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Original Article

Tab-in-tab formulation of ramipril and nifedipine for effective anti-hypertensive activity

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ABSTRACT

Background: The aims of this work were to enhance the solubility of nifedipine in acidic medium; to formulate and characterize tab-in-tab dosage form for immediate release of nifedipine and controlled release of ramipril and to avoid the mutual interactions of drugs. This combination appreciably intended to reduce the incidence of peripheral edema and reflex tachycardia.

Methods: Ramipril was firstly wet granulated with a HPMC polymer to form stable granules and then was directly compressed to form a core tablet. Enteric coating was given with a water insoluble polymer to withstand the acidic pH of stomach. Initially, nifedipine microcapsules were prepared, granulated with excipients and then compressed, keeping the inner tablet in between the granules.

Results and discussion: This novel tab-in-tab dosage form allowed the nifedipine to release for stomach-specific absorption and ramipril to the intestine-specific absorption. Distinctive release profiles were obtained for immediate- and controlled-release tab-in-tab formulations, giving better bioavailability with no metabolic side-effects.

Conclusion: Tab-in-tab drug delivery system used to formulate combination drugs with different pharmacokinetic profiles provide reduction in dosage, dosing frequency, reduction in side effects, additive effects and single pill convenience.

1. Introduction

In current years, combination of different drugs in anti-hypertension therapy in the form of single-dose is significant alternative that combines effectiveness of blood pressure reduction and a low side effect profile with convenient once-daily dosing to enhance patient compliance.[1] Also, because of the lower dose of each antihypertensive drug in a combination, metabolic and clinical adverse effects are decreased.[2] ACE inhibitors and a calcium channel blockers (CCB's) work effectively in combination to lower blood pressure, to promote reduction of left ventricular mass, to decrease mediators of vascular disease and for renal-protective effect. The combinations of CCB and ACE inhibitor may outcome in lesser or

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milder side effects than occur with either agent alone. The addition of an ACE inhibitor to therapy with a dihydropyridine calcium antagonist significantly reduces the incidence of peripheral edema and reflex tachycardia.[3]

Tab-in-tab is the synonym of tablet-in-tablet formulation or compression/press coated tablet or dry coated tablet. The tablet-in-tablet structure can be used for ordered or biphasic fast/slow release, in which the core and shell sections both contain drugs[4] and is differ from layer tablets.[5] This is an economical method and plays an important role in the manufacturing of different pharmaceutical dosage forms like tablet, microparticles, nanoparticles etc. Tab-in-tab formulation containing immediate release solid dosage can be compressed around a press-coated thereby avoiding the use of a drug solution.[6] The aims of this work were to enhance the solubility of nifedipine (NIF) in acidic medium; and to formulate and characterize tab-in-tab dosage form of effective two anti-hypertensive drugs viz. ramipril (RAM) and NIF. The inner tablet of RAM, an ACE inhibitor, was formulated as controlled release (CR) tablet because of its shorter half-life, less volume of distribution and fast clearance; and outer core of NIF, a CCB, as in the form of immediate release (IR) to treat hypertension and angina. This combination appreciably intended to reduce the incidence of peripheral edema and reflex tachycardia. The advantage of this solid formulation is single dosage form comprising the two drugs and also a built-in time programmed manner.

2. Materials and methods

RAM and NIF were gifted from Torrent Pharma, India. Ac-Di-Sol and avicel pH-101, lactose monohydrate, magnesium stearate and pre-gelatinized starch were purchased from Qualigens Chemicals, India. HPMC E-5, Eudragit L-100 grades were procured from Degussa, India. Ethyl cellulose 10 cps was gifted by Signet, India. SSG, aerosil 200, gelatin and SLS were purchased from S. D. fine, India. All other reagents were used of analytical grade.

2.1. Preparation of NIF-loaded gelatin microcapsules

Accurately weighed 40 g of gelatin was dissolved in 700 ml of water to attain aqueous gelatin solution. Then, 6 g of SLS and alcoholic NIF solution (5 g NIF in 380 ml ethanol) were added to aqueous gelatin solution and prewarmed to 50 °C. The resulting solution was spray dried (Labultima, India) at 105 °C by maintaining inlet temperature 5 ml/min using a peristaltic pump.

2.2. Characterization of microcapsules

The size, shape and surface of NIF-loaded gelatin microcapsules were examined using a SEM (Jeol, USA). For encapsulation efficiency (EE), NIF-loaded microcapsules were dissolved in methanol–water solution (50 %w/w) and then quantified by UV-spectrophotometer (Perkin Elmer, USA) at the wavelength of 335 nm. About 200 mg of NIF-loaded gelatin microcapsules were introduced into the basket type dissolution tester (Electrolab, USA). Dissolution test was performed at 37 ± 0.5 °C at 100 rpm with 500 ml simulated gastric fluid (SGF) pH 1.2 as a dissolution medium. At predetermined interval, the filtrate was analyzed by UV-spectrophotometer ($\lambda = 335$ nm).

2.3. Micromeritic properties

The loose and tapped bulk densities of RAM, NIF and other excipients were determined by using a density apparatus (Serwell, India). The Compressibility index (CI %) and the Hausner's ratio (HR) were calculated.

2.4. Compatibility studies

Drug-excipients compatibility was carried out by FTIR spectroscopy and DSC. FTIR spectra of drugs and excipients were taken by using KBr pellet technique using a Shimadzu FT-IR spectrophotometer (Japan) in the wavelength region of 4000 to 400 cm^{-1}. Thermal analysis of samples (drug or mixture of drug/s and excipients) were carried out using DSC (Perkin–Elmer, USA) method with a heating rate of 10 °C/min from 0 to 300 °C.[7]

2.5. Preparation of core and outer tablets

The composition of the tablets is shown in Table 1. The core tablets containing RAM and HPMC in IPA (T1–T3) were prepared by granulation and later mixed with avicel. Magnesium stearate and Ac-Di-Sol were added to each blend and further mixed. The resultant blends were tableted to 80 mg using 10 stations Cadmach tablet press (India). Enteric coating was given with Eudragit 10% solution using a Gans coater (India) and the coating solution was applied till 2% weight gain was achieved (tablet weight: 90 mg).

All materials such as NIF-loaded microcapsules and excipients were passed through sieve no. 80. The outer tablets containing microcapsules of NIF, starch, SSG and avicel were prepared by granulation. Magnesium stearate and aerosil were added to each blend and further mixed. The resultant blends were tableted keeping the core tablet in between to 450 mg (core: 90 mg + outer: 360 mg) using a 10 stations Cadmach tablet press.

2.6. Evaluation of core tablets and tab-in-tab formulations

Thickness of tablets ($n = 3$) was determined using Vernier caliper (Mitutoyo, Japan). USP stated weight variation test of the tablets ($n = 20$) was carried out using electronic balance (Shimadzu, Japan). The hardness of tablets ($n = 5$) was tested using Monsanto hardness tester (Electrolab, USA). For each formulation, the friability of 6 tablets was determined using the Friabilator (Electrolab, USA). For determining the drug content of core tablets, 20 tablets ($n = 3$) were crushed and 100 mg of powder was dissolved in 100 ml of HCl buffer pH 1.2 for outer tablet and phosphate buffer pH 6.8 for core tablet respectively. These filtered solutions were analyzed by UV-spectrophotometer at 335 nm and 210 nm for NIF and RAM respectively. Disintegration tests were performed on tablets as per USP using disintegration apparatus (Electrolab, USA).