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Research Article

Formulation and Evaluation of Bilayer Floating Matrix Tablets For Captopril

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ABSTRACT

The importance of the present investigation was to formulate a bilayer-floating tablet (BFT) for captopril using direct compression technology. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The floating mechanism and *in vitro* dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). Final formulation released approximately 95% drug in 12 hrs *in vitro*, while the floating lag time was 10 min and the tablet remained floatable throughout all studies. Final formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or *in vitro* dissolution pattern after storage at 45 °C / 75% RH for three months. Thus, it seems that an increase in gastric retention time may increase the extent of absorption and bioavailability of the drug. In the present study, we have attempted to formulate a floating system of captopril.

Keywords: Bilayer floating tablet, Higuchi, HPLC, X-ray, Captopril

INTRODUCTION

Development of oral gastroretentive controlled-release systems has been a challenge to formulators, because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. When the drug is formulated with a gel forming polymer such as semisynthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than

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one. Controlled / sustained release preparations using alternative routes have been formulated but the oral route still remains preferable. It then remains buoyant and floats in the gastric fluid, affecting a prolonged gastric residence time (GRT). This floating dosage form is well known as a hydrodynamically balanced system (HBS) [1 – 3]. It has been suggested for the following instances that an active material should be formulated in the form of an HBS to enhance bioavailability: (*i*) having a dissolution and/or stability problem in the small intestine fluids, (*ii*) being locally effective in the stomach, (*iii*) being absorbed only in the stomach and/or upper part of the intestine [4]. Floating tablets, capsules, beads, microspheres and chambers have been reported in literature [5].

Captopril, an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. It has been reported, however, that the duration of antihypertensive action after a single oral dose of captopril is only 6 to 8 h, so clinical use requires a daily dose of 37.5 – 75 mg to be taken three times [6]. It is most stable at pH 1.2 and as the pH increases; it becomes unstable and undergoes a degradation reaction [7]. The virtue of the prolonged release dosage form of captopril has been reviewed [8]. Researchers have developed a single layer floating tablet of captopril [9]. In comparison with the single layer tablet, a double layer matrix offers advantages; this formulation of the matrix dosage form with two distinct layers allows separate regulation of the floating capabilities and drug release kinetics. The present investigation aims to develop a BFT of captopril with a view of prolonging GRT with a controlled release mechanism.

MATERIAL AND METHOD

Captopril was obtained as a gift sample from Lupin Pharmaceuticals, India. Ranbaxy Laboratories Ltd., India, kindly donated HPMC-K100M, Carbopol 934p and PVP-K30. HPMC-K4M and HPMC-K15M were obtained from the Dabur Research Foundation, India. All the polymers received were of pharmaceutical grade and were used as received. Other materials and solvents used were of analytical grade or better. All the studies were carried in HPLC grade water.

Formulation: Floating layer: Various floating layer formulations were formulated with HPMC-K4M, HPMC-K15M and HPMC-K100M polymers alone or/and in combination. Adding an effervescent mixture of sodium bicarbonate and critic acid provided floating (formulation not shown). Polymers and the effervescent mixture were blended in a mortar. Using direct compression technology, floating layers were compressed at compression forces of 39.2 – 49.0 kN in a eight station tablet press with a 8 mm flat plain punch diameter (Shakti Tablet press,

India). Before compression, 0.2% magnesium stearate was added as lubricant. Each layer formulation was blended and compressed (100 tablets) and tested for hardness (n = 10), mass variation (n = 20) and floating behavior (n = 6). The hardness of floating layers was in the range (49.0–58.8) × 104 Nm^{-2} on a Monsanto Hardness Tester (Nirmal Instrument, India). The mass of floating layer was 200 ± 10 mg.

Bilayer floating matrix tablet: HPMC-K15M, PVP-K30 and Carbopol 934p were employed in the release layer formulation for the controlled delivery of captopril. Various formulations of BFT are given in Table 1. Matrix tablets were prepared by direct compression technology. To each layer, 0.2% magnesium stearate was added as lubricant before compressing into the tablet. At the beginning, the optimizing floating layer (FX1) was placed in the dye cavity and preparatory pressing was done. Thereafter, a release layer formulation was added and subjected to compression force of 39.2–49.0 kNm^{-2}. Each BFT formulation was compressed (100 tablets)

Table 1: Composition of captopril BFT

Layer	Formulation Code	Captopril (mg)	HPMC-K15M (mg)	PVP-K30 (mg)	Carbopol-934p (mg)	HPMC-K100M (mg)	Citric acid (mg)	Sodium bicarbonate (mg)
Floating	FX1	-	-	-	-	160	20	20
Release	RA1	25	25.0	-	-	-	-	-
Release	RA2	25	50.0	-	-	-	-	-
Release	RA3	25	75.0	-	-	-	-	-
Release	RA4	25	100.0	-	-	-	-	-
Release	RA5	25	125.0	5.0	-	-	-	-
Release	RB1	25	120.0	12.5	-	-	-	-
Release	RB2	25	112.5	20.0	-	-	-	-
Release	RB3	25	105.0	27.5	-	-	-	-
Release	RB4	25	97.5	35.0	-	-	-	-
Release	RB5	25	90.0	5.0	-	-	-	-
Release	RC1	25	75.0	5.0	12.5	-	-	-
Release	RC2	25	75.0	5.0	25.0	-	-	-
Release	RC3	25	75.0	5.0	37.5	-	-	-

and subjected to testing for mass variation (n = 20), hardness (n = 10), drug content (n = 6), floating behavior (n = 6), and in vitro dissolution (n = 3). Hardness of the tablets ranged from (49.0–58.8) × 10^4 Nm^{-2} on a Monsanto Hardness Tester and the thickness was of 3.78 ± 0.13 mm.

Floating behavior: Floating behavior studies were performed on both the floating layer and BFT, carried out in a USP 23 paddle apparatus 2 at a paddle speed 50 rpm in 900 mL SGF (pH 1.2, no enzyme) at 37 ± 0.2 °C for 12 hrs to mimic in vivo conditions [10]. The following parameters were determined: the time needed to go upward and float on the surface (floating lag time), floating duration and relative matrix integrity. The latter parameter was determined on the basis of mass loss by gravimetry and visual inspection after the floating studies.

In vitro dissolution: The captopril release from different BFT formulations was determined using a USP 23 paddle apparatus 2 under sink condition. The dissolution medium was 900 mL SGF (pH 1.2, no enzyme) at 37 ± 0.2 °C; paddle speed 75 rpm, to simulate in vivo conditions. All experiments were done in triplicate and average values were taken. The formulation prepared was subjected to dissolution tests for 12 hrs Sample (4 mL) was withdrawn at predetermined time intervals, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined by HPLC. Dissolution data were corrected for the dilution effect [11] and tablet density was determined by the benzene displacement method before and after floatation.

HPLC analysis: Quantitative determination of captopril was performed by HPLC. A gradient HPLC system (Shimadzu HPLC Class VP series, Shimadzu, Japan) with two LC 10AT VP pumps, a variable wavelength programmable UV-Vis detector SPD-10A VP, a system controller SCL-10AVP and RPC-18 column (150 mm x 4.6 mm I.D., particle size 5 µm, Merck, Germany) was used. The HPLC system was equipped with the software Class VP series version 5.0 (Shimadzu). Quantitation was performed according to the earlier reported method with a slight modification [12]. The mobile phase consisted of n-propanol/phosphate buffer (pH 3.0, 0.4% triethylamine), 20:80 (V/V). The filtered mobile phase was pumped at a flow rate of 0.6 mL min^{-1}. 20 µL of sample was injected into the column and the retention time of captopril was found to be 4.0 min. the elute was detected by UV at 240 nm.

Stability: To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines [13]. Optimized BFT (RC3), sealed in aluminum packaging coated inside with polyethylene, and various replicates were kept in the humidity chamber maintained at 45 °C and 75% RH for 3 months (Yorco Scientific Industries, India). At the end of studies,

samples were analyzed for the drug content, in vitro dissolution, floating behavior and other physicochemical parameters.

RESULTS AND DISCUSSION

First, the floating layer was prepared and evaluated on the basis of floating behavior studies. It contained the effervescent mixture and K-grade HPMC to retain the carbon dioxide produced from the effervescent mixture. From the results of floating behavior studies (results not shown), it was found that as the concentration of effervescent mixture increased, the floating lag time, floating duration and matrix integrity decreased and *vice versa*. A reverse trend was observed on increasing the polymer concentration. Therefore the concentration of the effervescent mixture was chosen so as not to compromise the matrix integrity with the possible shortest lag time and floating duration of up to 12 hrs The optimized floating layer formulation (FX1 shown in Table 1) had the floating lag time of 3 min, good matrix integrity and floating duration of more than 12 hrs The floating layer for the development of BFT was found to be HPMC-K100M 80%, sodium bicarbonate 10% and citric acid 10%. BFT was prepared, containing the optimized floating layer (FX1) and release layer containing captopril (25 mg) and various polymers alone and/or in combination. BFT containing HPMC-K15M in the release layer (RA1, RA2, RA3, RA4 and RA5) showed the initial burst effect and decreased final release rate. This biphasic pattern of drug release is characteristic of matrix diffusion kinetics [14]. As the concentration of HPMC-K15M increased, not only the burst effect but also the final release rate decreased (Fig. 1). This could be due to the increased path length for the drug to diffuse from the matrix. Furthermore, formulation containing HPMCK-15M and PVP-K30 in the release layer (RB1, RB2, RB3, RB4 and RB5) showed that not only the final release rate but also the burst effect increased (Fig. 1). This was due to the fact that PVP-K30, which is hydrophilic in nature, allowed easy penetration of the medium into the matrix and a more rapid release of captopril. Moreover, formulations containing HPMC-K15M, PVP-K30 and Carbopol 934p in the release layer (RC1, RC2, and RC3) showed a more controlled release profile (Fig. 1).

Initial burst effect decreased and the final release increased with the Carbopol 934p concentration. This was because of the fact that Carbopol 934p which has p*K*a of 6.0, remains unionized in the acidic environment of dissolution medium. Therefore the release rate was controlled by HPMC-K15M and PVP-K30, with the particles of Carbopol 934p acting as a physical barrier to drug release [15].

To analyze the captopril release mechanism as well as to select the BFT formulation for *in vivo* studies, the *in vitro* release data were fitted into various release equations and kinetic models (first order [16], zero order, Higuchi [17] and Korsmeyer and Peppas [18]). The RC3 BFT was chosen as the optimized formulation because it showed more linearity between the cumulative percentage captopril released *versus* time, as indicated by the highest value of the correlation coefficient *R* or *R*2 in all the selected models, among all BFT formulations, and best fitted both Higuchi (*R*2 = 0.987) and zero order (*R*2 = 0.983) model. In the optimized BFT formulation (RC3) floating layer was found to be: HPMC-K100M 46.7%, citric acid 5.8%, sodium bicarbonate 5.8%; release layer: captopril 7.3%, HPMC-K15M 21.9%, PVP-K30 1.5% and Carbopol 934p 10.9% (density 1.30 and 0.75 gcm^{-3} before and after floatation, respectively). As indicated by the value of R^2, the Higuchi model was found to be efficient in describing the kinetics of captopril release from the BFT formulation, with drug release being proportional to the square root of release time. To explore the release pattern, results of the *in vitro* release data of optimized BFT (RC3) were fitted to the Korsmeyer and Peppas equation ($M_t/M_\infty = k\ t^n$, where M_t/M_∞ is the fraction of drug released after time *t* in respect to amount of drug released at infinite time, *k* is the rate constant and *n* is the diffusional exponent) [19] which characterize the transport mechanism. The value of *n* was 0.392 (*R*2 = 0.995), indicating release governed by Fickian diffusion.

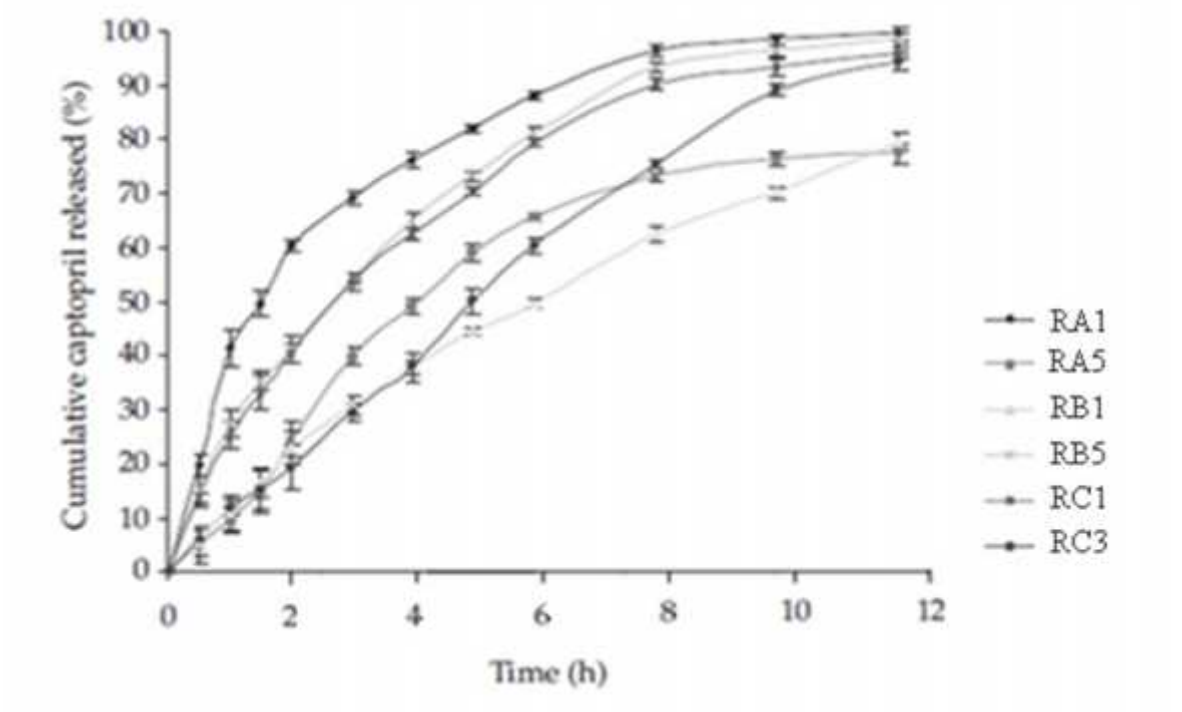

Fig. 1: Cumulative percentage of captopril released versus time (mean ± SD, n = 3).

In view of the potential utility of the formulation, stability studies were carried out at 45°C and 75% RH for three months (climatic zone IV condition for accelerated testing) to assess their long-term (2 years) stability. The protocols of stability studies were in compliance with the guidelines in the WHO document for stability testing of products intended for the global market. After storage, the formulation was subjected to a drug assay, floating behavior and *in*

Table 2: Captopril released from optimized BFT (RC3)

Time (h)	Captopril released (before storage, %)[b]	Captopril released (after storage, %)[a,b]
2	12.0 ± 0.4	11.4 ± 1.6
4	29.5 ± 2.3	29.4 ± 4.9
6	50.1 ± 1.2	49.8 ± 3.4
8	67.4 ± 3.3	65.9 ± 1.6
10	89.2 ± 1.3	87.9 ± 1.6
12	94.4 ± 4.8	92.5 ± 1.5

[a] *Storage at 45 °C / 75% RH for three months.*

[b] *Mean ± SD, n = 3.*

Tabe3: Characteristics of optimized captopril BFT (RC3)

		Hardness	Floating behavior		
	Drug (%)[b]	$\times 10^4$ ($N\ m^{-2}$)[b]	Floating lag time (min)[b]	Floating duration (h)[b]	Matrix integrity[b]
Before storage	100.3 ± 1.1	53.70 ± 1.96	10.0 ± 0.9	39.5 ± 4.5	very good
After storage[a]	99.2 ± 1.2	54.88 ± 8.82	10.5 ± 1.3	37.2 ± 5.5	very good

[a] *Storage at 45 °C / 75% RH for three months.*

[b] *Mean ± SD, n = 6 (floating and drug content studies), n = 10 (hardness test).*

vitro dissolution studies. The statistical analysis of the parameter dissolution efficiency[20] of dissolution data (Table 2), floating behavior and drug content (Table 3) after storage at 45 °C and 75% RH for three months showed no significant change by Student's *t*-test indicating that BFT formulation (RC3) could provide a minimum shelf life of 2 years.

CONCLUSIONS

The present study was carried out to develop the floating drug delivery with controlled release of captopril using HPMC, K-grade polymer as a carrier. *In vitro* dissolution studies showed controlled release for 12 hrs, followed by the Higuchi diffusion mechanism and *in vivo* studies indicated increased GRT. Thus, results of the current study clearly indicate, a promising potential of the captopril floating system as an alternative to the conventional dosage form.

However, further clinical studies are needed to assess the utility of this system for patients suffering from hypertension. Bilayer floating matrix tablet of captopril give good floating and a controlled release. *In vitro* release rate studies showed that the maximum drug release was observed in RC3 formulations upto 12 hrs.

From the present study, it is evident that a promising controlled release bilayer floating tablets of captopril can be developed. Further detailed investigations are required to establish efficacy of these formulations.

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