



DESIGN AND EVALUATION OF FLOATING MICROCARRIERS OF CAPTOPRIL

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ABSTRACT

The present study involves preparation and evaluation of floating microcarriers of Captopril as model drug for prolongation of gastric residence time. The microcarriers were prepared by Ionotropic gelation technique using polymers Sodium alginate along with Hydroxyl propylmethylcellulose and Ethyl cellulose. The microcarriers were evaluated for angle of repose, bulk density, tapped density, carr's index, hausner's ratio, percent yield and drug entrapment. The shape and surface morphology of prepared microcarriers were characterized by optical and scanning electron microscopy, respectively. *In-vitro* drug release studies were performed and the dissolution data were fitted to zero order, first order, matrix, hixon-crowell, peppas model. The prepared microcarriers exhibited prolonged drug release and remained buoyant for > 12 h. The mean particle size increased and the drug release rate decreased as the concentration of polymer increases.

Keywords: Floating microcarrier, Captopril, *in-vitro* release, HPMC (K4M), Ethyl cellulose.

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 /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).¹⁻³ It has been suggested for the following instances that an active material should be formulated in 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, microcarriers 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 6–8 h, so clinical use requires taken in three times. It is most stable at pH 1.2 and as the pH increases; it becomes unstable and undergoes a degradation reaction.⁶ The virtue of the prolonged release dosage form of captopril has been reviewed.⁷ Researchers have developed a floating microcarrier of captopril.⁸ The single-unit floating systems are more popular but have a disadvantage owing to their 'all or nothing' emptying process leading to high variability of the gastrointestinal transit time. Still, the multiple-unit dosage forms may be better suited because they are claimed to reduce the inter subject variability in absorption and lower the probability of dose dumping.

The present investigation aims to develop a floating microcarrier of captopril with a view of prolonging GRT with a controlled release mechanism.

MATERIALS AND METHODS

Materials

Captopril was obtained as a gift sample from Lupin Pharmaceuticals, India. Ethyl cellulose (EC) was obtain from JCPL, Jalgaon. Hydroxypropylmethylcellulose (HPMC) was obtained from Unichem laboratories, Mumbai. Sodium alginate, Calcium chloride and Calcium carbonate purchased from S.D fine chemicals, Mumbai.

Method

Compatibility study

To determine the possible incompatibilities between drug and other excipients, the Captopril, HPMC (K4M), Ethyl cellulose, Sodium alginate were subjected to FTIR study.

Preparation of microcarriers

The microcarriers were prepared by ionic crosslinking technique. The 25 mg of drug was dispersed uniformly in aqueous mucilage of Sodium alginate. To this dispersion desired polymer was mixed in suitable proportion. Then, 500 mg of gas-forming agent such as CaCO₃ was separately added to the solution. The resulting solution was dropped through a 26G syringe needle into 5% (w/v) CaCl₂ solution which is prepared in water containing 10% (v/v) acetic acid. The solution containing suspend microcarriers was kept for 1.5 hr. To improve the mechanical strength of the microcarriers and allowed to complete the reaction to produce gas.⁹⁻¹² The fully formed microcarriers were collected, washed with distilled water and subsequently air dried. The composition of floating microcarriers are shown in Table 1.



Table 1: Composition of Floating Microcarriers

Formulation no.	Drug (mg)	Polymer Sodium alginate (w/v)	Drug : HPMC*	Drug: EC*	CaCo ₃ (gm)	CaCl ₂ (%)
A-1*	25	5	-	-	0.5	5
H-1	25	5	1:1	-	0.5	5
H-2	25	5	1:2	-	0.5	5
H-3	25	5	1:3	-	0.5	5
H-4	25	5	1:4	-	0.5	5
H-5	25	5	1:5	-	0.5	5
E-1	25	5	-	1:1	0.5	5
E-2	25	5	-	1:2	0.5	5
E-3	25	5	-	1:3	0.5	5
E-4	25	5	-	1:4	0.5	5
E-5	25	5	-	1:5	0.5	5

*A- Formulation without copolymer i.e HPMC (K4M) and Ethyl cellulose

*H- Formulation with HPMC (K4M); *E- Formulation with Ethyl cellulose

Evaluation of floating microcarriers¹³

Evaluation of micromeritic properties of microcarriers:

The prepared formulations were evaluated for angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Percent yield: The total amount of microcarriers was weighed and the percentage yield calculated by equation no.1, taken into consideration the weight of drug and polymer.

Production Yield = Practical yield (Microcarriers) / Theoretical yield (Polymer + Drug) X 100 -- (1)

Incorporation efficiency: Microcarriers (50 mg) were crushed in a glass mortar-pestle and the powdered microcarriers were suspended in 50 ml of distilled water and sonicated for 1 hr. The solution was filtered to separate shell fragments and the filtrate was analyzed spectrophotometrically for the drug content. Incorporation efficiency can be calculated by following equation no. 2.

Incorporating Efficiency = Actual drug content / Theoretical drug content X 100 ----- (2)

Particle shape and size: The size of microcarriers was determined using a microscope fitted with an ocular micrometer and stage micrometer. Scanning Electron Microscopy (SEM) (FEI Philips-XL-VNIT, Kholhapur) was performed to characterize the surface of formed microcarrier. Microcarriers were mounted directly onto the sample stub and coated with gold film and analyse for surface morphology.

Percentage buoyancy:¹⁴ About 50 mg of the floating microcarriers were placed in 30 ml of 0.1 N HCl in beaker. Floated microcarriers were collected at 1, 2, 4, 6, 8 and 12 hr. The percentage of floating microparticles was calculated by the following equation no.3.

% Floating Microcarrier = $\frac{\text{Weight of floating microcarriers}}{\text{Initial weight of floating microcarriers}} \times 100$ --- (3)

In-vitro release

The drug release was studied using USP XXVII paddle apparatus at 37±0.5°C and at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. Withdrawn 10 ml of the sample solution at pre determined time intervals. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample.¹⁵ Test sample diluted suitably and analyzed spectrophotometrically at λ_{max} 211 nm. The results are fitted into suitable release kinetics.

Stability study¹⁶

The optimized formulation was kept at room temperature and 75% relative humidity for 30 day. Then the microcarriers are evaluated for percent drug entrapment and dissolution study.

RESULTS AND DISCUSSION

Compatibility study

From the result of FTIR studies, there is no significant changes were observed when pure drug, HPMC (K4M), Ethyl cellulose, Sodium alginate were subjected to FTIR study.

Characterization of floating microcarriers

The prepared microcarriers were evaluated for percentage yield, drug entrapment efficiency, average particle size. The results are shown in the Table no.2.

From the Table 2, the angle of repose, bulk density, tapped density, carr's index and hausner's ratio were found to be within the limit as per reported literature. The carr's index and hausner's ratio shows good flow properties for all the formulation. Also lower values for hausner's ratio indicates excellent flow properties of the formulation. The prepared microcarriers were evaluated for percentage yield, drug entrapment efficiency, average particle size. The results are shown in table 3.



Table 2: Micromeritic properties of microcarriers

Formulation Code	Angle of repose (θ)	Bulk Density (gm/cm ³)	Tapped Density (gm/cm ³)	Carr's Index (%)	Hausner's ratio
A1	21.48±0.54	0.855±0.08	0.875±0.06	20.564±0.56	1.4±0.67
H1	22.41±0.98	0.746±0.02	0.933±0.03	20.429±0.91	1.5±0.03
H2	20.56±0.92	0.661±0.01	0.793±0.02	16.66±0.97	1.19±0.05
H3	21.42±0.74	0.861±0.03	0.952±0.04	9.60±1.55	1.10±0.03
H4	21.12±0.54	0.830±0.01	0.922±0.04	9.99±0.80	1.11±0.03
H5	21.64±1.04	0.804±0.04	0.960±0.04	16.25±1.29	1.19±0.01
E1	22.50±1.04	0.812±0.03	0.999±0.06	18.71±0.69	1.23±0.03
E2	21.98±0.86	0.800±0.03	1.00±0.03	20.00±0.88	1.25±0.02
E3	21.54±1.25	0.750±0.05	0.88±0.04	14.77±0.91	1.17±0.02
E4	20.83±1.56	0.882±0.04	1.25±0.04	29.6±1.30	1.42±0.02
E5	20.43±1.09	0.900 ±0.02	1.20±0.05	25.00±1.05	1.33±0.02

Mean ± S.D., n=3

Table 3: Evaluation parameter of microcarriers

Formulation Code	Yield (%)	Entrapment (%)	Particle size (µm)
A1	76.34±1.67	60.78±1.32	780.40±1.23
H1	72.25±1.56	67.42 ±1.44	675.90±1.76
H2	74.63±1.16	73.82±2.19	736.00±1.45
H3	75.26±0.69	75.79±1.44	740.42±2.34
H4	76.00±0.91	74.07±2.88	756.91±1.50
H5	86.47±1.71	40.30±1.66	890.24±2.45
E1	70.47±1.19	58.73±1.29	704.16±3.45
E2	75.51±2.19	60.51±2.19	823.34±4.67
E3	76.60±2.19	66.66±2.19	856.27±31.46
E4	77.67±2.57	51.06±2.57	870.78±2.37

Mean ± S.D., n=3

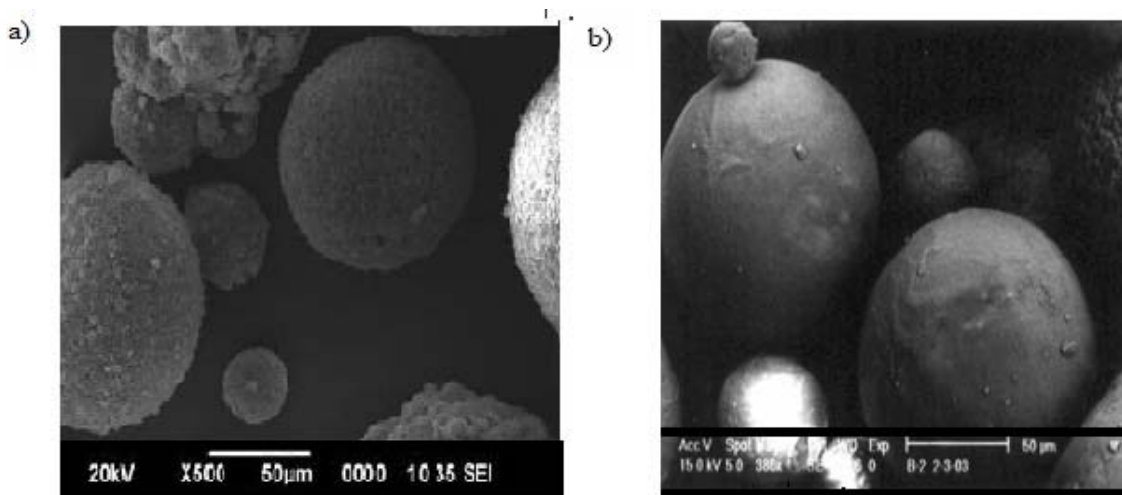


Figure 1: SEM photographs of microcarrier a) Formulation of H3 b) Formulation of E3

From the Table 3, the percent yields of the all formulations were found to be in the range of 58.36±2.87 to 86.47±1.71. The low percentage yield in some formulations may be also due to microcarriers lost during the washing process.

The drug entrapment of Sodium alginate with HPMC (K4M) was found to be in the range of 40.30±1.66 to 75.79±1.44. The drug entrapment of Sodium alginate with Ethyl cellulose was found to be in the range of 51.06±2.57 to 66.66±2.19. The mean particle size might be affected

by different types of polymers which are used in preparation of microcarrier. The average particle size of microcarriers was found to be in the range of 675.90±1.76 to 890.76±7.45 µm. The particle size increases as the polymer concentration increases and formation of the large droplets during addition of polymer solution to the gelling agent.

From the result, it was observed that the drug entrapment efficiencies increased progressively with increasing the concentration of copolymer resulting in the

formation of larger microcarriers entrapping the greater amount of the drug, this may be attributed to the greater availability of active calcium binding sites in the polymeric chains and consequently, the greater the degree of cross-linking as the amount of the polymer increases.

Scanning electron microscopy (SEM)

The view of the microcarriers showed a spherical shape with a smooth surface morphology. The SEM photographs are shown in figure no 1 a and b.

Floating capacity

In order to investigate the floating capacity of prepared formulation H1-H5, E1-E5 were subjected to floating capacity in 0.1N HCl.

From the Figure 2, 3 the floating capacity of formulation A1-H5 were found to be in the range of 99.72 ± 0.02 to 85.38 ± 0.72 . The floating capacity of formulations E1 to E5 was found to be in the range of 99.76 ± 0.10 to 74.11 ± 0.17 . The microcarrier floated for prolong time over the surface of medium. All the formulation shows excellent floating capacity.

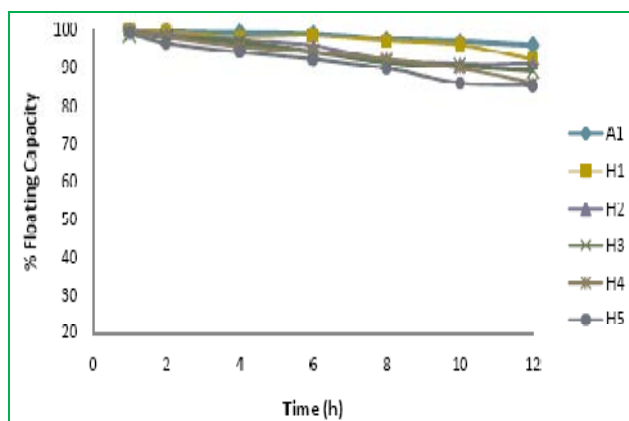


Figure 2: Results of Floating Capacity of Formulation A1 to H5

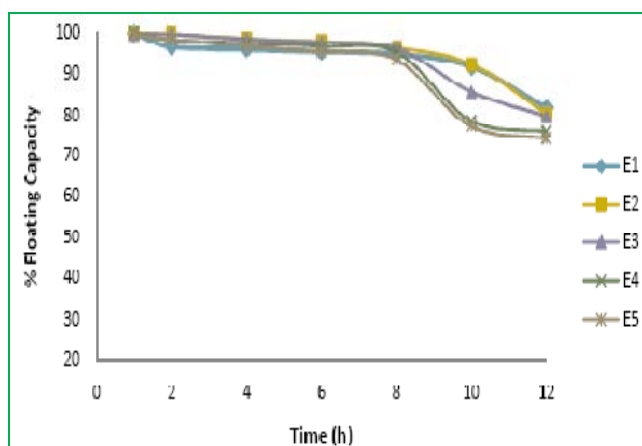


Figure 3: Results of Floating Capacity of Formulation E1 to E5

The formulation containing HPMC (K4M) shows the high percentage of floating capacity than the Ethyl cellulose. The probable reason is HPMC (K4M) forms

gel layer in contact with 0.1 N HCl, CO₂ gas which entrapped in gel network of HPMC (K4M) and help for floatation of microcarriers. As the polymer ratio increases, the density of the microcarriers increases with decreasing in floating ability of the microcarriers.

In-vitro drug release studies

Effect of HPMC (K4M)

In order to study the effect of HPMC (K4M) on microcarrier, the formulation A1-H5 were prepared in the ratio of 1:1 to 1:5. The results are shown in Figure no 4.

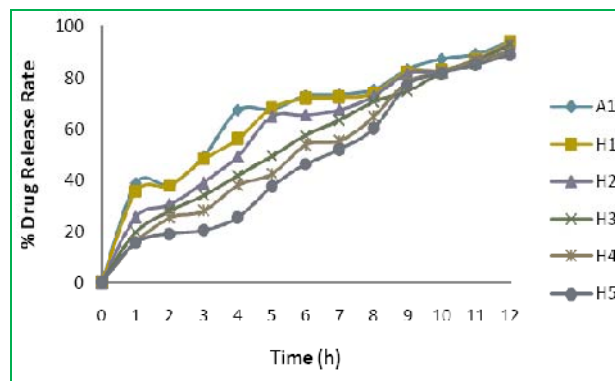


Figure 4: In-vitro Drug Release Study of Formulations A1 to H5

From the Figure 4, the formulation A1 is prepared without copolymer to act as a control formulation for other. Due to absence of copolymer formulation shows variable drug release rate. The concentration of HPMC (K4M) in the release layer was the key factor governing drug release. The microcarriers containing the gelling agent forming a gelatinous barrier which controls the drug release rate. As the concentration of HPMC (K4M) increases in the formulation, the release rate was found to be decreases. It was shown that an increase in polymer concentration causes an increase in viscosity of the polymer solution as well as a decreasing in drug release rate.

Effect of ethyl cellulose

In order to study the effect of Ethyl cellulose on microcarriers, the formulation prepared in the ratio of 1:1 to 1:5. The results are shown in Figure no 5.

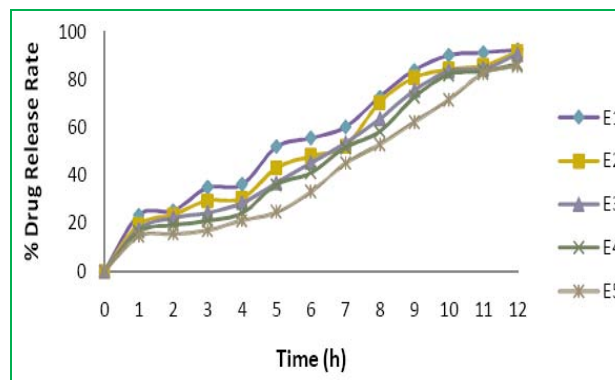


Figure 5: In-vitro Drug Release Study of Formulations E1 to E5



From the Figure 5, the Ethyl cellulose formulation showed slower drug release rate as compared to the HPMC (K4M). The probable reason behind this, the Ethyl cellulose is hydrophobic polymer and act as a barrier for penetration medium there by retarding the diffusion of drug from the swollen microcarrier.

Drug release kinetics

To study the release behavior, kinetic analyses were performed on the optimized formulation. The dissolution data were fitted to zero order, first order, matrix, Hixson-Crowell, Peppas model. Several of the applied models were well fitted dissolution profile as indicated by the value of determination coefficient (r^2)

as shown in Table 4. A criterion for selecting the most appropriate model was based on best goodness of fit with determination coefficient (r^2) nearer to 1.

Stability study

The optimized formulation was kept at room temperature and 75% relative humidity for 30 day. Then the microcarriers are evaluated for percent drug entrapment and dissolution study. The results are shown in Table 5.

From the results of dissolution test, there is no significant change in Drug entrapment and dissolution release rate pattern of formulation after stability study.

Table 4: Results of Release Kinetic of Optimized Microcarriers

Formulation Code	Regression Coefficient (r^2)				
	Zero order	First order	Matrix	Hixson Crowell	Korsemeier-Peppas
H3	0.9764	0.9414	0.9385	0.9630	0.9665
E3	0.9656	0.8979	0.8675	0.9280	0.8426

Table 5: Results of Stability Study

Formulation code	Drug entrapment (%)	Drug release rate (%)
H3	74.77±0.87	91.62±0.34
E3	65.64±0.54	89.443±0.54

Mean ± S.D., n=3

CONCLUSION

Floating microcarriers of captopril showed excellent yield, good floatability, good entrapment efficiency and prolonged drug release. Microcarriers of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Thus, the prepared floating microcarriers may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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