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Valsartan floating bioadhesive compression-coated mini-tablets: Formulation and pharmacokinetics

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ABSTRACT

An attempt is made in the present study to develop the valsartan floating bioadhesive compression-coated mini-tablets. Among the various methods described, combination of floating and bioadhesive drug delivery systems is a promising way in gastro retention with few limitations, which has a great impact on the drug delivery to its intended site of administration. Mini-tablets have the advantages of both tablets as well as multiparticulates like pellets. The prepared mini-tablets were evaluated for weight variation, thickness, friability, hardness, drug content, *in vitro* buoyancy, *in vitro* release and *in vivo* studies. Prepared core mini-tablets were compression coated using polymers such as HPMC K4M and Carbopol 934P. From the results, formulations with HPMC K4M with Carbopol 934P in 1:1 ratio showed controlled release. Formulation F3 showed a satisfactory dissolution profile, detachment stress and floating characteristics, which can increase the gastric residence time as well as bioavailability. Pharmacokinetic studies of F3 formulation in albino male rabbits showed 2.25-fold higher bioavailability and 1.5-fold higher C_{max} compared to immediate release core mini-tablets. Hence development of valsartan floating mini-tablets using combination of floating drug delivery and bioadhesive drug delivery systems is the best way to obtain gastro retention to gain therapeutic benefits.

1. Introduction

Oral drug delivery is reckoned as the most desirable route owing to ease of administration, high patient compliance, and industrial scalability and it has progressed over time from simple immediate-release to modified-release and site-specific delivery [1,2]. Floating drug delivery is one of such developments in the oral drug delivery for local as well as systemic action. One of the major drawbacks of floating system is a requirement of high level of fluids in the stomach for the system to float and it is effective only when the fluid level in the stomach is sufficiently high. To overcome the disadvantages of floating drug delivery, combination of floating drug delivery and bioadhesive drug delivery systems is a significant approach for gastro retention [3]. Hence the development of floating bioadhesive drug delivery systems (FBDDS) by incorporating bioadhesive polymers to normal floating system is becoming one of the fruitful approaches to design single-unit and multiple-unit floating systems by offering the advantage of increased gastric residence time. This method is mainly to improve the bioavailability of drugs by the extended gastric retention and also to deliver the drug to the upper gastric tract [4,5].

Over single-unit systems, multiple-unit systems like pellets or mini-tablets are act as prominent floating systems that shows avoiding all or nothing emptying, less chance of localized mucosal damage, high predictable drug release kinetics and administration of units with different release profiles [6,7]. Development of mini-tablets is a significant alternative to pellets and other multiple-unit systems that show the following advantages like ease of manufacturing, packaging, storage and minimum scalability problems and also exhibits equal dimensions and weight with smooth regular surface in a reproducible and continuous way unlike pellets [8]. Some of the research examples on mini-tablets of various delivery systems are flurbiprofen [9], ketorolac tromethamine [8], levofloxacin [10], theophylline [11], furosemide [12], ibuprofen [13], diclofenac sodium [14].

Present study is intended to develop floating-bioadhesive mini-tablets that show combination of both floatation and bioadhesion with the advantages of mini-tablets to prolong residence in the

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stomach using valsartan as a model drug. Valsartan, an angiotensin II receptor antagonist is used for the maintenance and treatment of hypertension, chronic hypertension attacks, treats congestive heart failure and also myocardial infarction. The main drawback of conventional valsartan tablets is that it shows plasma or biological half-life 5–7 h, with a very low bioavailability of 23% [15]. Hence the present work is aimed to formulate the floating-bioadhesive compression coated mini-tablets using hydroxypropyl methylcellulose (HPMC K4M) and carbopol 934P to improve the biological half-life as well as bioavailability of valsartan.

2. Materials and methods

2.1. Materials

Valsartan was obtained from KP labs, Hyderabad, India. HPMC K4M and carbopol 934P were belongs to Finar Chemicals Ltd, India. All other materials and solvents used were of analytical grade, purchased from SD Fine Chemicals India.

2.2. Preparation of floating bioadhesive compression-coated mini-tablets

With the incorporation of Avicel PH 102 as a diluent, valsartan mini-tablets (core tablets) were prepared by wet granulation method using 4 mm round flat punches on 8 station rotary tabletting machine (Riddhi, India) at low speed of 10 rpm (Table 1). Then the core tablets were compression coated with HPMC K4M and carbopol 934P using 8 mm circular flat punches (Table 2). The present study followed the procedure given in Veerareddy & Vemula, 2012 [16].

2.3. Determination of tabletting parameters

To ensure the uniformity and mechanical integrity of the prepared tablets, following parameters like weight variation, hardness, friability and drug content were measured. Using the standard procedures, the above parameters were calculated [17]. Drug content uniformity was assessed by randomly picked ten tablets (drug powder equivalent to 100 mg) in 100 ml of 0.1N HCl buffer at λ_{max} of 248 nm using UV-Visible Spectrophotometry. Floating lag time and total floating time were determined using the procedure described in Rosa et al., 1994 [18]. The tablets were also evaluated for the swelling behaviour by calculating the percentage swelling index using the standard procedure described in Tadros, 2010 [19]. To determine the mucoadhesion capacity of carbopol polymer used in floating bioadhesive tablets, *in vitro* bioadhesion strength was measured using modified physical balance by following the method described in Siddam et al., 2016 [3].

2.4. In vitro drug release studies

The *in vitro* drug release studies were conducted in 0.1N HCl solution using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L) at 50 rpm speed and 37 ± 0.5 °C temperature. 2 ml samples were collected (n = 6) and restored the same level of fresh pre-warmed media at scheduled time intervals for 24 h, filtered through 0.45 μm membranes (Millipore, USA) and analyzed by HPLC method [20] Then the dissolution data was interpreted to zero order, first order and Higuchi models and Koresmeyer–Peppas model [21] to elucidate the drug release mechanism. Also calculated the mean dissolution time, dissolution efficiency [22], T50% and T80% (time in hours to take 50% and 80% drug release) from above data to explain the drug release pattern.

Table 1
Composition of valsartan core mini-tablets.

Ingredients	Quantity (mg)
Valsartan	20
Avicel PH 102	35.2
Crosspovidone	3
Starch paste (10%)	Q.S.
Talc	1.2
Magnesium stearate	0.6
Core weight	60

2.5. Stability studies

F3 floating tablets were selected based on the above evaluations to conduct the stability studies using ICH guidelines i.e., stored at 40 ± 2 °C and 75 ± 5% RH in the humidity chamber for six months [23]. Then the collected samples were determined for assay and *in vitro* dissolution rate and statistically analyzed using paired *t*-test at 0.05 significance level [24]. Then the similarity factor (f_2) was calculated between dissolution rates of optimized tablets before and after storage.

2.6. In vivo studies

In vivo studies were conducted in albino male rabbits weighing 2 kg after obtaining approval from the Institutional Animal Ethical Committee (IAEC/VCP/2015/6/1).

2.6.1. In vivo buoyancy studies

To study the *in vivo* buoyancy of prepared floating tablets in the stomach, an x-ray imaging study was employed using three albino rabbits. With the incorporating barium sulphate into the F3 formulation, it is possible to observe the exact position and status of floating tablets. Rabbits were kept fasting for 36 h allowing free access to water before the x- ray imaging studies. To the each rabbit the barium sulphate included floating tablet is given orally with sufficient quantity of water and the abdominal radiographs were taken after 30 min, 2 h, 5 h, and 8 h.

2.6.2. In vivo pharmacokinetics-study design

The present study was designed to compare the valsartan compression coated floating bioadhesive compression coated tablets with valsartan immediate release core mini- tablets using a two-way crossover design with 2 weeks of washout period. Albino male rabbits were divided into two groups (n = 6), in which group I animals were treated with immediate release core mini-tablets (20 mg dose) and group II with compression coated floating mini-tablets of same dose in the first phase whereas vice versa in second phase of study. Blood samples (0.5 ml) were collected from marginal ear vein at 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 h post oral dose in EDTA coated Eppendorf tubes. Plasma was separated by centrifuging at 4000 rpm for 15 min and stored at − 20 °C until analysis.

2.6.3. HPLC analysis of valsartan in plasma

Valsartan plasma concentration from above samples was determined by HPLC method adopted from Chella et al. [20] with slight modifications. To the 1 ml of above plasma sample 1 ml of acetonitrile was added and centrifuged for 10 min at 3000 rpm and the supernatant liquid was separated and filtered through 0.2 m filter and 20 ml was injected in to the system. The analysis was carried out using Shimadzu HPLC (Shimadzu Corporation, Kyoto, Japan) equipped with C18 column and UV detector. The mobile phase consisted of acetonitrile and water (55:45 v/v), pH adjusted to around 3.2 with dilute *ortho*-phosphoric acid and the eluents