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RESEARCH ARTICLE

FABRICATION DEVELOPMENT, OPTIMIZATION AND CHARACTERIZATION OF GASTRORETENTIVE MICROSPHERES OF AN ANTIHYPERTENSIVE DRUG

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ABSTRACT:

The objective of the present study was to develop floating microspheres of Captopril in order to achieve an extended retention in the upper GIT which may enhance the absorption and improve the bioavailability. In the present study, preparation of captopril floating microspheres, evaluation of Floating Drug Delivery System (FDDS) in vitro, forecast of the release, and optimization of stirring speed and polymers ratio to match target release profile was investigated. The microspheres were prepared by solvent evaporation method using different ratio of hydroxyl propyl methyl cellulose (HPMC K4M) with drug in the mixture dichloromethane and ethanol at ratio of (1:1), with tween80 as the surfactant. Differential Scanning Calorimeter (DSC) study shows that drug and other excipients are compatible with each other. The effects of polymers concentration on drug release profile were investigated. The floating microspheres were characterized by and results obtained are % yield, particle size analysis, drug entrapment efficiency, surface topography, buoyancy percentage, *in-vitro* drug release was studied for 12 hour and scanning electron microscopy. Accelerated stability study was also performed for three months indicated that optimized formulation was stable. The floating microspheres showed better result and it may be use full for prolong the drug release in stomach and improve the bioavailability. The outcome showed that the polymer ratio and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h), floating time (> 12 hr) and the best results were obtained at the ratio of HPMC K4M: EC (1:6). The mean particle size of prepared floating microspheres increased but the drug release rate from the microspheres decreased as the polymer concentration increased. The developed floating microspheres of captopril may be used for prolonged drug release for at least 12 hrs, thereby improving the bioavailability and patient compliance.

Key words: Floating microspheres (FDDS), captopril, hydroxyl propyl methyl cellulose, ethyl cellulose, *in-vitro* release studies, bioavailability.

INTRODUCTION:

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time by using gastro-retentive dosage forms (GRDFs). It remains in the gastric region for several hours and hence prolongs the gastric residence time of drug. It has several advantages over immediate release dosage form including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered and reduction of administration frequency leading to improved patient compliances[1, 2] Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. These microspheres are characteristically free flowing powders having a size less than 200 µm and remain buoyant over gastric contents and for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[3,4]

Captopril is classified as an antihypertensive drug. It has mean plasma half-life of 2-3 hour and only 40 % of the drug reaches to the systemic circulation due to hepatic first pass metabolism. Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. CP has a short half life and low bioavailability in the upper part of GIT hence it is suitable for gastro-retentive system. [4, 5]

In the present investigation floating microsphere of captopril were prepared by solvent evaporation using two different polymer hydroxypropylmethyl cellulose (HPMC) and ethyl cellulose (EC). The aim of the work was to evaluate microspheres for size, *in-vitro* release, buoyancy and incorporation efficiency. The effect of an assortment of formulation variables on the size and drug release were also investigated.

MATERIAL & METHODS:

Materials:

Active pharmaceutical ingredient:

Captopril (CP) was obtained as a gift sample from Ruskin chemipharm, Mumbai,India

Polymers & Reagents:

HPMC K4M, are provided by Coloron Asia Private Limited; Goa. and all polymers and solvents used were of pharmaceutical or analytical grade.

Preparation of floating microspheres:

Microspheres containing Captopril drug as a core material were prepared by a Non-aqueous Solvent Evaporation method. Drug, EC and HPMC K4M were mixed in the mixture dichloromethane and ethanol at 1:1 ratio. The slurry was slowly introduced into 100 ml of liquid paraffin containing 0.01%. Tween 80 while being stirred at 1200 rpm using mechanical stirrer equipped with three bladed propellers at room temperature. The solution was stirred for 2 hour and allowed the solvent to evaporate completely and filtered by using filter paper. The microspheres obtained were washed repeatedly with petroleum ether (40^{o}-60^{o}C) until free from oil. The collected microspheres were dried at room temperature and subsequently stored in desiccators. Same procedure was repeated for all the three batches.[7]

Characterization of microspheres:

Scanning electron microscopy:

The external and internal morphology of the microspheres were studied using scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The stub containing the coated samples was placed in the scanning electron microscope (JSM- 6360A; JEOL, Tokyo, Japan) chamber. The samples were then randomly scanned, and photomicrographs were taken at the acceleration voltage of 20 kV, original magnification 30´ to investigate the internal morphology.[8]

Buoyancy percentage:

The microspheres weighed (equivalent to 100 mg) were spread over the surface of USP XXIV. Dissolution apparatus (Type II) filled with 900 ml of 0.1N HCl containing 0.02% of Tween80. The medium was agitated with a paddle rotating at 100 rpm for 12h. 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.[9-11]

Percentage Buoyancy = Microsphere remained floating / Total mass of microsphere x 100

Determination of drug entrapment efficiency:

Microspheres equivalent to 100 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 repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured at 217 nm against appropriate blank. The amount of drug entrapped in the microspheres was calculated by the following formula: [12, 13]

Drug entrapment efficiency = Experimental drug content / Theoritical drug content

***In-vitro* drug release study:**

In-vitro dissolution of CP from floating microspheres was carried out using the USP dissolution test apparatus (Type-I). A weighed amount of floating microspheres of CP were filled into a capsule and placed in the basket. Dissolution media used was 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. At predetermined time intervals, 10 ml of sample was withdrawn and replaced with equal amount of 0.1 N HCI (pH 1.2). The collected samples were filtered and suitably diluted with 0.1 N HCI and analyzed spectrophotometricaly at 217 nm to determine the amount of drug released in the dissolution medium.[14]

Kinetics of drug release:

The mechanism of release was determined by fitting the release data to the different kinetic equations such as zero-order, first-order, Higuchi, and Korsmeyer- Peppas and finding the R2 values of the release profile corresponding to each model.[15, 16]

RESULT AND DISCUSSION:

Scanning electron microscopy:

The morphology of microspheres was examined using SEM. The view of the microspheres showed a hollow spherical structure with a smooth surface morphology (Figure 1 (a) and (b)) and exhibited a range of sizes within each batch. Some of the microspheres showed a dented surface structure (Figure 1 (c)), but they showed good floating ability on the surface of the medium indicating intact surface. The outer surface of the microspheres was smooth as shown in figure 1 illustrating the microphotographs of formulation FM 6. The floating microspheres were spherical with no visible major surface irregularity.

Particle size analysis:

The particle size of floating microspheres varied to some extent among the formulation due to disparity in the symphony of formulations. The effects of stirring speed and polymer to polymer ratio on the particle size of microspheres are shown in Table 1 and Table 2. Formulation FM 6 showed relatively higher percentage of large size and formulation FM1 showed relatively small size floating microspheres because as viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at elevated viscosities. This outcome in the configuration of larger particles. As stirring speed increases from 300 rpm to 1000rpm particle size decrease from 272.11 µm to 167.36µm due to agitation speed break up the bulk of the polymer into finer droplets.

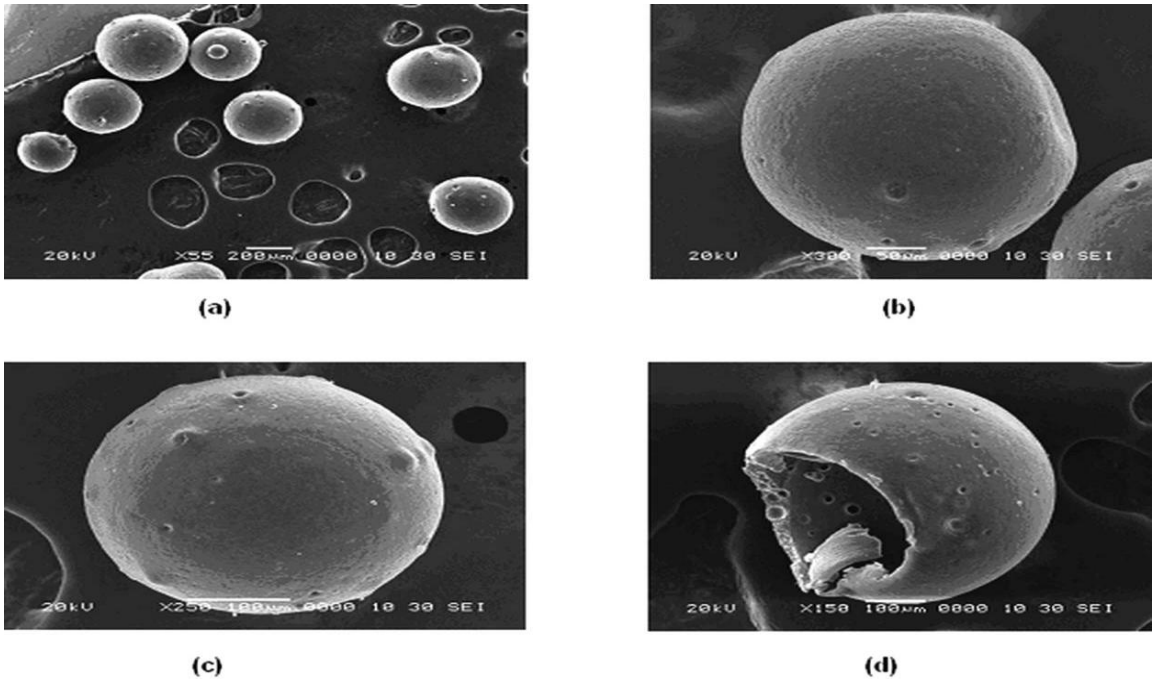

Figure 1: SEM of floating microspheres

Table 1: Optimization of stirring speed with regards to average particle size and average percent drug entrapment

Batch	Resolution Per Minute	Particle size	Drug entrapment efficiency
A	300	272.11±0.75	57.73±1.38
B	500	212.116±2.32	62.57±0.37
C	1000	167.36±1.22	39.94±0.85

Table 2: Optimization of polymer ratio with regards to average particle size and average percent drug entrapment:

S.NO	Batch Code	HPMC K4M: EC	Mean particle size (µm)	Entrapment efficiency (%)	Buoyancy (%)	Cumulative percentage drug release after 12 hours
1.	FM1	1:1	220.119±1.16	58.11±1.11	71.05±3.4	97.46
2.	FM2	1:2	246.765±2.11	61.09±0.8	74.98±1.7	96.35
3	FM3	1:3	281.123±2.45	67.34±1.67	80.11±0.8	93.42
4.	FM4	1:4	348.876±0.78	72.89±1.98	82.65±0.4	87.97
5.	FM5	1:5	368.139±18.11	78.65±1.48	87.43±2.3	84.76
6.	FM6	1:6	465.999±0.33	86.12±1.33	89.65±2.2	81.78

Mean ± S.D., n=3

Table 3: Interpretation of drug release kinetics of optimized batch FM 6

Batch Code	Zero order		First order		Higuchi		Korsmeyer Peppas	
FM6	R^2	$K_0(day^{-1})$	R^2	$K_0(day^{-1})$	R^2	$K_0(day^{-1})$	R^2	$K_0(day^{-1})$
	0.783	0.234	0.934	0.011	0.986	4.246	0.978	0.386

Drug entrapment efficiency:

Drug entrapment efficiency was found to be optimum (62.57 %) at the stirring speed of 500 rpm. As the stirring speed reduced to 300 rpm or increased to 1000 rpm there was significant decrease in entrapment efficiency shown in Table 1. The entrapment efficiency was found to be 58.11% to

86.12% for formulation FM1 to FM6. Drug entrapment efficiency was increased with increasing polymer concentration in floating microspheres. Results are given in Table 2. Among the different polymer-drug ratios

investigated, 1:6 polymer- drug ratios had the optimum capacity for drug encapsulation.

Buoyancy (%):

The buoyancy percentage for all batches was almost above 75%, which was studied for 12 h. Average buoyancy in percentage was found to be 71.05% to 89.65%. The highest percentage was obtained with formulation FM6. In general with increase in the amount of polymer (Ethyl Cellulose), there was an increase in the buoyancy percentage. From the table 2, it was concluded that on increasing ethyl cellulose concentration incorporation efficiency and % buoyancy increase continuously.

***In-vitro* dissolution study:**

Ethyl cellulose is low permeable and water insoluble polymer. Floating microspheres showed sustained release of the drug in acidic environment and the drug release was found to be approximately linear. Approximately 15% of the drug was released initially. Furthermore, the drug release from the floating microspheres matrix was controlled by the polymer. As the ethyl cellulose was increased, the release of drug was decreased significantly this may be due to 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)

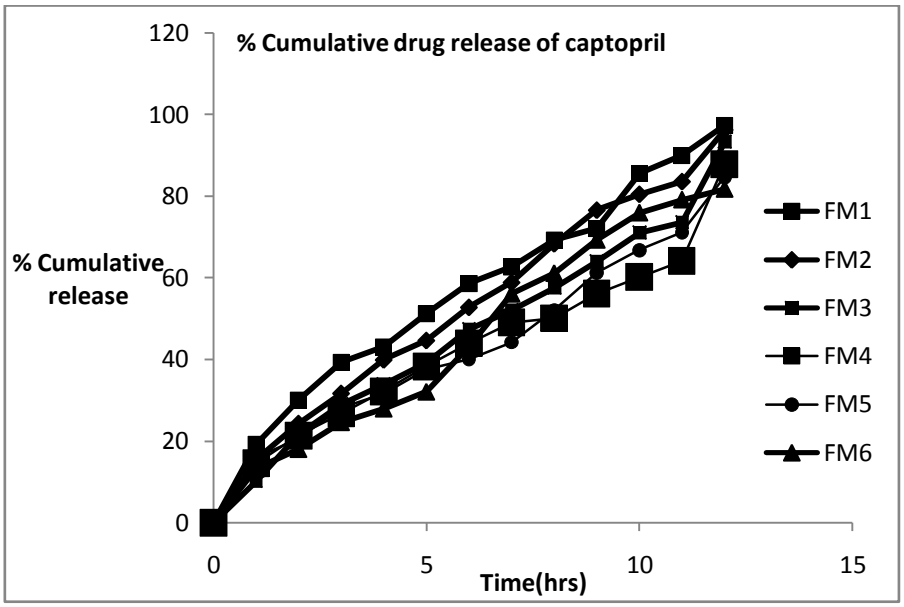

Figure 2: % Cumulative drug release of Captopril

Kinetics of drug release:

The data obtained for *in-vitro* release were fitted into equations for the zero-order, first- order and higuchi release models. The interpretation of data was based on the value of the resulting regression coefficients. The *in-vitro* drug release showed the highest regression coefficient values for higuchi model, indicating diffusion to be the predominant mechanism of drug release. (Table-3)

Stability studies:

The samples subjected to stability studies were then analyzed. The results of the stability studies (Table 4) indicated that the formulations were able to retain their stability for a period of 3 months at 40°C/75% RH. (Table 4)

Table 4: Stability study

Days	Drug entrapment efficiency (%)	Buoyancy (%)	Drug release (%)
Before storage (0 days)	86.12±1.33	75.48±0.17	81.78±0.23
After storage			
7	85.78±0.45	75.23±0.23	81.00±0.13
15	85.56±0.67	75.21±0.89	80.23±0.54
30	85.34±0.78	75.10±0.45	81.12±0.29
60	85.00±0.90	75.00±0.17	80.34±0.71
90	85.00±0.10	75.00±0.28	80.20±0.12

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CONCLUSION:

In-vitro data obtained for floating microspheres of captopril showed good incorporation efficiency, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. From the results it can be concluded that the drug release from the floating microspheres matrix was controlled by the polymer proportion. Prepared formulation showed best appropriate balance between buoyancy and drug release rate. The *in-vitro* release studies showed that the better release profile with the formulation FM6, therefore FM6 can be considered as best formulation while compared with other batches. This can be concluded that by formulating captopril as floating microspheres can improve the low oral bioavailability by expended drug release in the upper part of stomach.

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