*) by agar diffusion method. Compound having electron withdrawing group show significant activity and having electron donor group show moderate activity.

Keywords: Antibacterial activity, Molecular docking, Dihydropyrimidine, Benzimidazole.

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INTRODUCTION

Day by day there has been increasing consumption of various antibiotics for the treatment of microbial infections which leads to emergence of multi-drug resistant microbial pathogens. Therefore, there is an urgent demand for research and synthesis of novel of antimicrobial agents having different mode of action which should be effective against various types of bacteria and fungi to solve the problem of microbial resistance.

Heterocyclic compounds containing nitrogen are promising structure moiety for drug design. Benzimidazole and Pyrimidines, Dihydropyrimidines are one of the important heterocyclic compounds, show a diverse range of biological activities such as, antibacterial, antimicrobial, antifungal, antitubercular, anti-inflammatory, anticancer.

Benzimidazole nucleus is the key building block for a variety of compounds that play crucial roles in the function of a number of biologically important molecules. The recent identification of a DHPM analog as a potential new antibacterial lead.

Hence, many synthetic methodologies have been established to synthesis many benzimidazole and DHPM derivatives. On present work chalcone was react with thiourea to form substituted dihydrophrimidine. It was conjugated with benzimidazole with Sulphur atom.

Accordingly, the focus of the present work is the synthesis and characterization of some new benzimidazole-pyrimidine conjugate moieties. All targets have been checked as antibacterial agents using agar diffusion method against gram-positive bacteria (Staphylococcus aureus and B. subtilis), gram-negative bacteria (Escherichia coli). The possible mode of action was tested using molecular docking study.

Molecular docking is a theoretical approach aiming to accurately predict the binding of macro molecules and a small ligand. In this aspect, we employed docking analysis to predict the docking

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Research article

Molecular docking studies of novel dihydro Pyrimidine derivatives as potential antibacterial agents

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ABSTRACT

A new compound of dihydropyrimidine derivatives was designed and predicted to have antibacterial effect. Synthesis of dihydropyrimidine derivatives could be carried out by reaction between Chalcone and thiourea to form dihydropyrimidine. It is incorporated with benzimidazole heterocycle. This study evaluated the mechanism of dihydropyrimidine derivatives in inhibition of DNAG with molecular docking. Docking was performed on the receptor file DNAG (PDB ID: 4DUH) using Auto Dock 1.5.6 program and visualized by Discovery Studio. The docking score of ligand standard, ciprofloxacin and dihydropyrimidine derivatives APUS17, APUS 20, APUS 9, APUS14 towards 4DUH were -8.0, -8.12, -12.1,-11.82, -10.96,-10.1 Kcal/mol respectively. From that derivatives having electron withdrawing group show highest binding affinity and having electron donating group show moderate binding affinity.

Keywords: Molecular Docking, Auto Dock, DNA gyrase, Dihydropyrimidine

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INTRODUCTION

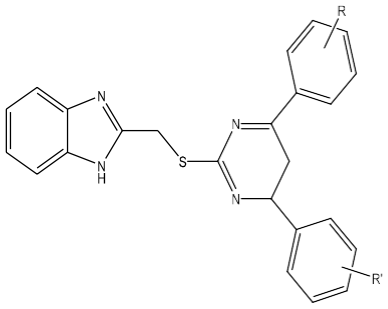
Molecular docking is a theoretical approach aiming to accurately predict the binding of macromolecules and a small ligand. In this aspect, we employed docking analysis to predict the docking models of the tested compounds in the binding pocket of bacterial proteins DNA gyrase subunit B that are known targets for some antibiotics.

The molecular-docking study was used to determine the binding modes of tested compounds against (DNAG) which are important targets for the development of antibacterial agents to gain perspective into the mechanism of action of the tested compounds. Based on their key roles in the formation of bacterial cells, these targets have been selected, so targeting this 4DUH proteins provides perceived benefits in killing bacteria. Using Auto Dock 1.5.6 to reflect the position and orientation of the ligand found in the crystal structure.

MATERIALS AND METHODS

Auto Dock 1.5.6 was used to perform all docking simulations. A set of new dihydro pyrimidine derivatives as antibacterial agents were subjected to docking with DNA gyrase subunit b (PDB ID : 4DUH). From the Protein Data Bank (RCSB) (rcsb.org/pdb). To carry out in silico studies, the 2D structures of the synthesized ligands APUS1 –APUS21 were drawn and converted to energy minimized 3D structures in the pdb file format. By removing the water molecule and cofactors, the target protein file was prepared by leaving the associated residue with protein by using Auto Dock 1.5.6). Preparation of target protein file Auto Dock 1.5.6 tool has been done, Docking simulations for the compounds APUS 1 – APUS 21 were performed against the 4DUH protein, and finally Discovery Studio Visualizer was used to visualize docking results [1-8].

Figure 1: Molecular Structure



2-((4-substituted phenyl-6- substituted phenyl-4,5-dihydropyrimidin-2-ylthio)methyl)-1H-benzoimidazole

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RESEARCH ARTICLE

QbD Stressed Development and Validation of Stability-Indicating RP- HPLC Method for the Simultaneous Estimation of Linagliptin and Metformin HCl in Pharmaceutical Dosage Form

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ABSTRACT:

A new simple stability indicating reverse phase liquid chromatography method was developed by employing Quality by Design (QbD) approach for the simultaneous determination of Linagliptin and Metformin HCl. Within QbD paradigm, the present study aimed to establish the optimization of the RP-HPLC (Reverse phase high performance liquid chromatography) by means of design of experiments and response surface mythology like, Centre composite design (CCD) in order to achieve a good separation and resolution. The developed method is effective to separate Linagliptin and Metformin HCl with a good chromatographic resolution of 6.4. Chromatographic separation was acquired with column Water C_{18} (250mm x 4.5mm x 5µm) at flow rate 1.0 ml/min with the mobile phase consists of acetonitrile and methanol (75:25 % v/v). The detection of Linagliptin and Metformin HCl was carried out at 245nm. The proposed method was validated according to ICH guidelines. The method was linear in range of 0.5-3µg/ml and 100-600µg/ml of Linagliptin and Metformin HCl respectively and recovery were in the range of 98% to 102%. The degradation product found in stress patterns were well separated among the drug compounds. The method was validated to be specific, rapid, precise and robust for routine analysis in its pharmaceutical dosage form.

KEYWORDS:. Quality by Design, Design of Experiments, Linagliptin, Metformin HCl, RP-HPLC, Stability indicating, Validation.

INTRODUCTION:

Linagliptin is a class of dipeptidyl peptidase- 4 (DPP- 4) inhibitors. It works by increasing level of incretins. Incretins help to control blood sugar level by releasing insulin when level of glucose is high.

Linagliptin is used with diet, together with exercise and some time with other oral hypoglycemic agents. Linagliptin used for lowering blood sugar level in type – II diabetes, not in type-I diabetes.[1] Metformin HCl is used as an oral antidiabetic agent in type – II diabetes. It helps to control blood sugar by decreasing the amount of glucose absorption in intestine and decrease the amount of glucose made by liver.[2]

Linagliptin (LINA), a Xanthine derivative is chemically described as 8-[(3*R*)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-3,7-dihydro-1*H*-purine-2,6-dione and molecular formula is $C_{25}H_{28}N_8O_2$. (Fig.1a)[3] Metformin Hydrochloride (MET) is chemically described as 1-carbamimidamido-

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ResearchPaper

Chemometric Assisted Spectrophotometric Method for the Simultaneous Determination of Olmesartan Medoxomil and Hydrochlorothiazide in Bulk and Tablet Dosage Form

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In this work, a numerical method, based on the use of spectrophotometric data coupled to partial least squares, multivariate calibration is evaluated for the simultaneous determination of olmesartan medoxomil and hydrochlorothiazide in bulk and tablet dosage form. Tablet Olmetor-H (HTZ 12.5 mg and OLM 20.0 mg) was used in this study. The equipment used was a Ultraviolet-Visible double beam spectrophotometer with a matching pair of 1 cm quartz cell and electronic balance. Spectra of olmesartan medoxomil and hydrochlorothiazide were recorded at concentrations within their linear ranges 2.5-20 µg/ml and 4-32 µg/ml, respectively and were used to compute a total of 25 synthetic mixtures involving 16 calibration and 9 validation sets between the wavelength range of 200 nm and 350 nm with the wavelengths intervals, lambda=3 nm in methanol. The analytical performances of these chemometric methods were characterized by relative prediction errors and recovery studies (%), and were compared with each other. The proposed method is simple, rapid and can be easily used as an alternative analysis tool in the quality control of drugs and formulation. PLS was applied successfully for the simultaneous determination of OLM and HTZ in laboratory mixtures and pharmaceutical formulation.

Key words: Hydrochlorothiazide, olmesartan medoxomil, partial least squares, chemometrics, ultraviolet-visible spectrophotometry

Olmesartan Medoxomil (OLM), chemically 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(O-1H-tetrazol-5-yl phenyl) benzyl] imidazole-5-carboxylate, cyclic 2,3-carbonate is a prodrug and it is hydrolysed to olmesartan during absorption from the gastrointestinal tract (fig. 1A). It is a selective Angiotensin 1 (AT1) subtype angiotensin II receptor antagonist. Hydrochlorothiazide (HTZ), chemically 6-chloro-3,4-dihydro-2,4-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (fig. 1B), is a widely used thiazide diuretic[1-3]. Olmesartan and HTZ are available in the market as a combined dosage form for the treatment of hypertension. An extensive literature survey revealed the determination of OLM in dosage form by Ultraviolet (UV)-visible spectrophotometry[4,5], High Performance Liquid Chromatography (HPLC)-UV[6,7] and capillary electrophoresis[8] and in biological fluids by HPLC[9] and Liquid Chromatography-Mass Spectrometry (LC-MS)[10,11]. Determination methods of HTZ in pharmaceutical dosage form and biological fluids include chemiluminescence[12], HPLC[13] and electrochemical study[14]. Determination methods of OLM and HTZ combination include UV-spectrophotometry[15-18], Reverse Phase (RP)-HPLC and High-Performance Thin Layer Chromatography (HPTLC)[19,20]. In this work, a simple, accurate, precise and inexpensive quantitative method has been developed for the simultaneous determination of the coexisting two drugs in the tablet dosage form. The method is based on a Partial Least Square (PLS) multivariate calibration chemometric procedure. Moreover, being simple and inexpensive, it is more appealing to use for

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RESEARCH ARTICLE

Development of Validated Stability-indicating Chromatographic Method for the Determination of Metformin and Teneligliptin and its Related Impurities in Pharmaceutical Tablets

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ABSTRACT

A simple, economical, precise, and selective reverse gradient phase high-performance liquid chromatography (RP-HPLC) method has been validated and developed to estimate related impurities of metformin and teneligliptin in a combined tablet dosage form. A RP-HPLC analysis was performed on Hypersil BDS C_{18} column, and its size was 250 mm X 4.6 mm, 5 µm with using mobile phase Acetonitrile and 0.05M potassium dihydrogen Phosphate with buffer pH-4.0 in the ratio of (20:80) at 225 nm detection wavelength with the flow rate of 1.0 mL/min. The analytical method was validated according to International Council for Harmonisation (ICH) guidelines. The linearity was observed in the Limit of Quantitation (LoQ)-37.5µg/ml range for Metformin and its related impurity A. Similarly, the LoQ-1.5 µg/mL range was observed linearity for Teneligliptin and its related impurity B. The correlation coefficient was more than 0.990 for both metformin and its related impurity A and teneligliptin and its related impurity B. The %recovery value was found to be a minimum of 96.181% and a maximum of 102.816% for metformin Impurity A. Similarly, the %recovery value was found to be a minimum of 96.999% and a maximum of 103.824% for teneligliptin impurity B. The relative standard deviation value for repeatability, interday precision, and intraday precision was less than 5%. The Limit of Detection (LoD) value was found to be 0.940 µg/mL for Metformin and 0.206 µg/mL for its related impurity A. The LoD value was found 0.038 µg/mL for Teneligliptin and 0.009 µg/mL for its related impurity B. The LoQ value was found at 2.849 µg/mL for Metformin and 0.623 µg/mL for its related impurity A. The LoQ value was found 0.116 µg/mL for Teneligliptin and 0.026 µg/mL for its related impurity B. The proposed method was found to be specific, linear, sensitive, precise, accurate, and robust in nature.

Keywords: ICH guidelines, Impurities, Metformin, Stability-indicating RP-HPLC, Teneligliptin, Validation.

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INTRODUCTION

Globally, about 463 million adults are living with diabetes. By 2045 this will rise to 700 million. The proportion of people with type 2 diabetes (T2D) is increasing in most countries. Diabetes caused 4.2 million deaths.[1] Diabetes mellitus type 1 is a disease caused by the lack of insulin secretion, and type 2 diabetes mellitus (T2DM) is a disease caused by insulin resistance by cells. Anti-diabetic drugs are used to treat diabetes mellitus by reducing the glucose level in the blood,[2] and the T2DM, which is characterized by polyphagia, polyuria, and polydipsia and needs a lifetime treatment with ant diabetic drugs.[3] The treatment goals involve reducing glycemic control and diabetes-associated cardiovascular risk. Hyperglycemia is associated with diminished life expectancy and quality due to microvascular and microvascular complications.[4] Patients suffering from the onset of diabetes are treated with insulin sensitizer and Metformin. The hypoglycemia risk is insignificant with Metformin treatment, drug interactions are less making, and it is a highly acceptable and safe first-line drug for the treatment of early-stage T2DM.[5] The etiology of T2DM is multiplex which involves several organs, and its treatments with different mechanisms of action by using a combination of drugs that effectively control the plasma glucose levels.[6]

Metformin hydrochloride (MET) is chemically N, N-dimethyl imidodicarbonimidic diamide hydrochloride (1, 1dimethylbiguanide hydrochloride). Metformin is an effective biguanide ant diabetic agent that has been used to control blood glucose levels of T2D patients for decades and has been considered the first line treatment according to international guidelines. Mitochondrial inhibition and activation of AMPK

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Original Article

A Recent Solidification Approach for Nanosuspension: Formulation, Optimisation and Evaluation of Canagliflozin Immediate Release Pellets

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Abstract

Introduction: Canagliflozin is a BCS class IV drug. Nanosuspension is known to enhance the saturation solubility and dissolution rate of poorly soluble drugs owing to the increased surface area of nanosized particles.

Aim: In the present study, we aimed to improve the dissolution characteristics of a poorly water-soluble drug canagliflozin by nanosuspension formulation and stability of this solubility enhancing system - nanosuspension can be improved by converting them into solidified forms as immediate release pellets.

Materials and methods: Canagliflozin nanosuspension was formulated using the media milling method. Poloxamer 407 was used to stabilise nanosuspension. Prepared nanosuspensions were subjected to the characterisation of particle size, polydispersity index (PDI), and drug content. Optimised nanosuspension (NS1) was solidified by converting into immediate release pellets: as improved stability, where canagliflozin nanosuspension was used as a binder. Pellets were prepared by +extrusion-spheronization technique using microcrystalline cellulose (MCC) as pelletizing aid and sodium starch glycolate as super disintegrant. Different important process parameters e.g. concentration of sodium starch glycolate (A), spheronization speed (B) and spheronization time (C) were investigated by 2^3 factorial design to accomplish desired disintegration time (R1) and drug release at 10 min (R2).

Results: The optimised nanosuspension had 120.5 nm particle size, 99.14% drug content and the optimised immediate release pellets (PF5) disintegrated within 23.29 second, and had 99.11% drug content. In vitro dissolution studies showed 89.59% drug release within 10 min in 0.75% w/v SLS. Scanning electron microscopy (SEM) confirmed uniform and spherically shaped pellets. Fourier transform infrared spectrometry (FTIR) and differential scanning calorimetry (DSC) analysis reveal no significant interaction between drug and excipients.

Conclusions: It can be concluded from the findings of this study that the formulation of nanosuspension and its use as a binder in the formulation of immediate release pellets should be investigated further in order to improve the dissolution rate and formulation stability.

Keywords

canagliflozin, extrusion, media milling, nanosized, spheronization

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Docking, Synthesis and Anticancer Activity of 4-(4-(3-(4-Chloro-3-(trifluoromethyl)-phenyl)ureido)phenoxy)-*N*-(2-morpholinoethyl)picolinamide Derivatives

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A new series of diaryl urea derivatives bearing pyridine moiety were designed, synthesized and evaluated for their biological activity. In this study, we applied the structure-based virtual screening (SBVS) on the high similar sorafenib approved drug, selected from the DrugBank database as well as on a series of derivatives, selected from the literature. Aim was to provide new potent anticancer agents. Analysis was performed using AutoDock VINA tools. Based on the ligand binding energy. Compounds will be synthesized by chlorination of pyridine acid derivative which further coupled with amine and form amide, amide further reaction with aminophenolic moiety and form ether which is react with other aromatic amine using CDI to produce final compound and these compounds characterized by IR, NMR and mass spectroscopic techniques. The synthesized derivatives have been evaluated to their anticancer activity *in vitro* by MTT assay using MCF-7 cell line. The anticancer activity indicates that compounds **C1**, **C3**, **C6** and **C9** have better anticancer activity.

Keywords: Diaryl urea derivatives, Anticancer agents, Molecular docking, MTT assay.

INTRODUCTION

Cancer is a one of the major causes of deaths globally [1]. In developed countries, it is a major human health problem and can become the most severe life-threatening disease in the near future [2]. Cancer treatments through targeted drugs, including imatinib, gefitinib and trastuzumab, could reduce severe adverse reactions and improve the cure rates due to their high specificity. Furthermore, these drugs usually lead to severe toxicity on and/or off targets [3]. Therefore, a highly target specific therapy having the minimum toxicity must be developed for disease-free survival and improvement of the life quality of patients with cancer.

Numerous kinases involve in transduction pathway signalling inside the cancer cells. Thus, for the discovery of novel antitumor agents, these kinases are excellent therapeutic targets [4,5]. RAF proteins (Ser/Thr kinase) play a critical role in the activation of the signalling pathway of RAS-RAF-MEK-ERK and promotion of normal cell development [6,7]. RAF is mainly activated by RAS, a G protein, in response to cancer cell mutations or through the over expression of various receptor protein tyrosine kinases, including epidermal, vascular endothelial, and platelet-derived growth factors [8]. Deregulation of normal RAF signalling pathways results in their over expression in different cancers, such as hepatocellular (14%), colorectal (15%), mammary gland (10%), prostate (10%) and melanoma (60%) cancer. FDA has approved several Raf inhibitors as anticancer drugs, including dabrafenib, sorafenib and vemurafenib and some inhibitors, such as WO201106818715, remain under clinical trials [9].

A diaryl urea moiety is commonly utilized for designing anticancer drugs, including regorafenib, sorafenib, tivozanib, and linifanib. Diaryl ureas can be employed to synthesize many heterocyclic compounds having diversified biological activities, such as antimalarial [10], antithrombotic [11], anti-inflammatory [12] and antibacterial [13] properties and are fragments with considerable importance in medicinal chemistry. They can form hydrogen bonds (HBs) with biotargets [14]. Carbonyl oxygen atoms act as proton acceptors, whereas two amide nitrogen atoms serve as proton donors. This unique

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FORMULATION AND EVALUATION OF MATRIX TABLET LOADED LYOPHILIZED BENIDIPINE

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ABSTRACT

An antihypertensive drug, Benidipine (BND) is Biopharmaceutical Classification System Class-II drug having low solubility and high permeability and has lower bioavailability. The present study describes the preparation of matrix tablet from lyophilized BND nanoparticles as lyophilization technique is used in order to improve the dissolution and oral bioavailability of the drugs with poor solubility and high permeability, matrix tablet was formulated to achieve extended drug release and to study its drug release pattern as well. BND has mean half-life 5.3 hr and requires frequent dosing every 5-6 hr to maintain optimal relive and used orally in the treatment of hypertension and angina pectoris, but this frequent administration produces side effects like dizziness and headache. So in present study we have achieved extended drug release for time up to 25 hr for treatment of hypertension, for continuous 24 hr control of blood pressure (BP), by using polymers HPMC K4, chitosan, MCC, magnesium stearate, lactose and talc in order to prepare the suitable formulation. Matrix tablets of lyophilized BND nanoparticles was formulated using 3^2 factorial design in order to study the effect of independent variables X_1 and X_2 (i.e. amount of HPMC K4 and Chitosan respectively) on dependent variable (i.e. % drug release in 10 hr (Q_{10}) and time require for 80% drug release (T_{80})) to evaluate extended drug release. The tablets were prepared by direct compression method. *In-vitro* drug release of different formulations was carried out under stimulated gastric and intestinal condition to achieve optimized drug release. Optimized batch F5 has achieved 99% drug release in 25 hr. The physiochemical characterizations of all prepared formulations

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DEVELOPMENT OF DELAYED RELEASE CAPSULES CONTAINING ENTERIC COATED MINI-TABLETS OF ESOMEPRAZOLE

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ABSTRACT

Now a day's innovative dosage forms like mini-tablets which having diameter ≤ 3mm attaining more eminence due to their simplicity of manufacturing and effective way of drug release mechanisms. They are more effective and patient friendly dosage forms than conventional dosage forms like tablets/capsules due to smaller size. They are manufactured just by modification in compression step using application of multi-tips tooling. Even they are more economical compare to complex and delicate pellets manufacturing process. Primary study shows that esomeprazole accomplishes better and more sustained acid control than other proton pump inhibitors but major problems accompanying are rapid degradation in gastric acid, BCS class III drug, short biological half-life and wide inter-intra individual variability in the bioavailability (50-90%) due to its low permeability. Enteric coated mini-tablets dosage form serves as promising approach as they can protect the drug substance from degradation in gastric media and avoids premature drug release due to smaller size, rapid transit time, higher surface area and higher dispersability in gastro-intestinal tract which leads to improved drug absorption compare to conventional dosage forms. Esomeprazole mini-tablets are manufactured using direct

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FEASIBILITY AND PROCESS OPTIMIZATION TRIALS FOR PREPARATION OF MINI-TABLETS OF ESOMEPRAZOLE BY DIRECT COMPRESSION TECHNIQUE

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ABSTRACT

In recent years the prominence of mini-tablets dosage forms continuously increasing. Mini-tablets are tiny solid oral dosage forms having diameters ≤ 3mm. They are like subunits of conventional tablets with same manufacturing process but only alteration is application of multi-tips tooling. These are patient friendly drug delivery system for patients having swallowing difficulties along with lesser inter-intra individual variability and reduced dose dumping risk. Simplicity and reproducibility of direct compression technique gives uniformity in dosage units compare to conventional granules and pellets manufacturing. The objective of this study is to evaluate feasibility by simple and easy direct compression process as well as process optimization of esomeprazole mini-tablets manufacturing with respect to different levels of drug loading, selection of excipients based on their particle size, particle size distribution and flow characteristics along with modification in conventional excipient addition steps.

Keywords: Multi-tips tooling, Dose flexibility, Drug loading optimization, Excipient selection, Particle size distribution, Reproducibility

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Review article

Analytical method development and validation of related substances by rphplc of sofosbuvir and velpatasvir tablets

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ABSTRACT

The developed method was a simple, accurate, precise, specific and robust method for the validation of Sofosbuvir and Velpatasvir Tablets by reverse phase high pressure liquid chromatography. For Sofosbuvir and Velpatasvir Tablets Chromatography was performed on Agilent 1200 series, UV and PDA Detector, Waters X-bridge C18 (150 mm x 4.6 mm, 3.5 µm) by using Mobile Phase A contains Buffer solution (0.6% Trifluroacetic acid in water adjusted pH to 2.2±0.05) : Acetonitrile (95:5)%v/v and Mobile Phase B contains mixture of purified water, methanol and acetonitrile in the ratio of (20: 30: 50) % v/v/v. at a flow rate of 1.0 mL/min and at 263 nm for Sofosbuvir and 320 nm for Velpatasvir wavelength. The retention times of About 48.0 minutes for Sofosbuvir and About 78.8 minutes for Velpatasvir respectively. Methyl Uridine and Impurity at RRT 0.39 found linear over the range of LOQ - 150 % of target concentration. Method also found precise by spiking impurities at specification level. Accuracy was demonstrate at LOQ - 150 % level by preparing sample in triplicate for each level and found accurate. Hence, the method could be successfully used for the analysis Impurities in Sofosbuvir and Velpatasvir Tablets Tablet.

Keywords: Sofosbuvir, Velpatasvir, HPLC, UV and PDA Detector, Dual Wavelength, Related Substances.

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INTRODUCTION

Antiviral drugs are a class of medication used specifically for treating viral infections rather than bacterial ones. Most antiviral are used for specific viral infections, while a broad-spectrum antiviral is effective against a wide range of viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development [1].

Chemical Name of Sofosbuvir is propan-2-yl (2S)-2-{[(S)-{[(2R,3R,4R,5R)-5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin1-yl)-4-fluoro-3-hydroxy-4-methyloxolan-2yl]methoxy}(phenoxy) phosphoryl] amino}propanoate with nucleotide polymerase inhibitors category. Sofosbuvir has chemical formula $C_{22}H_{29}FN_3O_9P$. Molecular formula is 529.498 g/mol. Sofosbuvir is a direct acting antiviral medication used as part of combination therapy to treat chronic Hepatitis C, an infectious liver disease caused by infection with Hepatitis C Virus (HCV). HCV is a single-stranded RNA virus that is categorized into nine distinct genotypes, with genotype 1 being the most common in the United States, and affecting 72% of all chronic HCV patients.

Velpatasvir acts as a defective substrate for NS5A (Non-structural Protein 5A), a non-enzymatic viral protein that plays a key role in Hepatitis C Virus replication, assembly, and modulation of host immune responses [4].

Chemical Name of Velpatasvir is Methyl {(2S)-1-[(2S,5S)-2-(9-{2[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)-2-pyrrolidinyl]-1H-imidazol-4-yl}1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methyl-1-pyrrolidinyl]-3-methyl-1-oxo-2-butanyl}carbamate with NS5A inhibitors category. Velpatasvir has chemical formula C49H54N8O8.Molecular formula is 883.019 g/mol. Velpatasvir is a Direct-Acting Antiviral (DAA) medication used as part of combination therapy to treat chronic Hepatitis C, an infectious liver disease caused by infection with Hepatitis C Virus (HCV). HCV is a single stranded RNA virus that is categorized into nine distinct genotypes, with genotype 1 being the most common in the United States, and affecting 72% of all chronic HCV patients [2-3].

MATERIALS AND METHODS

Materials

Sofosbuvir (400 mg) and Velpatasvir (100 mg) Tablets received as gift sample.

Instrumentation

The LC system consisted of an Agilent 1260, DAD,