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Brief/Technical Note

Design and Evaluation of a Sustained Release Gastroretentive Dosage Form of Captopril: A Technical Note

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INTRODUCTION

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 release preparations using alternative routes have been formulated but the oral route still remains preferable.

Amongst the various approaches to target the drug to the stomach or proximal region of small intestine, high density systems have a technical difficulty in formulating a dosage form having a density in the range of 2.4–2.8 g/cm^3, swelling systems require an optimum balance between the rate of swelling and rate of erosion of the polymer to avoid unwanted side effects and bio/mucoadhesive systems which can be dislodged from its site of adhesion, may not provide the optimum benefits.

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 on the gastric fluid, prolonging gastric residence time (GRT). This floating dosage form is well known as a hydrodynamically balanced system (HBS) (1,2,3). It has been suggested for the following instances that an active material can be formulated as an HBS to enhance bioavailability: (1) having a dissolution and/or stability problem in the small intestinal fluids, (2) being locally effective in the stomach, (3) 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). Floating systems can be developed by two approaches. First is the effervescent system which needs a gas generating agent that may alkalinize the microenvironment of the stomach and whose buoyancy would be dependent on the gas generating agent unlike the second which is a non-effervescent approach.

CAP, 1-[(2*S*)-3-mercapto-2-methyl-1-oxopropyl]-L-proline, is an angiotensin converting enzyme inhibitor. It has been widely used for the treatment of hypertension and congestive heart failure. It has been reported that the duration of antihypertensive action after a single oral dose of CAP 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 present investigation aims to develop a sustained release non-effervescent floating matrix tablet of CAP with a view of prolonging GRT as well as avoiding intestinal degradation.

EXPERIMENTAL

Materials

CAP was obtained as a gift sample from M. J. Biopharm, India. HPMC K15MCR, HPMC K100MCR and Ethyl Cellulose (EC) were received as gift samples from Colorcon, India. Other materials and solvents used were of analytical grade. All the studies were carried out using double distilled water.

Preparation of Floating Tablets

Formulations fulfilling minimum requirement are shown in Table I. For each formulation CAP, lactose, HPMC K15MCR and/or K100MCR were manually blended homogeneously with a mortar. The mixture was wetted using either isopropyl alcohol (IPA) or alcoholic solution of PVP K-30 or EC, passed through a 10 mesh screen, and dried in a hot air oven at 40°C overnight. The 20/40 fraction granules were collected and blended with talc. The homogeneous blend was then compressed into tablets on a single-punch tablet press

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ABBREVIATIONS: CAP, captopril; EC, ethyl cellulose; FLT, floating lag time; FT, floating time; GRT, gastric residence time; HBS, hydrodynamically balanced system; HCl, hydrochloric acid; HPLC, high performance liquid chromatography; HPMC, hydroxypropyl methylcellulose; IPA, isopropyl alcohol; PVP K-30, poly vinyl pyrollidone K-30; RH, relative humidity; SGF, simulated gastric fluid.

Table I. Formulation Ingredients of CAP Floating Tablets

Ingredients	Formulation						
	F1	F2	F3	F4	F5	F6	F7
CAP	100	100	100	100	100	100	100
HPMC K15MCR*	400	–	400	–	400	–	200
HPMC K100MCR*	–	400	–	400	–	400	200
PVP K-30	–	–	30	30	–	–	–
EC	–	–	–	–	20	20	20
Lactose	94	94	64	64	74	74	74
Talc	6	6	6	6	6	6	6
Total	600	600	600	600	600	600	600

equipped with 12.5 mm diameter flat punches. The tablet hardness was in the range 30–40 N on a Monsanto tablet hardness tester.

In Vitro Buoyancy Studies

The *in vitro* buoyancy was determined by FLT as per the method described by Rosa *et al.* (8) The tablets were placed in a 100-ml glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT). The total floating duration was also determined.

In vitro Drug Release

The dissolution test was carried out using USP XXIII dissolution testing apparatus II (paddle method). The test was performed at a paddle speed of 50 rpm using 900 ml of 0.1 N HCl as the dissolution medium, at 37±0.5°C (9). An aliquot of 5 ml of the sample solution was withdrawn at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 20 and 24 h interval; and the absorbance was measured by using UV-visible spectrophotometer at 212 nm after appropriate dilution.

Optimization

Formulation which showed good tablet integrity, appearance, low friability, no FLT, floating time (FT) of more than 24 h and drug release without initial burst effect was optimized using Statease Design Experts 7.1. Two factors were selected each at three levels and experimental trials were performed on all nine combinations. Amount of HPMC (X_1) and Amount of EC (X_2) were selected as independent variables. The FLT, time for 25 % drug release ($T_{25\%}$) and time for 80% drug release ($T_{80\%}$) were selected as dependent variables. The optimized formulation so obtained was further subjected to following evaluation tests.

Effect of pH and Osmolarity on Floating Behavior

Floating behavior of the tablet was studied at various pH and osmolar conditions. One hundred milliliters of acetate buffer pH 1.2, 4 and 6 were used to study the effect of pH and 100 ml of Hyper-osmolar (400 Osm), iso-osmolar (308 Osm) and hypo-osmolar (200 Osm) (10) solutions were used to observe the changes in floating behavior due to osmolar changes.

Determination of Swelling Behavior

The swelling behavior of tablets was determined in 0.1 N HCl (pH 1.2), SGF and different osmolar solutions at room temperature. The percent increase in diameter and thickness of the tablets were calculated and plotted against time to assess the swelling behavior.

The swelling indices were calculated by the following equations: (11)

$$\%\ \text{increase in diameter} = \frac{\text{diameter at time } t - \text{diameter at time } 0}{\text{diameter at time } 0} \times 100$$

$$\%\ \text{increase in thickness} = \frac{\text{thickness at time } t - \text{thickness at time } 0}{\text{thickness at time } 0} \times 100$$

Effect of pH and Osmolarity on Drug Release

This study was carried out to assess the effect of hyper-osmolar, iso-osmolar and hypo-osmolar conditions of the gastric contents on drug release. Dissolution profile was determined in hyper-osmolar (400 Osm), iso-osmolar (308 Osm) and hypo-osmolar (200 Osm) solutions (9), by following the same protocol as before. The dissolution profile was also determined in acetate buffer pH 1.2, 4 and 6.

Moisture Absorption Studies

Saturated solutions of different salts were prepared and placed into closed chambers. Chambers were allowed to equilibrate with the moisture to obtain different relative humidities (potassium carbonate—43.2 % RH, sodium chloride—75.3 % RH, potassium sulphate—97.3 % RH). Mesh of ≈1 mm pore size was placed above the surface (≈5 mm) of each salt solution. Three weighed tablets were placed on each mesh and chambers were closed. After specific time intervals the tablets were withdrawn and weighed. Graph of weight gain with respect to time were plotted.

RESULTS AND DISCUSSION

In vitro Buoyancy Studies

In vitro buoyancy of fabricated tablets was determined in 0.1 N HCl, and the results are presented in Table II. The tablets of batch F1 and F2 exhibited no FLT but quicker loss of integrity may be the reason for decreased floating duration.

Table II. Floating Behavior of Various CAP Formulations

Formulation code	FLT (s)	FT (h)
F1	0	18
F2	0	19
F3	0	22
F4	2	24
F5	2	>24
F6	3	>24
F7	0	>24

Both grades of HPMC are readily swellable polymers, made the tablets buoyant in less time. Incorporation of PVP K-30 and EC improved the integrity of tablets and increased their floating duration.

In Vitro Drug Release

The performance of floating formulations has been reported to be greatly affected by physiological conditions such as food transport, gastrointestinal motility, and so on.

Figure 1 shows *In vitro* drug release of various formulations. Initial formulations containing low concentration of polymer (HPMC K15MCR and HPMC K100MCR) showed poor tablet integrity and initial burst effect (data not shown). The results of dissolution studies of formulation F1 and F2 containing higher concentration of HPMC K15MCR and HPMC K100MCR respectively and prepared by using IPA as granulating fluid were as shown in Fig. 1. Formulations F1 and F2 showed initial burst release of 32% and 30% in first 0.5 h and 99% and 98% at the end of 18 h and 19 h respectively. Thus, different concentrations of HPMC K15MCR and HPMC K100MCR alone were not sufficient to decrease the initial burst effect and to give desired drug release pattern which is in accordance with observations made by Chivate *et al.* (12). Further formulations (F3, F4) were prepared by incorporating PVP K-30 in granulating fluid. The integrity of tablets was improved but the initial burst effect was not reduced. Next formulations (F5, F6) were tried with EC as secondary retardant in granulating fluid. Formulation F6 showed better control on initial burst effect than F5 but exhibited incomplete release which might be due to high viscosity of HPMC K100MCR. The formulation (F7) was made with the combination of HPMC K15MCR: HPMC K100MCR in the ratio 1:1 using IPA solution of EC as a binder. This formulation showed more than 96% drug release at the end of 24 h with better drug release pattern.

Optimization

Based on the results of optimization, formulation containing HPMC K15 MCR 200 mg, HPMC K100 MCR 200 mg as primary polymers and EC 20 mg as the retardant was devised as the optimized formula.

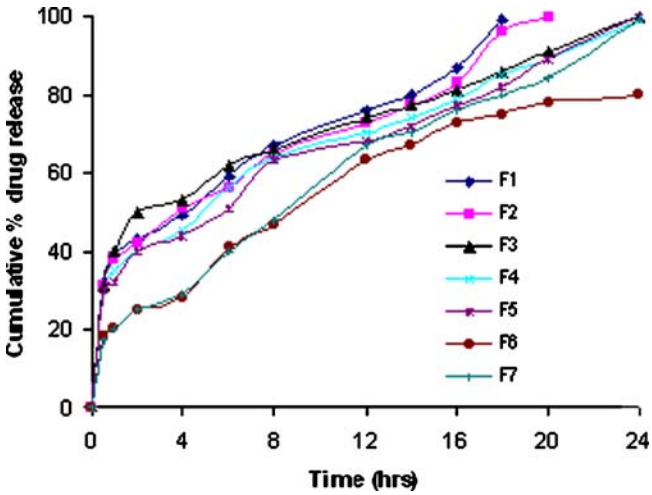

Fig. 1. Comparison of *in vitro* drug release profiles of floating formulations of CAP

Table III. Effect of pH and Osmolarity on Floating Behavior of CAP Tablets

Medium	FLT (s)	FT (h)
0.1 N HCl	0	≥24
SGF	0	≥24
Buffer pH 1.2	0	≥24
Buffer pH 4	0	≥24
Buffer pH 6	0	≥24
Hypo-osmolar solution (200 mmol/l)	0	≥24
Iso-osmolar solution (308 mmol/l)	0	≥24
Hyper-osmolar solution (500 mmol/l)	0	≥24

Effect of pH and Osmolarity on *In vitro* Buoyancy

The optimized formulation was subjected to study the effect of change in pH and osmolarity on floating behavior. From the results shown in Table III, it was concluded that the variations in pH and osmolarity due to change in the gastric contents might not affect the FLT and FT of the tablets

Determination of Swelling Behavior

Tablets composed of hydrophilic polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release as well as ensures floating (13,14). Food may induce changes in the environment and osmolarity of the gastric contents, which in turn may affect the swelling behavior of the formulation and hence the drug release. To eliminate this possibility, swelling behavior of the formulation was assessed in different osmolar solutions along with 0.1 N HCl and SGF.

It was observed that osmolarity or type of medium did not affect the swelling behavior of optimized tablets which contained 66.67 % of HPMC. The tablets showed good swelling until 6 h but after which due to saturation of high viscosity grade HPMC, swelling became gradual. This observation goes hand in hand with the results of Wan *et al.* who proved that the effect of HPMC concentration on swelling rates was less marked at higher polymer content (>50% HPMC of high viscosity grade) (15).

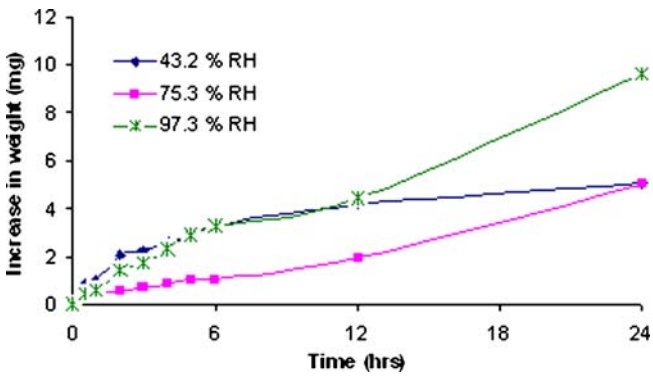

Fig. 2. Effect of % RH on weight gain by optimized formulation of CAP

Effect of Osmolarity and pH on Drug Release

As seen from the results of *in-vitro* buoyancy studies and swelling behavior, variations in the gastric contents might not affect the FLT and swelling behavior of the tablets and it might be assumed that the drug release may also remain unaffected. However it is important to know whether the drug release gets affected by change in osmolarity because of presence of food as this in turn might affect the bioavailability. Drug release was determined in different osmolar solutions. Thus concluding that, the variations in gastric environment would not have significant effect on drug release. Hence, it can be expected that *in-vivo* performance of formulation might not get affected by changes in osmolarity due to variation in food.

It is a known fact that food affects the pH of stomach. *In-vitro* drug release was carried out in buffers of pH 1.2, 4 and 6 to see the effect of pH on drug release. It was observed from present study that the tablets demonstrated pH-independent drug release.

Moisture Absorption Studies

Moisture absorption studies (Fig. 2) showed that at the end of 24 h the increase in weight at 43.2% RH, 75.3% RH and at 97.3% RH were 5, 5 and 10 mg respectively. The study proved that there was very less uptake of moisture (less than 2%), hence pointing to the fact that the tablets need no special precautions during packaging and storage.

Stability Studies

In view of the potential utility of the formulation, stability studies were carried out at 45°C and 75% RH for 3 months (climatic zone III condition for accelerated testing) to assess their long-term stability. The formulation was evaluated for drug content, *in vitro* dissolution studies and floating behavior. No significant changes were observed during stability studies with respect to percent drug content which was 99.2 at the end of 3 months as compared to 100.3 at the beginning, percent cumulative drug release after 24 h which decreased to 98 from its initial value of 101 and floating behavior.

SUMMARY AND CONCLUSION

The study was aimed at preparation of gastroretentive tablets of CAP. The non-effervescent-based floating approach was selected. The hydrophilic matrix containing HPMC K15MCR and HPMC K100MCR alone and in combination could not control the drug release pattern. Incorporation of hydrophobic polymer EC in granulation fluid showed good drug release pattern. *In vitro* drug release, *in vitro* buoyancy and swelling behavior remained unaffected by change in pH and osmolarity. The formulation was stable at 40°C/75% RH for three months. It was concluded that stable sustained release floating gastroretentive tablets of CAP with no FLT, FT greater than 24 h and desired drug release pattern could be successfully prepared.

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