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DESIGN AND EVALUATION OF GASTRO-RETENTIVE FLOATING TABLETS OF CAPTOPRIL

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ABSTRACT

In the present investigation, an attempt has been made to increase therapeutics efficacy, reduce frequency of administration and improve patient compliance by developing sustained release gastro retentive floating tablets of captopril using hydrocolloids like hydroxyl-propyl methylcellulose and Carbopol 934P by effervescent technique using direct compression method. The prepared tablets were evaluated in terms of their physical characteristics, *in vitro* release, buoyancy, buoyancy lag-time and swelling index. The results of the *in vitro* release studies showed that the optimized formulation sustained drug release for 24 h and tablets remained buoyant for more than 24 h. When these dissolution profiles were subjected to various kinetic release investigations and it was observed that the mechanism of drug release was diffusion controlled with a minor contribution from polymeric relaxation. It was found that optimized formulation showed no significant change in physical appearance, drug content, floatability and *in vitro* dissolution pattern after storage at 45 °C/75% RH for three months.

KEYWORDS

Captopril, HPMC, Carbopol934P, Gastro retentive floating tablets, Buoyancy.

INTRODUCTION

The oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems, including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8–12 h) and the existence of an absorption window in the upper small intestine for several drugs[1,2]. These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period [3, 4]. Attempt are being made to develop a controlled drug delivery system which can provide therapeutically effective

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plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady-state by delivering the drug in a controlled and reproducible manner [5]. Different methodologies have been reported in the literature to increase the gastric retention of drugs, like intra-gastric floating systems, hydrodynamically balanced systems, extendable or expandable and superporous biodegradable hydrogel system[6]. Floating drug delivery systems (FDDS) or hydrodynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. While the system is floating on the gastric contents the drug is released slowly at a desired rate from the system. After the release of drug residual system is emptied from the stomach. This results in increase in the gastric residence time and a better control of fluctuation in plasma drug concentration [7, 8]. It has been suggested for the following instances that an active material should be formulated in the form of an floating drug delivery systems 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 [9]. Captopril is 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 [10]. It is most stable at pH1.2 and as the pH increases, it becomes unstable and undergoes a degradation reaction [11]. Hence there is a need for system that resides in the stomach over a relatively long period of time and releases the active compound there in sustained manner. This necessitated the design and development of sustained release Gastroretentive drug delivery system for Captopril using suitable polymers. The aim of the present study is not only develop a floating system but also to release the drug in controlled fashion.

MATERIALS AND METHODS

Captopril was obtained as a gift sample from Micro Laboratories, Banglore, India. HPMC-K15M, HPMC-K100M and Carbopol 934p were obtained as a gift sample from the Colorcon Asia Pvt. Ltd., Goa, India. All other materials and solvents used were of analytical grade.

(i) Preparation of Floating tablets of Captopril :

The composition of different formulations of captopril floating tablets is shown in Table 1. Effervescent Floating tablets containing captopril were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, magnesium stearate was added as post lubricant and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine.

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Table 1

Formulation Design

Ingredient	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Captopril	25	25	25	25	25	25	25
HPMC K15M	225	-	-	50	50	50	50
HPMC K100M	-	225	-	200	200	200	200
Carbopol 934P	-	-	225	50	50	50	50
Lactose	-	-	-	-	80	-	40
Microcrystalline Cellulose	-	-	-	-	-	80	40
Sodium bicarbonte	40	40	40	40	40	40	40
Citric acid	30	30	30	30	30	30	30
PVP K30	10	10	10	10	10	10	10
Mag. Stearate	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5

(ii) Evaluation of granules :

Angle of Repose

Flow property of the granules was evaluated by determining the angle of repose and the compressibility index. Static angle of repose was measured according to fixed funnel method and free standing cone method of Banker and Anderson[12]. The angle of repose was calculated using the equation,

$$\tan \theta = h/r \quad \ldots\ldots\ldots\ldots (1)$$

Bulk density

Loose bulk density (LBD) and Tapped bulk density (TBD) were determined for the prepared granules. LBD and TBD was calculated using the formula,

LBD = Wt of Powder / Vol. of Powder …….. (2)

TBD = Wt of Powder / Tapped Vol. of Powder… ….. (3)

Compressibility Index[13]

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Carr's Compressibility Index for the prepared granules was determined by the equation,

Carr's Index (%) = TBD – LBD/TBD x 100 … … (4)

(iii) Evaluation of Tablets :

Tablets from all the formulations were evaluated for its various properties like hardness by using hardness tester (VanKel K200), friability by using Roche friabilator and weight variation by using electronic balance. The results were given in Table 2.

Table 2

Characterization of powder blend and captopril tablets

Preparation	Parameters	F1	F2	F3	F4	F5	F6	F7
I. Power Blend	Bulk density (g/ml)	0.391	0.431	0.446	0.373	0.362	0.352	0.368
	Tapped density (g/ml)	0.463	0.521	0.568	0.446	0.431	0.417	0.439
	Angle of repose (θ)	25.61	25.07	24.68	24.5	23.82	23.49	30.05
	% Compressibility	15.63	17.24	21.42	16.42	15.94	15.49	16.17
	Hausner ratio	1.172	1.196	1.164	1.17	1.135	1.14	1.207
II. Tablets	Weight variation* (%)	345 ±0.95	345 ±0.83	345 ±1.09	420 ±1.21	500 ±1.72	500 ±1.93	500 ±1.69
	Friability* (%)	0.73 ±0.01	0.76 ±0.14	0.79 ±0.11	0.74 ±0.02	0.78 ±0.07	0.80 ±0.09	0.69 ±0.10
	Hardness* (N)	60.0 ±2.83	64.0 ±3.12	62.0 ±4.02	61.0 ±3.53	62.3 ±4.21	64.3 ±3.88	63.5 ±4.06
	Content Uniformity*(%)	99.2 ±0.66	99.06 ±1.03	100.21 ±1.52	101.2 ±0.87	99.65 ±0.69	99.36 ±1.13	100.2 ±0.84
	Buoyancy lag time* (s)	38 ±6.06	40 ±5.66	35 ±5.12	33 ±4.18	50 ±3.45	40 ±4.04	30 ±4.27
	Total floating time* (h)	> 24 h	> 24 h	> 24 h	> 24 h	> 24 h	> 24 h	> 24 h
	Swelling chacteristics (%)	139.11	151.98	189.9	159.95	165.98	178.17	184.02

**All values are expressed as mean ± SD, (n=3)*

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(iv) Drug content estimation:

Twenty tablets from each batch were crushed in a mortar and the powder equivalent to 100 mg Captopril was shaken with 100ml of 0.1 N HCL in 100ml volumetric flask and from this 5 ml is pipette out and diluted up to 100 ml with 0.1 N HCL. From the standard solution again 5 ml sample was pipette out and diluted up to 100 ml with 0.1 N HCL. Resulting solution was filtered and assayed at 206 nm using UV-visible spectrophotometer (Shimadzu 1601, Shimadzu Corporation, Kyoto, Japan)[14].

(v) In Vitro Buoyancy studies :

In Vitro buoyancy studies was performed for all the seven formulations as per the method described by Rosa *et al* [15]. The randomly selected tablets from each formulation was kept in a 100 ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time.

(vi) In Vitro Dissolution studies :

The *in vitro* dissolution studies was carried out in 900 ml of simulated gastric fluid, pH 1.2 (enzyme free) using USP XXII Dissolution test apparatus employing paddle stirrer. One tablet was placed inside the dissolution medium and the paddle was rotated at 75 rpm. 5ml samples were withdrawn at specific time intervals and the same volume was replaced to maintain sink conditions. The samples were analyzed for drug content spectrophotometrically at 206nm.

(vii) Swelling Characteristic[16, 17] :

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet. From each formulation, one tablet was weighed and placed in a dissolution test apparatus, in 900 ml of enzyme free simulated gastric fluid at 37 ± 0.5°C. After predetermined time interval the tablet was removed from apparatus, blotted to remove excess water and weighed.

The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation 5

$$WU\% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100 \quad \text{----------} \quad (5)$$

(viii) Stability Studies :

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines.[18] Optimized formulation F7, 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

The effervescent floating tablets of captopril were formulated in seven different formulation F1 to F7 by using HPMC K100M, K15M and carbopol

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934P polymer along with effervescing agent sodium bicarbonate and citric acid using direct compression technique. The values of pre-compression parameters evaluated were within prescribed limit and indicated good free flowing property (Table 2). Angle of repose ranged from 23.49 to 30.05 and the compressibility index ranged from 15.49 to 21.42. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property. The prepared tablets of all the formulations were evaluated for their post compression parameters like hardness, friability, weight variation, buoyancy lag time, total floating time, drug content and in-vitro drug release and are showed in table 2. The measured hardness of tablets of each formulation ranged between 60.0 ±2.83 to 64.3 ±3.88 N. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits. The drug content estimations showed values in the range of 99.06 ±1.03 to 101.2 ±0.87 % which reflects good uniformity in drug content among different formulations. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. Floating lag time (FLT) and total floating time (TFT) of different formulation were noted. All formulations showed good floating lag time ranged between 30±4.27 to 50±3.45 sec. Total floating time (TFT) for all the formulations was found to be more than 24 hours.

DISCUSSION

1. In Vitro Dissolution studies:

All the formulations were subjected to *In vitro* dissolution studies. The influence of type of filler over floating property, swelling behavior and drug release were studied. All the formulations contained equal amount of gas generating agent (sodium bi carbonate and citric acid). The formulation up on contact with HCl liberates CO2 and expels from the dosage from creating pores through which water can penetrate into dosage form and the rate of wetting of polymer increases. The results of *in vitro* percentage release at different time intervals is plotted against time to obtain release profile (Fig.1) From the *in vitro* drug release studies, it was concluded that formulation having combination of polymers (F4, F5, F6, F7) showed more release retardant effect when compared to other formulations prepared with polymer alone (F1 F2 and F3). Formulation F1, F2 and F3 released 98.42%, 96.22%, and 95.65% of captopril respectively at the end of 16hrs while the batch F4, F5, F6 and F7 released 85.33%, 91.21%, 95.4% and 98.14% of captopril respectively at the end of 24hrs.

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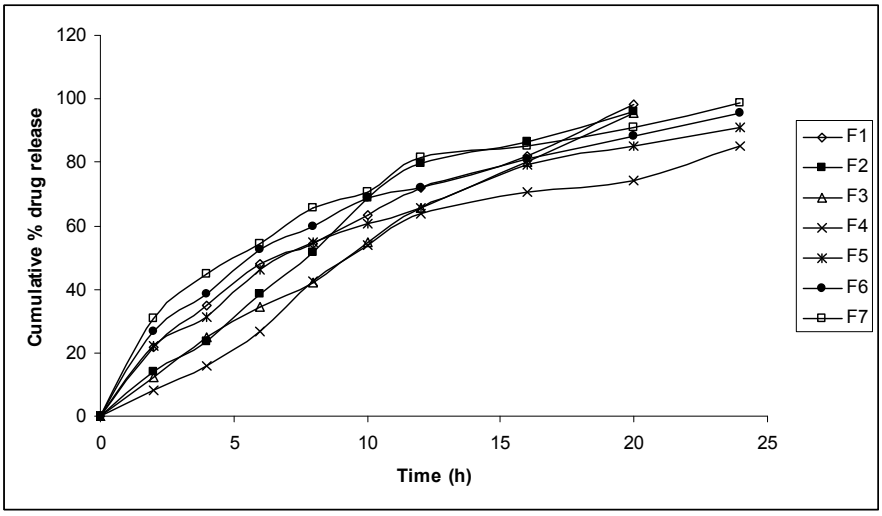
Fig.1

In vitro drug release profile of all formulations



From the swelling study it was observed that the higher swelling index was found for tablet with combination of HPMC K15M, K100M and Carbopol. It was also observed that fillers had significant influence over the swelling and erosion properties of the tablets. Tablets F5 prepared with water soluble lactose showed less swelling index as compared with Tablets F6 prepared with water insoluble MCC, because lactose has the tendency to leach out from the tablet when comes in contact with water. While with MCC swelling phenomenon was found to be dominating over the erosion, which might be due to the tendency of the MCC to form tight gel barrier around the hydrophilic matrix. The Effect of combination of hydrophilic and hydrophobic fillers were also studied (F7), which didn't show any drastic influence over swelling and erosion phenomenon.

From the in vitro dissolution study it was also cleared that water-soluble fillers (F5) showed release rate enhancing effects whereas water insoluble fillers (F6) showed release retardant effect. Further batch F7 was prepared to study the influence of the combination of the hydrophilic and hydrophobic fillers over the drug release, an intermediate release pattern was observed due to leaching action of Lactose compared to that observed with F5 and F6. From the overall observations of different evaluative studies, formulation F7 was selected as best and optimized on the basis of floating parameters, water uptake study and in vitro drug release study.

Hydration and porosity are two essential features for a tablet to remain buoyant on gastric fluid. The compression of tablets to a high degree of hardness may result in a reduction in porosity; moreover, the compacted hydrocolloid particles on the tablet surface do not hydrate rapidly affecting the floating capacity of the tablet significantly. Therefore, the effect of tablet hardness on the buoyancy of dosage forms was also studied. Increasing the hardness of tablets of batch F7 from 60 N to 80 N results in drastic increased in buoyancy lag-time. These results show that a lower hardness results in

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tablets with a higher porosity that facilitates water penetration while the subsequent effervescent reaction results in buoyancy.

2. Release Kinetics Analysis :

To analyze the mechanism of the drug release rate kinetics of the dosage form, the drug release data of batch F7 was fitted to various models like Zero order, Higuchi's model and Korsmeyer's model. The slope and r2 are shown in table 3. Optimized formulation F7 fitted best for Higuchi model with regression value 'r^2' was 0.9841. Further to know the exact mechanism of drug release data of batch F7 was fitted to Korsmeyer's model. Slope value ($0.5<n<1.0$) suggest that the release of captopril from floating tablets followed Fickian transport mechanism.[19,20]

Table 3
Drug release kinetic parameters of optimized formulation F7

Model	R^2	Slope
First order	0.9348	-0.0635
Higuchi model	0.9841	20.384
Korsemeyer - Peppas model	0.9847	0.4666

In view of the potential utility of the formulation, stability studies were carried out on optimized formulation F7 at 45 °C and 75% RH for three months 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 vitro* dissolution studies. The stability study showed no significant change after storage at 45 °C and 75% RH for three months (table 4) indicating that formulation (F7) could provide a minimum shelf life of 2 years.

Table 4
Characteristics of optimized formulation F7 before and after storage

	Content uniformity (%)	Hardness (N)	Buoyancy lag time (s)	Total floating time (h)	Drug release (%)
Before storage	100.2 ±0.84	63.5 ±4.06	30±4.27	> 24 h	98.65
After storage	99.2 ±1.12	60.5±2.21	32±5.27	> 24 h	97.14

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CONCLUSION

The present study was carried out to develop the floating drug delivery with controlled release of captopril to provide an effective and safe therapy for hypertention with a reduced dose and reduced length of treatment. *In vitro* dissolution studies of optimized F7 tablets formulation showed controlled release of captopril for 24 h by maintaining the buoyancy. Thus, results of the current study clearly indicate, a promising potential of the captopril floating system as an alternative to the conventional dosage form.

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REFERENCES

1. Agyilirah GA, Green M, Ducret R, Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablets, Int. J. Pharm., 75: 241-247, (1991).
2. Hoffman AF, Pressman JH, Code CF, Controlled entry of orally administered drugs: physiological considerations. Drug Dev. Ind. Pharm., 9: 1077-1085, (1983).
3. Deshpande AA, Rhodes CT, Shah NH, Controlled release drug delivery systems for prolonged gastric residence: an overview. Drug Dev. Ind. Pharm., 22: 531-539, (1996)
4. Hwang SJ, Park H, Park K, Gastric retentive drug delivery systems. Crit. Rev. Ther. Drug, 15: 243-248, (1998).
5. Sood A, Panchagnula R, Design of controlled release delivery systems using modified pharmacokinetic approach: a case study for drugs having a short elimination half life and a narrow therapeutic index, Int. J. Pharm., 261: 27-41, (2003).
6. Singh BN, Kim KH, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, J. Control. Release, 63: 235-259, (2000).
7. Talukder R, Fassinir R, Gastroretentive Delivery System: Hollow beads, Drug Dev Ind Pharm., 4: 405-12, (2004).
8. Klausner EA, Lavy E, Friedmon M and Hoffman A, Expandable gastroretenstive dosage forms. J Control Release, 90: 143-62, (2003).
9. Uzdemir N, Ordu S, Ozkan Y, Studies of floating dosage forms of furosemide: in vitro and in vivo evaluation of bilayer tablet formulations, Drug Dev. Ind. Pharm., 26: 857–866, (2000).
10. Ziyaur R, Mushir A, Khar RK, Design and evaluation of bilayer floating tablets of captopril, Acta Pharm, 56: 49-51, (2006).
11. Anaizi NH, Swenson C, Instability of captopril solution, Am. J. Hosp. Pharm., 50: 486–488, (1993).
12. Banker GS, Anderson NR, Tablets. In: Lachman L, Lieberman HA, Kanig JL, (eds.), The Theory and Practice of Industrial Pharmacy, 3rd ed. Varghese Publishing House, Mumbai,1984, pp. 283.
13. Carr R L, Evaluating flow properties of solids, Chem. Engg., 18: 163-168, (1965).

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14. United States Pharmacopia", XXIV NF 19, United State Pharmacopia Convention, Rockville, 2000, pp. 263-264.
15. Rosa M, Zia H, Rhodes T, Dosing and testing in vitro of a bioadhesive and floating drug delivery system for oral application, Int. J Pharm., 105: 65-70, (1994).
16. Senapati MK, Srinatha A, Pandit JK, In vitro release characteristics of matrix tablets: study of karaya gum and guar gum as release modulators, Int. J. Pharm. Sci., 68: 824-826, (2006).
17. El-Gibaly I, Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres, Int.J.Pharm., 249: 7-21, (2002).
18. Mathews BR, Regulatory aspects of stability testing in Europe, Drug Dev. Ind. Pharm., 25: 831–856, (1999).
19. Higuchi T. Mechanism of sustained action medication, Theoritical analysis of rate release of solid drugs dispersed in solid matrices, J Pharm Sci., 52: 1145-1149, (1963).
20. Korsmeyer RW, Gunny R, Peppas NA, Mechanism of solute release from porous hydrophilic polymers, Int J Pharmaceutics, 15: 25-35, (1983).