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Research Article

Formulation and Evaluation of Floating Microspheres of Captopril for Prolonged Gastric Residence Time

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ABSTRACT

The present study was an attempt to develop floating microspheres of captopril to prolong its gastric residence time in stomach. Floating microspheres was formulated using biocompatible polymers like Eudragit S100 and Ethyl cellulose in different proportions by solvent evaporation technique. The prepared microspheres were evaluated for percentage yield, micromeritic properties, particle size, morphology, drug entrapment, buoyancy studies, *In vitro* drug release studies. Practical yield of the microspheres was up to 76.40%. The formulated microspheres were free flowing with good packing properties. Scanning electron microscopy confirmed spherical structure and the particles were of the size range of 57.66 to 93.21µm. The microspheres with Ethyl cellulose showed higher buoyancy when compared with Eudragit S-100. All formulation showed good *in vitro* percent buoyancy. *In vitro* release studies showed cumulative % drug release between 75.95-88.27%. *In vitro* release studies demonstrated non-Fickian diffusion of drug from the microsphere.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation[1].

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 semi-synthetic 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, and prolongs gastric residence time (GRT)[2].

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Single-unit formulations are associated with problem being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand, a floating system made of multiple unit forms has relative merits compared to a single unit preparation. On each subsequent gastric emptying, sunk particles will spread out over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way. Moreover, since each dose consists of many subunits, the risk of dose dumping is reduced[1].

Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been

extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing during emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; This floating dosage form enhance bioavailability, having a dissolution and/or stability problem in the small intestine fluids, being locally effective in the stomach, being absorbed only in the stomach and/or upper part of the intestine[3,4].

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. It is most stable at pH 1.2 and as the pH increases; it becomes unstable and undergoes a degradation reaction[2].

Thus a sustained and controlled release dosage form of captopril is desirable. Hence an attempt has been made to design a floating microsphere system of captopril using Eudragit S100 and Ethyl cellulose for prolonged gastric residence time and improve the release profile of drug.

MATERIALS AND METHODS

Captopril was obtained as a gift sample from Wochardt Ltd., Aurangabad. Eudragit S-100 was gift sample from Evonik Degussa India Pvt. Ltd., Mumbai. Ethyl cellulose was purchased from Himedia Laboratories Pvt. Ltd., Mumbai. All chemicals and reagents used were of analytical grade.

Preparation of floating microspheres

Floating microspheres were prepared by the solvent evaporation method[5] using 500 mg of Captopril and with different proportion of polymer as shown in Table 1 were dissolved in dichloromethane (5 ml) and this pasty, flowable mass was introduced into 50 ml of aqueous saline phase(0.9% Nacl) containing 0.04 % polyvinyl alcohol (20 mg) and 10% methanol (5 ml). The system is stirred using propeller at 300 rpm at room temperature for 2-3 h. The drug loaded floating microspheres formed were filtered, washed and dried in a hot air oven at 60^0C. The detailed composition of each formulation is given in Table 1.

Table 1: Formulation Design of Captopril Floating Microspheres

Batch Code	Polymer	Drug: Polymer	Dichloromethane: Methanol
F1	Eudragit S-100	1:1	1:1
F2	Eudragit S-100	1:2	1:1
F3	Eudragit S-100	1:4	1:1
F4	Ethyl cellulose	1:1	1:1
F5	Ethyl cellulose	1:2	1:1
F6	Ethyl cellulose	1:4	1:1

Evaluation of floating microsphere

Percentage yield

The prepared microspheres of all batches were accurately weighed. The weight quantity of prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres. It was calculated by using following equation[6],

Percentage yield =

$$\frac{\text{Actual yield of product}}{\text{Total weight of excipients and drug}} \text{ X } 100$$

Micromeritic properties

Micromeritic properties such as Carr's index % (% I_c) and Hausner's ratio (H_R) were characterized by using the following equations:

$$H_R = \rho_t / \rho_b$$
$$\% I_c = (\rho_t - \rho_b / \rho_t) \text{ x } 100$$

Where, ρ_t = tapped density, ρ_b = bulk density

The angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by the fixed funnel method, using the following equation:

$$\tan \theta = H/R$$

Where, H is the height of the heap that formed after making the microspheres flow from the glass funnel and R is the radius[7,8].

Particle size determination

Microsphere size was determined by using an optical microscope under regular polarized light, and the mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer[9].

Morphological study using SEM

The morphological study was carried out by Scanning Electron Microscope (SEM). Microspheres were scanned and examined under Electron Microscope HITACHI SU 1500, Japan connected with fine coat, JEOL JFC-1100E Ion sputter. The sample was loaded on copper sample holder and sputter coated with carbon followed by gold[9].

Drug entrapment and drug loading

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 212 nm against appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulae[6,10]:

Percentage drug loading =

$$\frac{\text{Weight of the drug loaded in the microspheres}}{\text{Total weight of the microspheres}} \times 100$$

Percentage drug entrapment =

$$\frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

***In vitro* buoyancy study**

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N HCl containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres.

$$\% \text{ Buoyancy} = Q_f / (Q_f + Q_s)$$

Where Q_f and Q_s are the weight of the floating and the settled microspheres respectively.

At predetermined time intervals the radiograph of the abdomen was taken using an X-ray machine[1,11].

***In-vitro* release study**

The drug release study from microsphere was performed using USP dissolution apparatus Type I in 900 ml of 0.1 N HCl dissolution media (pH-1.2) at 100 rpm and 37^0 C. 10 ml of sample was withdrawn at predetermined time interval for 12 h and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 212 nm[6,11,12].

RESULTS AND DISCUSSION

Captopril, an antihypertensive agent, with short half-life, low single dose administration and oral bioavailability is 65 %, was selected as a model drug to formulate a controlled release formulation with improved oral bioavailability by prolonging the gastric residence time.

Formulation of floating microspheres

Floating microspheres were successfully prepared for the delivery of Captopril to enhance absorption and bioavailability by increasing the gastric retention time. In concern to this approach, the primary necessity is to float the beads in gastric environment. In this study, six formulations were prepared. In each formulation, the polymer concentration was varied. Eudragit S-100 (a synthetic polymer) and Ethyl cellulose (a cellulose-based derivative) are biocompatible, hydrophobic polymers, which prolong the release of water-soluble and water insoluble drugs from their matrices. Incorporation of NaCl to the aqueous phase was necessary to prevent the dispersed phase from settling due to high density of dichloromethane, thereby making the dispersion and stabilization of the droplets by stirring difficult.

Percentage yield of all formulation F1 to F6 were calculated and results are shown in Table 2. The percentage yield slightly decreased as the ratio of polymer increased.

Table 2: Various Formulation Parameters for Captopril Floating Microspheres.

Formulation Code	% Yield	Average particle size (µm)	% Drug loading	% Entrapment efficiency	% Buoyancy	% Drug release after 12 hrs.
F1	76.40±2.06	57.66±7.27	38.36±0.39	76.72±2.57	86.67±1.65	84.20±0.62
F2	73.13±1.39	87.45±5.30	27.50±0.73	82.48±3.61	83.00±1.23	81.11±0.53
F3	68.84±0.84	93.20±9.63	18.18±0.61	90.90±1.07	79.33±1.41	75.95±0.78
F4	74.70±0.93	62.46±6.58	39.44±0.45	78.88±4.05	90.33±1.27	88.25±0.53
F5	72.33±2.37	66.30±8.43	28.30±0.36	84.89±3.84	87.33±1.72	84.42±0.48
F6	65.64±1.12	85.52±6.32	18.60±0.27	93.00±1.26	85.67±1.19	78.29±0.47

n=3, Mean ±SD

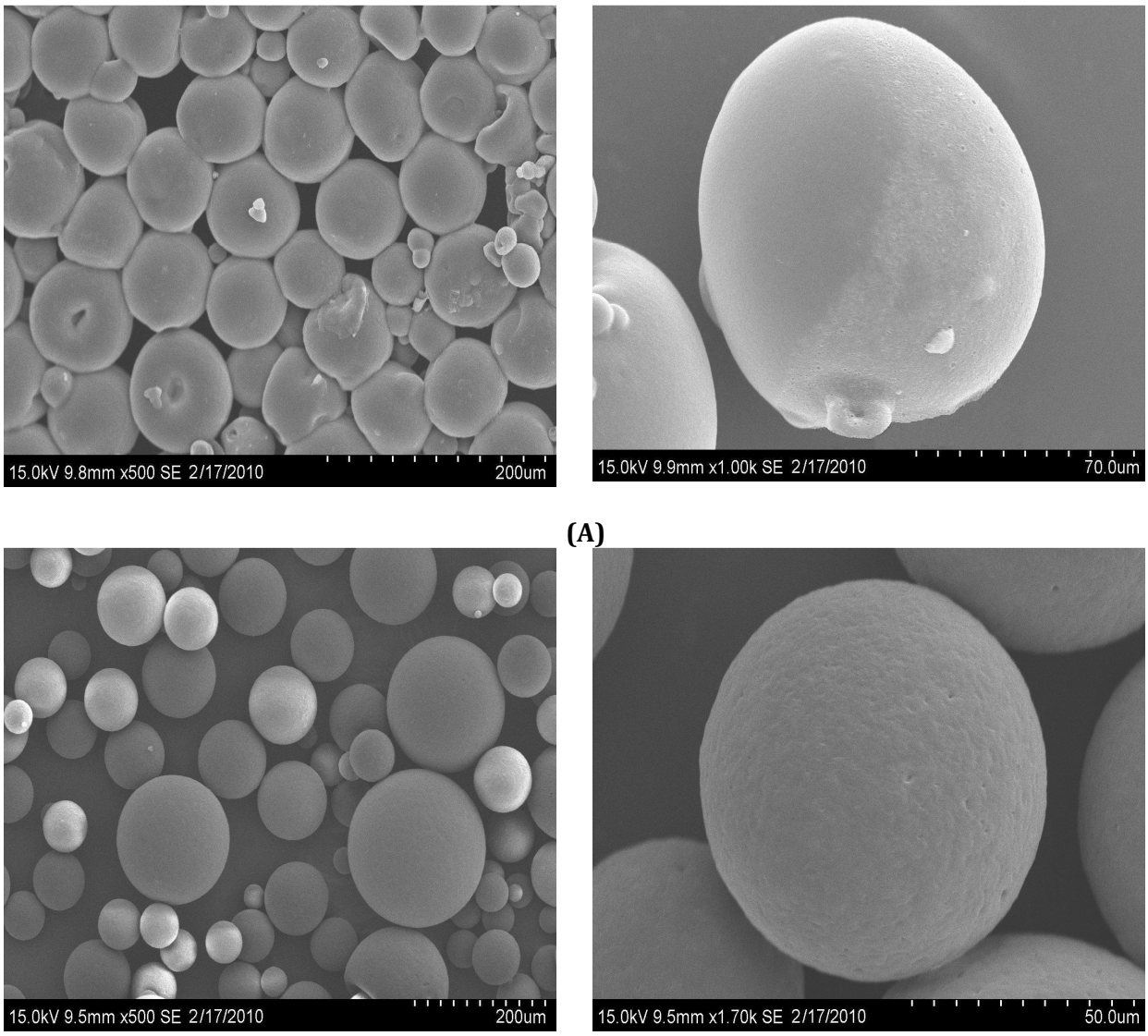

Figure 1: Scanning electron microphotographs of Captopril floating microspheres formulation F3 (A) and F6 (B)

Micromeritic Properties

All formulations F1 to F6 of Floating microspheres were evaluated for variable micromeritic parameters such as bulk density, tapped density, % Compressibility index, Hausner's ratio and angle of repose.

The % Compressibility index was in the range of 11-18 for all the formulations F1 to F6 indicating good flow property.

The value of Hausner's ratio for the all formulation F1to F6 was below 1.25 which indicates good flow property.

The values of angle of repose for formulations F1to F5 was found to be in the range of 25^{o}-30^{o} which indicated the good flow potential and the formulation F6 showed below 25^{o} which indicated excellent flow.

Particle size

Average particle size of microspheres as determined by optical microscopy by using stage micrometer and ocular micrometer is shown in Table 2. With increase in Eudragit S-100 and Ethyl cellulose concentration in the microspheres from F1 to F3 and F4 to F6, the particle size of microspheres increases respectively. This is because the viscosity of the polymer solution increases with increasing polymer concentration, which in turn decreases the stirring efficiency[5]. The polymer rapidly precipitates leading to hardening and avoiding further particle size reduction during solvent evaporation. The average particle size of Eudragit S-100 was greater due to the greater viscosity than Ethyl cellulose.

SEM of microspheres

The microspheres of Captopril with Eudragit S100 were smooth, spherical and slightly aggregated when compared with the microspheres of Captopril with ethyl cellulose which were porous, rough, grossly, discrete spherical. Scanning electron photomicrographs of the formulations F3 and F6 are shown in Fig 1.

Drug loading and Entrapment efficiency

The values of drug loading % and entrapment efficiency % are as shown in Table 2. As the polymer concentration was increased the drug loading % decreased and entrapment efficiency % was increased due to increase in the viscosity of the solution. Microspheres with Ethyl cellulose showed higher incorporation efficiency than those with Eudragit S-100.

***In vitro* buoyancy studies**

To assess the floating properties, the microspheres were placed in 0.1N HCl containing 0.02% Tween 80, to simulate gastric conditions. The use of Tween 80 was to account for the wetting effect of the natural surface-active agents in the GIT. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was in the range of 79.33% - 86.66% for formulation F1 to F3 and 85.66% - 90.33% for formulation F4 to F6 at the end of 12 h. The nature of the polymer influenced the floating behavior of the microspheres.

The floating behavior of the formulations of Eudragit S-100 and Ethyl cellulose was studied in dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.02% Tween 80. The results of *in vitro* % buoyancy for formulations F1to F6 are given in Table 2. The microspheres prepared by using higher polymer concentrations shows high density. So the microspheres having higher polymer concentrations were less buoyant than those with lower polymers concentrations[5]. Captopril-Eudragit S-100 microspheres showed lesser buoyancies when compared to the Captopril-Ethyl cellulose microspheres because of the lesser number of pores in the former. The floating abilities persisted until disintegration of the microspheres began.

***In vitro* drug release study**

Dissolution studies on all the six formulations of Captopril floating microspheres were carried out using a USP dissolution apparatus Type I. 0.1N HCl was used as the dissolution medium.

The *In vitro* drug release data for pure drug and formulations is shown in Table 2 and Fig 2. The cumulative percent drug release after 12 h was found to be 84.20, 81.11 and 75.95% for the formulations F1, F2 and F3 respectively whereas cumulative percent drug release after 12 h was 88.25, 84.42 and 78.30 for formulations F4, F5 and F6 respectively. The cumulative drug release significantly decreased with increase in polymer concentration. The increased density of the polymer matrix at higher concentrations results in an increased diffusional pathlength. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.

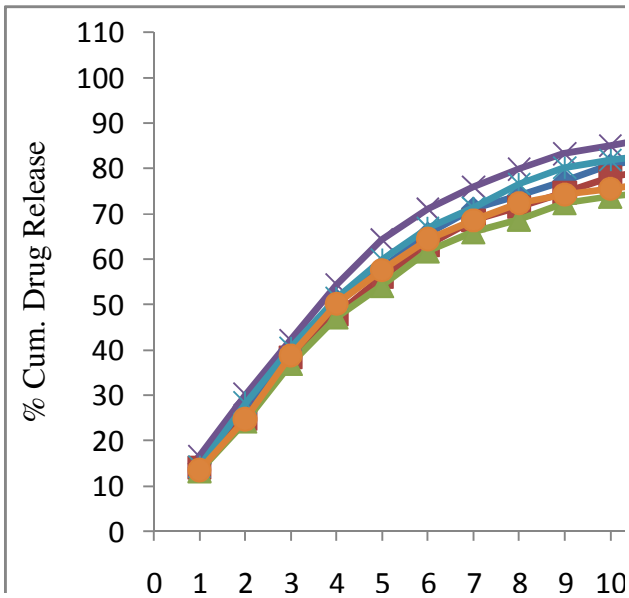

Figure 2: *In vitro* drug release profile of pure drug and formulations F1 to F6.

The data obtained from *in vitro* dissolution studies were fitted to zero-order, first-order and Korsemeyer-Peppas equations. Fitting of the release rate data to the various models revealed that the formulation F1, F2, F4 and F5 followed first order release kinetics and the formulations F3 and F6 followed Higuchi model.

In the case of the Fickian release mechanism, the rate of drug release is much less than that of polymer relaxation (erosion). So the drug release is chiefly dependent on the diffusion through the matrix. In the non-Fickian (anomalous) case, the rate of drug release is due to the combined effect of drug diffusion and polymer relaxation. Case II release generally refers to the polymer relaxation. The n values for formulations F1 to F6 ranged from 0.674 to 0.709, indicating that the release mechanism was non-Fickian or anomalous release ($0.5 < n < 1$). Based on the n values, F1 to F6, drug release from microsphere were controlled by polymer relaxation (erosion) as well as diffusion.

CONCLUSION

In this study sustained release Captopril Floating Microspheres were prepared successfully using solvent evaporation method. It may be concluded that Captopril microspheres would be promising drug delivery system for oral administration of Captopril to sustained the drug release upto 12 h. The formulation was found to be efficient with good recovery yield, percentage drug entrapment. The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules dosage form. So, Sustained release floating microspheres of Captopril may provide a convenient dosage form for achieving best performance regarding flow, drug entrapment and release.

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