

Design and evaluation of bilayer floating tablets of captopril

ZIYAUR RAHMAN*
MUSHIR ALI
RK KHAR

*Department of Pharmaceutics
Faculty of Pharmacy
Hamdard University
New Delhi-110062, India*

The objective of the present investigation was to develop a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behavior 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 24 h *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. Placebo formulation containing barium sulphate in the release layer administered to human volunteers for *in vivo* X-ray studies showed that BFT had significantly increased the gastric residence time.

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Development of oral controlled-release systems has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable. 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 one. 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).

* Correspondence, e-mail: ziyaur_rahman2@rediffmail.com

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 6–8 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 (5). The present investigation aims to develop a BFT of captopril with a view of prolonging GRT with a controlled release mechanism.

EXPERIMENTAL

Materials

Captopril (99.98% purity, Batch No-C10604) was obtained as a gift sample from Lupin Pharmaceuticals, India. HPMC-K4M and HPMC-K15M were obtained from the Dabur Research Foundation, India. Ranbaxy Laboratories Ltd., India, kindly donated HPMC-K100M, Carbopol 934p and PVP-K30. 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 citric 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 single tableting hand press with a 12-mm flat plain punch diameter (Cadmach Machinery, 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 $(49.0\text{--}58.8) \times 10^4 \text{ N m}^{-2}$ on a Monsanto Hardness Tester (Nirmal Instrument, India). The mass of floating layer was $200 \pm 10 \text{ mg}$.

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 I. 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 (FD2) 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 kN m^{-2} . Each BFT formulation was compressed (100 tablets) and subjected to testing for mass variation ($n = 20$), hardness ($n = 10$), drug content ($n = 6$), floating behavior ($n = 6$), and *in vi*

Table I. Composition of captopril BFT

Layer	Formulation code	HPMC-K100M (mg)	Citric acid (mg)	Sodium bicarbonate (mg)	HPMC-K15M (mg)	Captopril (mg)	PVP-K30 (mg)	Carbopol-934p (mg)
Floating	FD2	160	20	20	–	–	–	–
Release	RH1	–	–	–	25.0	25	–	–
	RH2	–	–	–	50.0	25	–	–
	RH3	–	–	–	75.0	25	–	–
	RH4	–	–	–	100.0	25	–	–
	RH5	–	–	–	125.0	25	5.0	–
	RJ1	–	–	–	120.0	25	12.5	–
	RJ2	–	–	–	112.5	25	20.0	–
	RJ3	–	–	–	105.0	25	27.5	–
	RJ4	–	–	–	97.5	25	35.0	–
	RJ5	–	–	–	90.0	25	5.0	–
	RK1	–	–	–	75.0	25	5.0	12.5
	RK2	–	–	–	75.0	25	5.0	25.0
	RK3	–	–	–	75.0	25	5.0	37.5

tro dissolution ($n = 3$). Hardness of the tablets ranged from $(49.0\text{--}58.8) \times 10^4 \text{ N m}^{-2}$ on a Monsanto Hardness Tester and the thickness was of $3.78 \pm 0.13 \text{ mm}$.

Floating behavior

Floating behavior studies were performed on both the floating layer and BFT, carried out in a USP 23 paddle apparatus 2 (10) at a paddle speed 50 rpm in 900 mL SGF (pH 1.2, no enzyme) at $37 \pm 0.2 \text{ }^\circ\text{C}$ for 24 h to mimic *in vivo* conditions. 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 (10) under sink condition. The dissolution medium was 900 mL SGF (pH 1.2, no enzyme) at $37 \pm 0.2 \text{ }^\circ\text{C}$; paddle speed 50 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 24 h. 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 × 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 (RK3), 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.

In vivo X-ray studies

The *in vivo* X-ray studies were approved by the institutional ethical committee vide project No. JH/Pharmaceutics/11/2002 and performed on 10 healthy human volunteers (Majeedia Hospital, Delhi, India). Volunteers aged 18–25 years and weighing 50–60 kg were selected for these studies. Before participation of human volunteers in these studies, a written consent was obtained from them and an expert radiologist and physician supervised the studies. BFT (RK3) was modified by adding 20 mg X-ray grade barium sulfate (this amount was determined experimentally to allow X-ray visibility but not to shun floatation of the tablet) in the release layer and excluding the captopril. A labeled tablet was given to every subject with 200 mL water after overnight fasting (water was available *ad libitum*) and after an hour interval a glass of water was given to the subject, after tablet ingestion. Gastric radiography was done at 0, 2, 4, 6 and 8 h. Duration of the tablet in the stomach was determined.

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. There-

fore 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 24 h. The optimized floating layer formulation (FD2 shown in Table I) had the floating lag time of 3 min, good matrix integrity and floating duration of more than 24 h. 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 (FD2) and release layer containing captopril (25 mg) and various polymers alone and/or in combination. BFT containing HPMC-K15M in the release layer (RH1, RH2, RH3, RH4 and RH5) 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 (RJ1, RJ2, RJ3, RJ4 and RJ5) 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 (RK1, RK2, and RK3) 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 pK_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

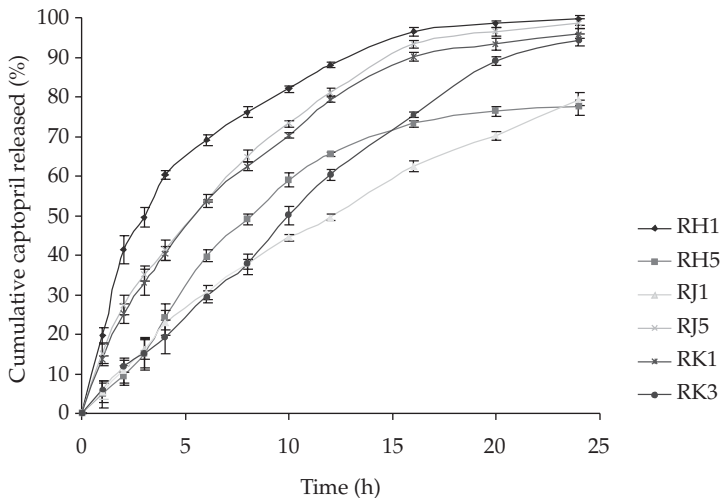


Fig. 1. Cumulative percentage of captopril released *versus* time (mean \pm SD, $n = 3$).

(18)]. The RK3 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 (RK3) 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 g cm⁻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 (RK3) 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.

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 (13) for stability testing of products intended for the global market. After storage, the formulation was subjected to a drug assay, floating behavior and *in vitro* dissolution studies. The statistical analysis of the parameter dissolution efficiency (20) of dissolution data (Table II), floating behavior and drug content (Table III) after storage at 45 °C and 75% RH for three months showed no significant change by Student's *t*-test indicating that BFT formulation (RK3) could provide a minimum shelf life of 2 years.

Table II. Captopril released from optimized BFT (RK3)

Time (h)	Captopril released (before storage, %) ^b	Captopril released (after storage, %) ^{a,b}
2	12.0 ± 0.4	11.4 ± 1.6
4	19.2 ± 1.8	18.0 ± 2.9
6	29.5 ± 2.3	29.4 ± 4.9
8	37.8 ± 0.8	37.9 ± 4.3
10	50.1 ± 1.2	49.8 ± 3.4
12	60.4 ± 4.3	59.5 ± 0.8
14	67.4 ± 3.3	65.9 ± 1.6
16	75.3 ± 4.3	74.6 ± 2.4
18	81.5 ± 2.2	80.5 ± 3.9
20	89.2 ± 1.3	87.9 ± 1.6
22	92.8 ± 1.8	91.2 ± 4.3
24	94.4 ± 4.8	92.5 ± 1.5

^a Storage at 45 °C/75% RH for three months.

^b Mean ± SD, $n = 3$.

Table III. Characteristics of optimized captopril BFT (RK3)

	Drug (%) ^b	Hardness ×10 ⁴ (N m ⁻²) ^b	Floating behavior		
			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).



Fig. 2. X-ray radiogram of abdomen 6 h after ingestion of optimized placebo BFT formulation.

After ingestion of the final placebo formulation developed by using barium sulphate in the release layer, the duration the tablet in the stomach and upper part of the intestine was monitored by radiograms (Fig. 2). It was found that the tablet stayed in the stomach for 6.4 ± 0.8 h.

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 24 h, 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.

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S A Ž E T A K

Dizajniranje i evaluacija dvoslojnih plutajućih tableta kaptoprila

ZIYAUR RAHMAN, MUSHIR ALI i RK KHAR

U radu je opisana priprava dvoslojnih plutajućih tableta (BFT) kaptoprila metodom izravne kompresije. Plutajući dio tablete izrađen je iz HPMC, K-sloja i efervescentne smjese limunske kiseline i natrijevog bikarbonata. Sloj s aktivnom supstancijom sadrži kaptopril i različite polimere kao što su HPMC-K15M, PVP-K30 i Carbopol 934p, sam ili u smjesi s ljekovitom tvari. Sposobnost plutanja i *in vitro* oslobađanje ispitivano je u aparaturi 2 prema USP 23 u simuliranom želučanom soku (bez enzima, pH 1,2). Iz pripremljenih tableta oslobodilo se približno 95% ljekovite tvari tijekom 24 h u navedenim *in vitro* uvjetima, a zastojno vrijeme bilo je 10 min. Tablete su plutale tijekom cijelog pokusa. Pripravak je slijedio Higuchijev model oslobađanja. Za vrijeme skladištenja na 45 °C/75% RH nisu uočene nikakve značajne promjene u izgledu, sadržaju ljekovite tvari, sposobnosti plutanja i oslobađanju kaptoprila u *in vitro* uvjetima. Placebo pripravci s barijevim sulfatom u sloju za oslobađanje davani su volonterima. *In vivo* pokusi s rentgenskim zračenjem pokazali su da BFT pripravci imaju značajno produženo vrijeme zadržavanja u želucu.

Ključne riječi: dvoslojne plutajuće tablete, HPLC, Higuchi, rentgensko zračenje