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RESEARCH ARTICLE

Formulation, Optimization and Evaluation of Floating Microspheres of Captopril.

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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. 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. A 3^2 full factorial design was applied to systemically optimize the drug release profile. Polymer to drug ratio (X_1) and stirring speed (X_2) were selected as independent variables. The floating microspheres were characterized by and results obtained are % yield, particle size analysis, drug entrapment efficiency, 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.

KEYWORDS: Floating microspheres, captopril, hydroxyl propyl methyl cellulose, ethyl cellulose, *in-vitro* release studies, bioavailability

1. 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]

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. [5, 6]

The aim of present work was preparation and evaluation of floating microspheres of CP using 3^2 full factorial design

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layout by selecting independenant variables like polymer HPMC K4M in different proportions with drug (polymer to drug ratio, X_1) and stirring speed (X_2).

MATERIALS AND METHODS:

MATERIALS:

Captopril (CP) was obtained as a gift sample from Ruskin Chemipharm, Mumbai and HPMC K4M, are provided by Coloron Asia Private Limited; Goa. and all polymers and solvents used were of pharmaceutical or analytical grade.

METHODS:

DRUG-EXCIPIENTS INTERACTION STUDIES:

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of solid dosage form12. Differential Scanning Calorimeter (DSC) allows the fast Evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and final tablet were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C. [7]

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°-60°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]

FULL FACTORIAL DESIGN:

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The polymer to drug ratio (X1) and stirring speed (X2) were selected as independent variables. Percentage yield, particle size, DEE (%), drug release (%) and buoyancy (%) were selected as dependent variables

EVALUATION OF FLOATING MICROSPHERES:

Yield of Microspheres: The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.[8, 9]

$$\% \text{ Yield } = \frac{\text{Actual weight of powder}}{\text{Total weight of excipient and drug}} \times 100 \qquad (1)$$

Particle Size: The particle size of the microspheres was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.[10]

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.[11-13]

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: [14, 15]

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100 \qquad (2)$$

Micromeritic Properties: The floating microspheres were characterized by their micromeritic properties such as particle size, bulk density, tapped density, hausners ratio, carr's index and angle of repose.[15]

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 HCl (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 HCl (pH 1.2). The collected samples were filtered and suitably diluted with 0.1 N HCl and analyzed spectrophotometrically at 217 nm to determine the amount of drug released in the dissolution medium.[16]

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, and microballoons were divided into two pieces by using a knife.[10]

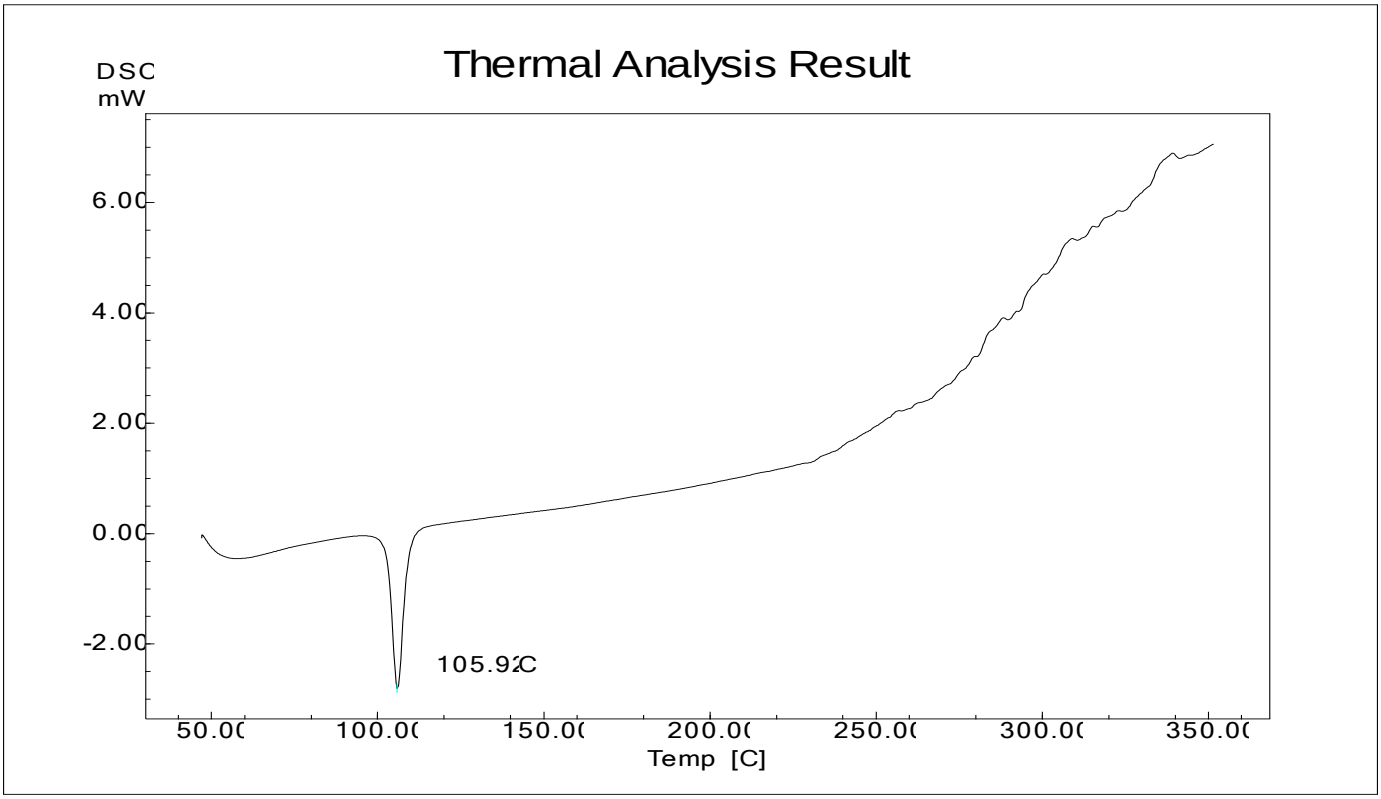
Stability studies:

The stability studies were carried out at an optimized formulation, i.e., formulation F_5. The formulation was stored at 40º ± 2ºC/75% ± 5% RH for 3 months (Climatic zone IV condition for accelerated testing) to assess their stability. The protocol of stability studies was in compliance with the WHO guidelines for stability testing intended for the global market. After intervals of 7, 15, 30, 60, and 90 days, samples were withdrawn and retested for drug content, floating behavior, and drug release studies.[10]

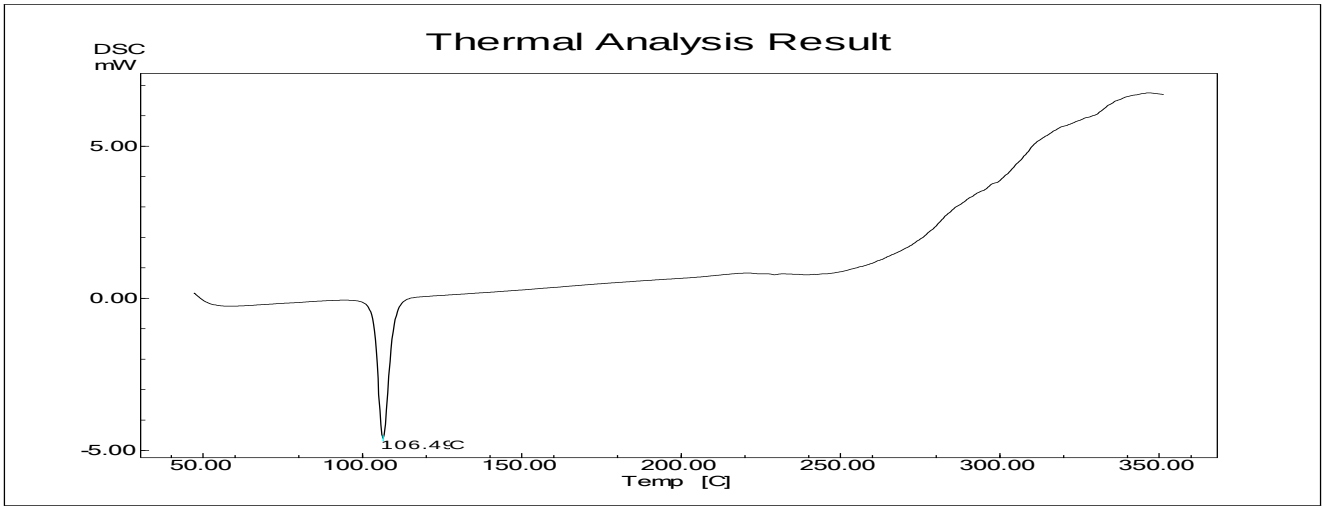
RESULT AND DISCUSSION:

DSC STUDY:

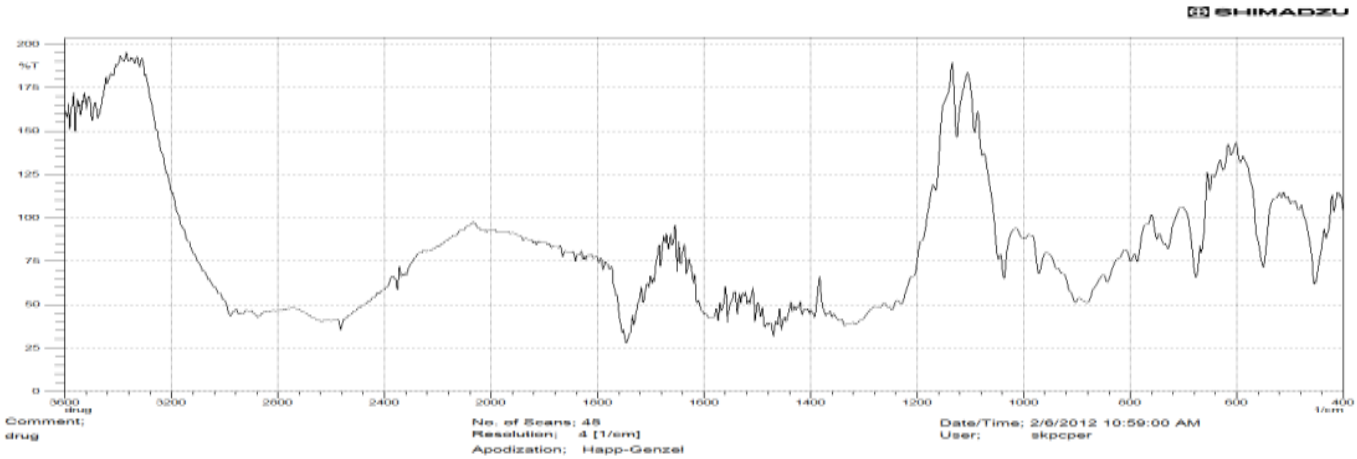
Drug excipient interactions play a vital role with respect to release of drug from the formulation amongst others. DSC has been used here to study the physical and chemical interaction between the drug and excipients used. In the present study, it has been observed that there is no chemical interaction between captopril and the polymer used.



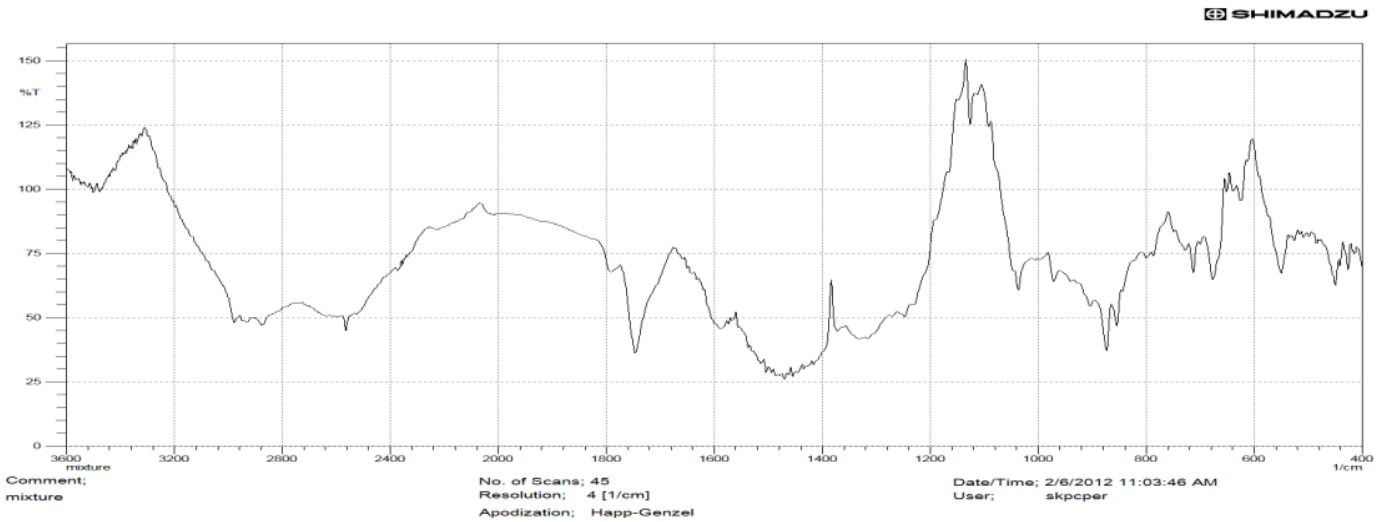
DSC Thermogram of Captopril



DSC Thermogram of Captopril+Physical Mixture



IR spectra of Captopril



IR spectra of physical mixture

3^2 Factorial Designs

Batch No.	Variables levels in coded form		Yield (%)	Particle size (mm)	Drug entrapment efficiency (%)	% Drug release (Q12)	Buoyancy (%)
	X_1	X_2					
F1	-1	-1	**48.21**	60.4	52.12	99.2	**68.13**
F2	-1	0	**64.92**	56.7	50.23	99.5	**69.34**
F3	-1	+1	**68.15**	49.3	47.09	99.3	**70.47**
F4	0	-1	**72.34**	67.1	70.34	97.3	**85.52**
F5	0	0	**77.17**	64.9	75.00	97.5	**75.48**
F6	0	+1	**78.58**	61.6	74.24	96.3	**71.33**
F7	+1	-1	85.34	96.0	74.58	85.7	86.33
F8	+1	0	87.01	88.2	71.87	83.5	88.33
F9	+1	+1	86.09	71.8	68.01	78.5	80.33

Translation of coded levels in actual units

Variables level	Low (-1)	Medium (0)	High (+1)
Polymer to drug ratio (X_1)	1:1	3:1	5:1
Stirring speed (X_2)	600	900	1200

Table 1: Formulation parameters for microspheres of Captopril

Coefficient	B0	B1	B2	B11	B22	B12	Multiple R^2
Yield (%)	78.24	12.89	4.48	-2.71	-3.31	-4.79	0.986
Particle size (mm)	66.02	14.93	-6.8	5.86	-2.23	-3.275	0.972
Drug entrapment efficiency (%)	73.78	10.66	-1.167	-12.67	-1.16	-0.25	0.974
% Drug release (Q12)	97.55	8.38	-1.35	-6.08	-0.78	-1.825	0.995
Buoyancy (%)	77.90	7.84	-2.97	-0.29	-0.70	-2.085	0.943

Table 2: Summary of results of regression analysis for floating microspheres of Captopril

Factorial equation for Yield (%)= $78.24 + 12.89X_1 + 4.48X_2 - 2.71X_1^2 - 3.31X_2^2 - 4.79X_1X_2$

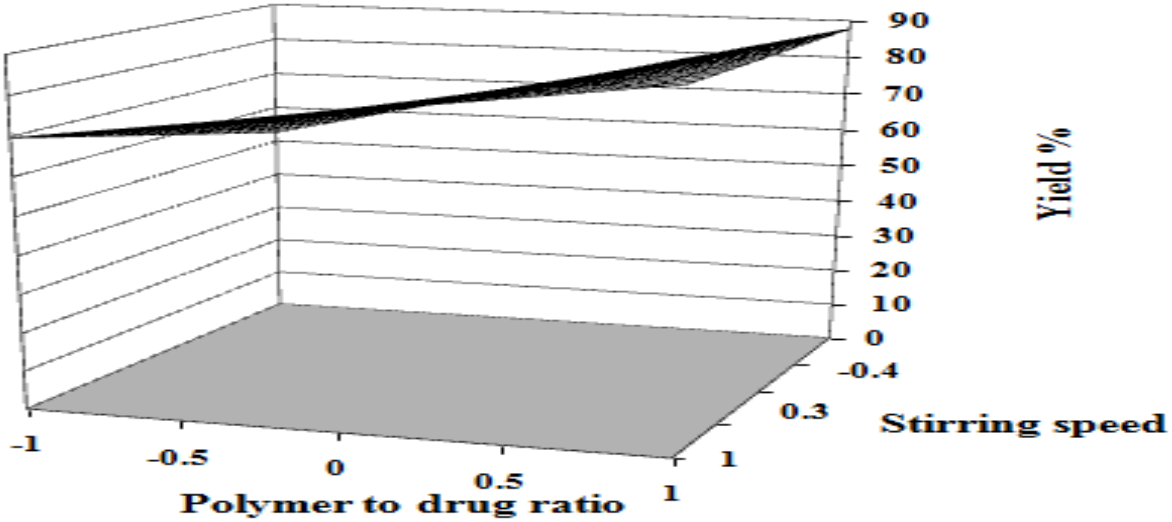


Figure 1: Effect of variable on Yield (%)

Yield (%) for all the batches F1 to F9 varied from 48.21 % to 87.01 % (Table 1) showed good correlation coefficient as **0.986**. Results of the equation (3) indicated that both the concentration of the X1 and X2 were responsible for the yield.

Factorial equation for Particle size (mm)

Particle size (mm) = $66.02 + 14.93X_1 - 6.8X_2 - 5.86X_1^2 - 2.23X_2^2 - 3.27X_1X_2$

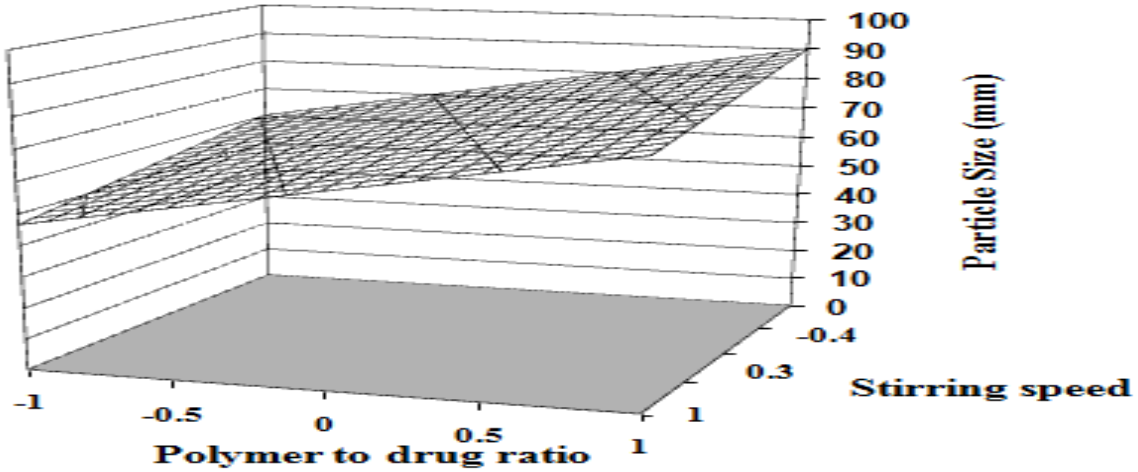


Figure 2: Effect of variable on Particle size

Particle size (mm) for all the batches F1 to F9 varied from 49.3 % to 96.0 % (Table 1) showed good correlation coefficient as **0.972**. Results of the equation (4) indicated that both the concentration of the X1 and X2 were responsible for the Particle size.

Factorial equation for Drug entrapment efficiency (%) DEE (%) = $73.78 + 10.66X_1 - 1.167X_2 - 12.67X_1^2 - 1.16X_2^2 - 0.25X_1X_2$

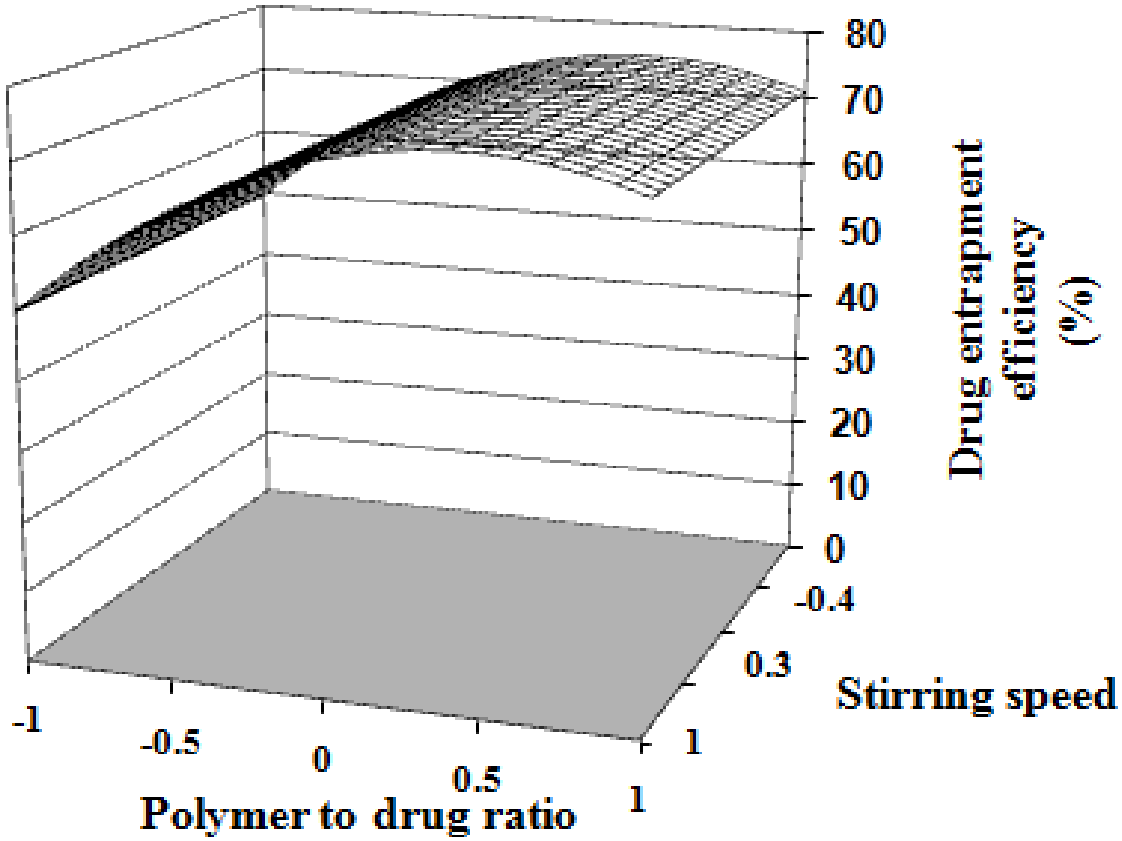


Figure 3: Effect of variable on Drug entrapment efficiency (%)

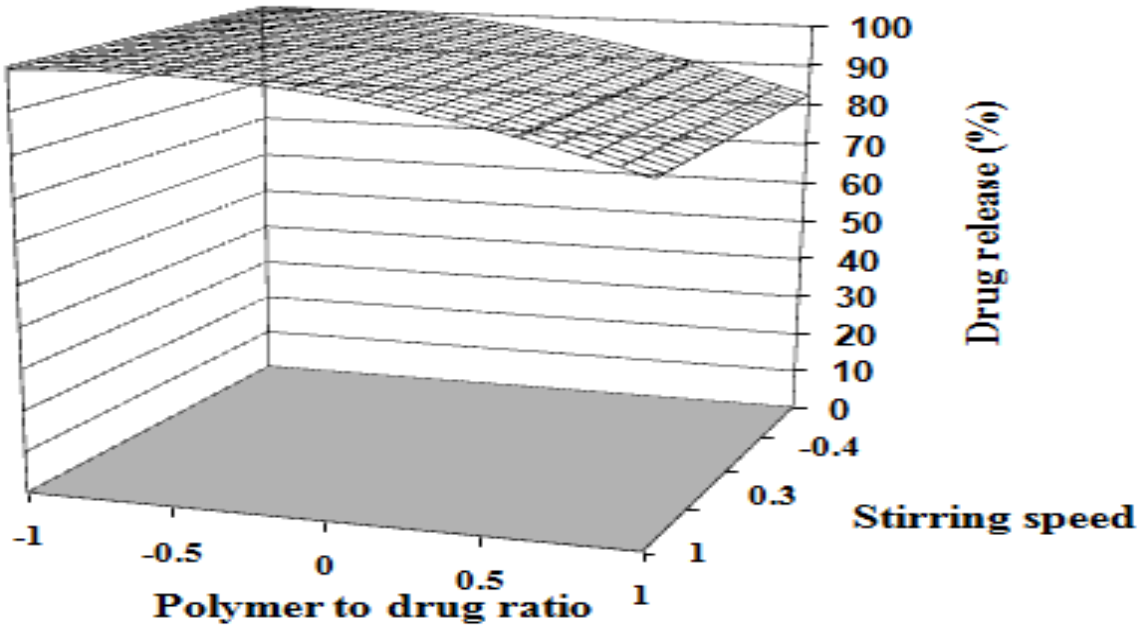


Figure 4: Effect of variable on Drug release (%)

DEE (%) for all the batches F1 to F9 varied from 78.5 % to 99.5 % (Table 1) showed good correlation coefficient as **0.995**. Results of the equation (6) indicated that the X1 was more responsible than X2 for the drug release (%).The increase in HPMC K4M concentration leads to the increased density of polymer matrix into the microspheres which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix Factorial equation for Buoyancy (%)

Buoyancy (%) = 77.90 + 7.84X_1 - 2.97X_2 -0.29X_1^2 -0.70X_2^2 – 2.085X_1X_2

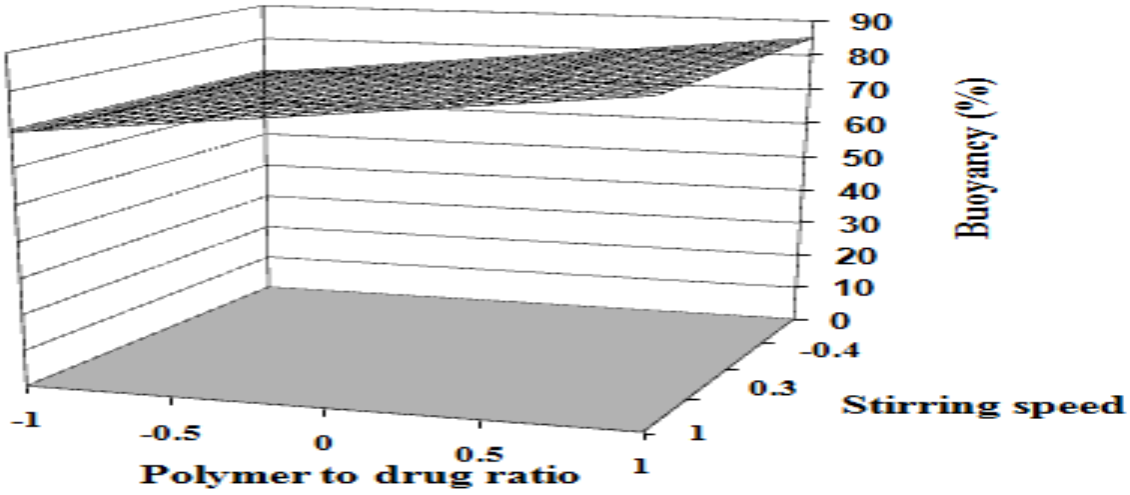


Figure 5: Effect of variable on Buoyancy (%)

Buoyancy (%) for all the batches F1 to F9 varied from 68.13 % to 88.33 % (Table 1) showed good correlation coefficient as **0.943**. Results of the equation (7) indicated that the X1 was more responsible than X2 for buoyancy (%).

MICROMERITIC PROPERTIES:

The bulk density, tapped density, hausner's ratio of formulation F_1 to F_6 ranges from 0.62±0.30 to 0.78± 0.64 gm/cm³, 0.652 ± 0.05 to 0.84± 0.73 gm/cm³, 1.054 ± 0.25 to 1.232 ±0.81 respectively. The carr's index ranges between 5.19± 0.93 to 10.1± 0.84%. The angle of repose of microspheres ranges from 17.01± 0.240 to 27.21±0.350 (Table 3). The values of carr's index and angle of repose indicate excellent flow properties.

Evaluation Parameters	Formulation Batches								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Angle of Repose (^{0})	19.11± 0.20	17.01± 0.24	27.21± 0.35	21.24± 0.25	18.42±0 .37	20.66±0 .36	19.11± 0.20	17.01± 0.24	27.21± 0.35
Bulk density (gm/cm^3)	0.62±0 .30	0.63± 0.42	0.67± 0.56	0.68± 0.24	0.73± 0.46	0.78± 0.64	0.67± 0.56	0.68± 0.24	0.73± 0.46
Tapped Density (gm/cm^3)	0.69± 0.43	0.68± 0.36	0.72± 0.27	0.75± 0.89	0.77± 0.28	0.84± 0.73	0.68± 0.36	0.72± 0.27	0.75± 0.89
Carr's Index (%)	10.10± 0.84	7.35± 0.38	9.33± 0.93	9.33± 0.85	5.19± 0.93	7.73± 0.29	10.1± 0.84	7.35± 0.38	9.33± 0.93
Hausner's Ratio	1.12± 0.03	1.08± 0.21	1.07±0 .68	1.232± 0.81	1.05± 0.25	1.05± 0.54	1.115± 0.03	1.04± 0.21	1.07±0 .68

Table 3: Physical parameters for microspheres of Captopril

IN-VITRO DISSOLUTION STUDY:

It was observed that as the concentration of HPMC K 4 M increased, the % cumulative release of CP decreased. The increase in HPMC K 4 M concentration leads to the formation of high-density polymer matrix into the microspheres, which results in an increased diffusional path length and consequent retardation in drug release. The effect of speed stirring on the particle size of microspheres has already been studied. Smaller microspheres were formed at lower concentrations of HPMC K4M and have larger surface area exposed to the dissolution medium giving rise to faster drug release.

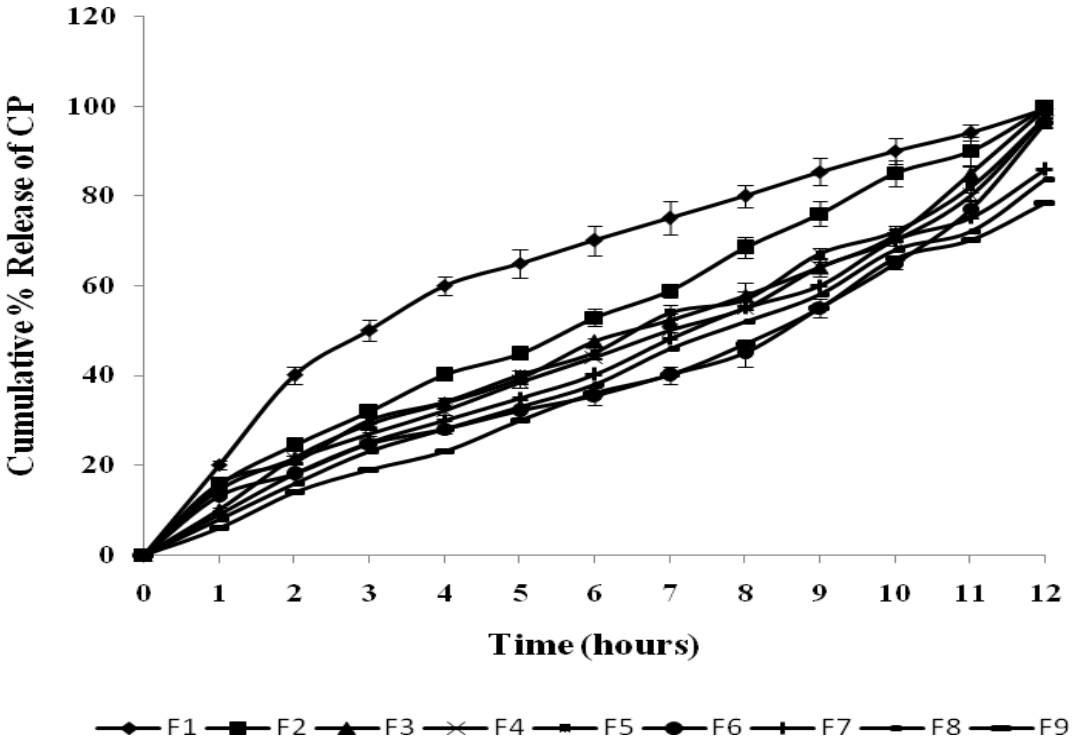


Figure 6: In-vitro dissolution profiles release of batches F_1 to F_9

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 7 (a) and (b)) and exhibited a range of sizes within each batch. Some of the microspheres showed a dented surface structure (Figure 7 (c)), but they showed good floating ability on the surface of the medium indicating intact surface. The outer surface of the microspheres was smooth.

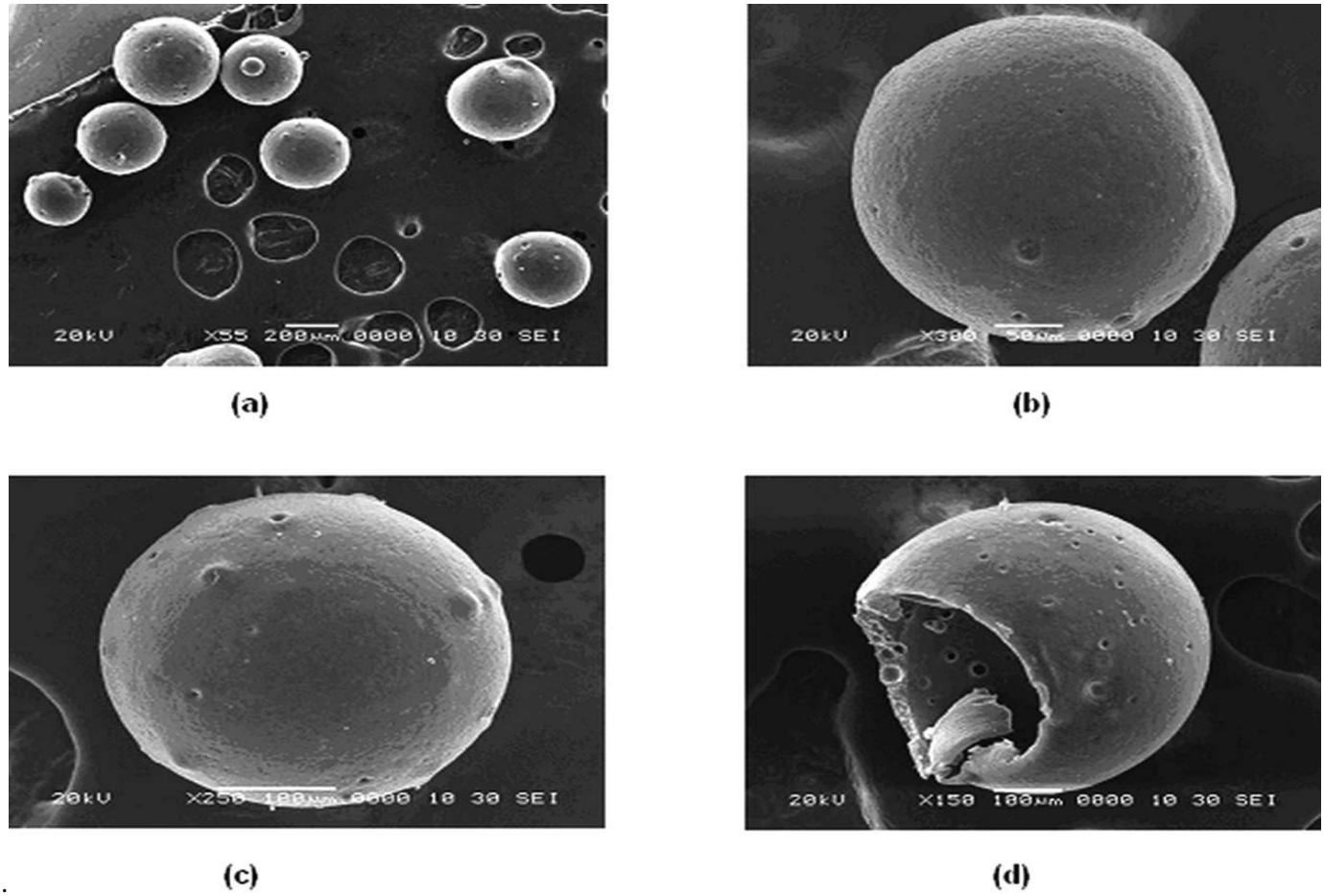


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Figure: 7 SEM of floating microspheres

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.

Days	Drug entrapment efficiency (%)	Buoyancy (%)	Drug release (%)
Before storage (0 days)	75±0.24	75.48±0.17	85.7±0.12
After storage			
7	74.78±0.45	75.23±0.23	85.00±0.23
15	74.56±0.67	75.21±0.89	84.23±0.54
30	74.34±0.78	75.10±0.45	84.12±0.29
60	74.00±0.90	75.00±0.17	84.34±0.71
90	74.00±0.10	75.00±0.28	84.20±0.12

Table 4: Stability study

CONCLUSION:

In the present study floating microspheres of CP showed better results. It was observed that the increase in polymer concentration, the entrapment efficiency as well as percentage yield increases. The *in-vitro* release studies showed that the better release profile with the formulation F_5, therefore F_5 can be considered as best formulation while compared with other batches. This can be concluded that by formulating CP as floating microspheres can improve the low oral bioavailability by expended drug release in the upper part of stomach.

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Conflict of Interest: None Declared

