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Formulation and Evaluation of Floating Microsphere of Captopril using Different Gas Forming Agents.

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ABSTRACT

The present study involves preparation and evaluation of floating microsphere of Captopril as model drug for prolongation of gastric residence time. the different gas forming agents are used such as sodium bicarbonate and calcium carbonate. The microsphere were prepared by Ionotropic gelation technique using polymers Sodium alginate along with HPMC (K4M) and Ethyl cellulose. The microsphere was 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 microsphere were characterized by optical and scanning electron microscopy, respectively. *In-vitro* drug release studies were performed by using an USP dissolution test apparatus (type I) at 37±0.5ºC and 50 rpm speed. To study the release behaviour, kinetic analyses were performed on the optimized formulation. The dissolution data were fitted to zero order, first order, matrix, Hixson-Crowell, Peppas model. The prepared microsphere exhibited prolonged drug release (~ 12 hr) and remained buoyant for > 12 hr. The optimized formulations H3, H6 were kept for short term stability study. The conditions for stability study were 40ºC and relative humidity of 75% from the study; it was observed that there is no significant change in drug entrapment and drug release rate.

Key-words: Floating microsphere, Captopril, *In-vitro* release, HPMC (K4M), Ethyl Cellulose

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INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968. It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high-density systems and low density systems that increase the gastric residence time. Gastric retention is useful for drugs which (i) act locally (ii) have a narrow absorption window in the small intestinal region; (iii) unstable in the intestinal environment (iv) low solubility at high pH environment.[1] Various dosage forms developed for gastric retention include, floating tablets, floating beads, pellets, floating granules, floating microspheres.[2]

Captopril, an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. It has been reported the duration of action after a single oral dose of captopril is only 6–8 h, so it requires dose of 37.5–75 mg to be taken three times.[3] It is most stable at pH 1.2 and as the pH increases; it becomes unstable and undergoes a degradation reaction.[4] The virtue of the prolonged release dosage form of captopril has been reviewed.[5] 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 microsphere of captopril using various gas forming agents such as sodium bicarbonate and calcium bicarbonate with a view of prolonging GRT with a controlled release mechanism. There were two principle objectives to this study. Firstly, the use of CaCO3 and NaHCO3

For the production of floating microsphere was investigated using a simple dripping method. The data presented here has established that these gas-forming agents are highly effective for floating microsphere formation. The second objective was to assess the effects of formulation variables on microsphere characteristics and to compare CaCO3and NaHCO3 as gas-forming agents.

MATERIALS AND METHODS

Captopril was a gift sample from Lupin pharmaceutical Aurangabad, HPMC (K4M) gifted from Unichem laboratories, Mumbai. Sodium alginate, calcium carbonate and sodium bicarbonate were purchased from S.D fine laboratories. All other reagents used were of analytical grade.

Compatibility study

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

Preparation of microsphere

The microsphere was prepared by ionic cross linking 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 $CaCO_3$ and sodium bicarbonate was separately added to the solution. The resulting solution was dropped through a 26G syringe needle into 5% (w/v) $CaCl_2$ solution which is prepared in water containing 10% (v/v) acetic acid. The solution containing suspend microsphere was kept for 1.5 hr. To improve the mechanical strength of the microsphere and allowed to complete the reaction to produce gas. [9-12] The fully formed microsphere were collected, washed with distilled water and subsequently air dried. The composition of floating microsphere are shown in Table 1.

Table 1: Composition of Floating Microsphere

Formulation	Drug (mg)	Sodium alginate (w/v)	Drug : HPMC*	$CaCo_3$ (gm)	$NaHCO_3$	$CaCl_2$ (%)
A-1*	25	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
H-6	25	5	1:1	0.5		5
H-7	25	5	1:2	0.5		5
H-8	25	5	1:3	0.5		5
H-9	25	5	1:4	0.5		5
H-10	25	5	1:5	0.5		5

*A- Formulation without copolymer i.e HPMC (K4M) and Ethyl cellulose
*H-1 to H-5 Formulation with sodium bicarbonate
H-6 to H-10 Formulation with calcium carbonate

Evaluation of floating microsphere[13]

Evaluation of micromeritic properties of microsphere

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 microsphere was weighed and the percentage yield calculated by equation no.1, taken into consideration the weight of drug and polymer.

Production Yield = Practical yield (Microsphere)/Theoretical yield (Polymer + Drug) X 100. (1)

Incorporation efficiency

Microsphere (50 mg) were crushed in a glass mortar-pestle and the powdered microsphere 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 10----- (2)

Particle shape and size

The size of microsphere 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. Microsphere 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 microsphere were placed in 30 ml of 0.1 N HCl in beaker. Floated microsphere were collected at 1, 2, 4, 6, 8 and 12 hr. The percentage of floating micro particles was calculated by the following equation no.3.

%Floating Microcarrier=Weight of floating microsphere /Initial weight of floating microsphere x100------ (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 study[16]

The optimized formulation was kept at room temperature and 75% relative humidity for 30 day. Then the microsphere 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 microsphere

The prepared microsphere was evaluated for percentage yield, drug entrapment efficiency, and average particle size. The results are shown in the Table 2.

Table 2: Micromeritic properties of microsphere

Formulation Code	Angle of repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
A1	20.48± 0.54	0.849± 0.08	0.887± 0.06	4.284±0.56	1.044±0.67
H1	19.41±0.98	0.746±0.02	0.785±0.03	4.968±0.91	1.052±0.03
H2	18.56±0.92	0.659±0.01	0.787±0.02	16.264±0.97	1.194±0.05
H3	20.42±0.74	0.861±0.03	0.982±0.04	12.321±1.55	1.140±0.03
H4	19.12±0.54	0.830±0.01	0.932±0.04	10.944±0.80	1.122±0.03
H5	21.64±1.04	0.804±0.04	0.960±0.04	16.25±1.29	1.194±0.01
H6	21.50±1.04	0.812±0.03	0.919±0.06	11.64±0.69	1.131±0.03
H7	20.98±0.86	0.800±0.03	0.987±0.03	18.946±0.88	1.233±0.02
H8	19.54±1.25	0.750±0.05	0.880±0.04	14.772±0.91	1.173±0.02
H9	20.83±1.56	0.882±0.04	0.985±0.04	10.456±1.30	1.116±0.02
H10	19.43±1.09	0.900 ±0.02	1.20±0.05	25.00±1.05	1.333±0.02

Mean ± S.D., n=3

Table 3: Evaluation parameter of microsphere

Formulation Code	Yield (%)	Entrapment (%)	Particle size (µm)
A1	86.34±1.67	51.78±1.32	750.40±1.23
H1	71.25±1.56	57.42 ±1.44	670.60±1.76
H2	72.63±1.16	62.52±2.19	721.00±1.45
H3	75.26±0.69	66.79±1.44	730.22±2.34
H4	76.00±0.91	68.07±2.88	756.81±1.50
H5	79.47±1.71	70.30±1.66	889.14±2.45
H6	72.47±1.19	58.73±1.29	619.16±3.45
H7	73.51±2.19	63.51±2.19	813.34±3.67
H8	75.60±2.19	68.66±2.19	826.27±1.46
H9	77.67±2.57	72.06±2.57	871.78±2.17
H10	79.57±1.2	74.58±1.02	950.17±1.30

Mean ± S.D., n=3

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

From the Table 3, the percent yields of the all formulations were found to be in the range of 71.25±1.56 to 86.34±1.67 The low percentage yield in some formulations may be also due to microsphere lost during the washing process.

The drug entrapment of Sodium alginate with HPMC (K4M) using sodium bicarbonate as a gas forming agent was found to be in the range of 51.78±1.32 to 70.30±1.66 The drug entrapment of

Sodium alginate with HPMC (K4M) using calcium carbonate 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 gas forming agent which are used in preparation of microcarrier. The average particle size of microsphere was found to be in the range of 619.16±3.45 to 950.17±1.30µm. The particle size increases as the polymer concentration increases with increase in gas forming agent 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 with calcium carbonate resulting in the formation of microsphere entrapping the greater amount of the drug, as compared to sodium bicarbonate 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 microsphere showed a spherical shape with a smooth surface morphology. The SEM photographs are shown in figure 1 a) and b)In general, CaCO3 -formed smaller and stronger floating Microsphere than NaHCO3.

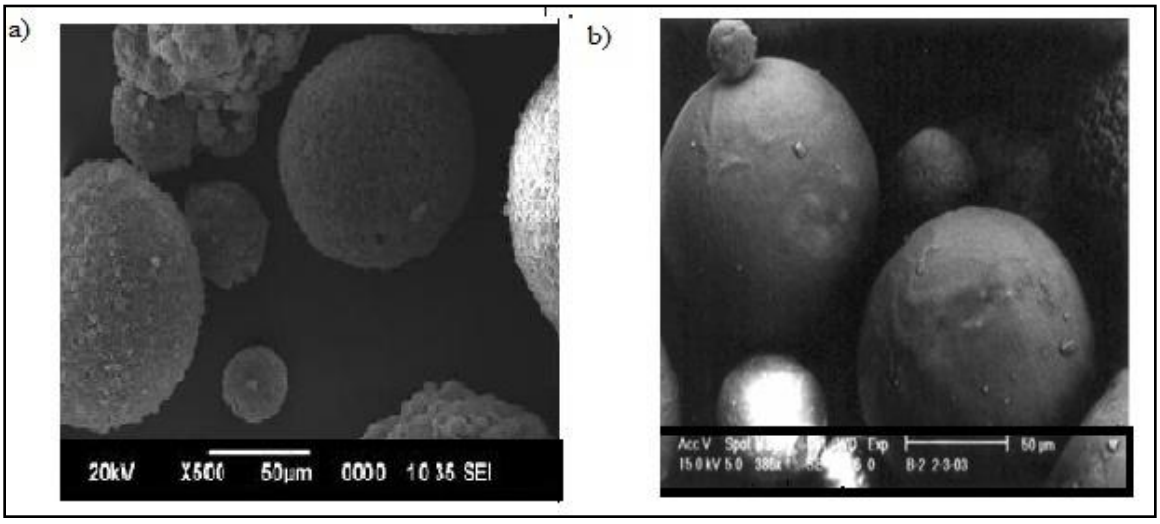

Figure 1. SEM photographs of microcarrier a) Formulation of H3 b) Formulation of H8

In general, CaCO3 -formed smaller and stronger floating microsphere than NaHCO3

Floating capacity

In order to investigate the floating capacity of prepared formulation A1,H1-H5(Figure 2), H6-H10 (Figure 3) 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 H6 to H10 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.

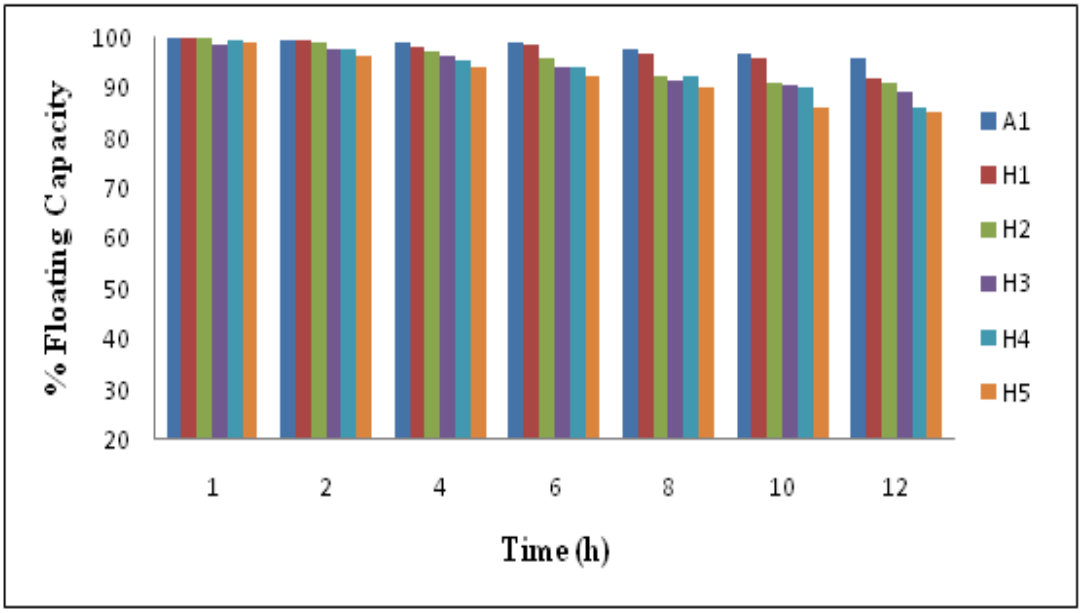

Figure 2. Results of Floating Capacity of Formulation A1 to H5

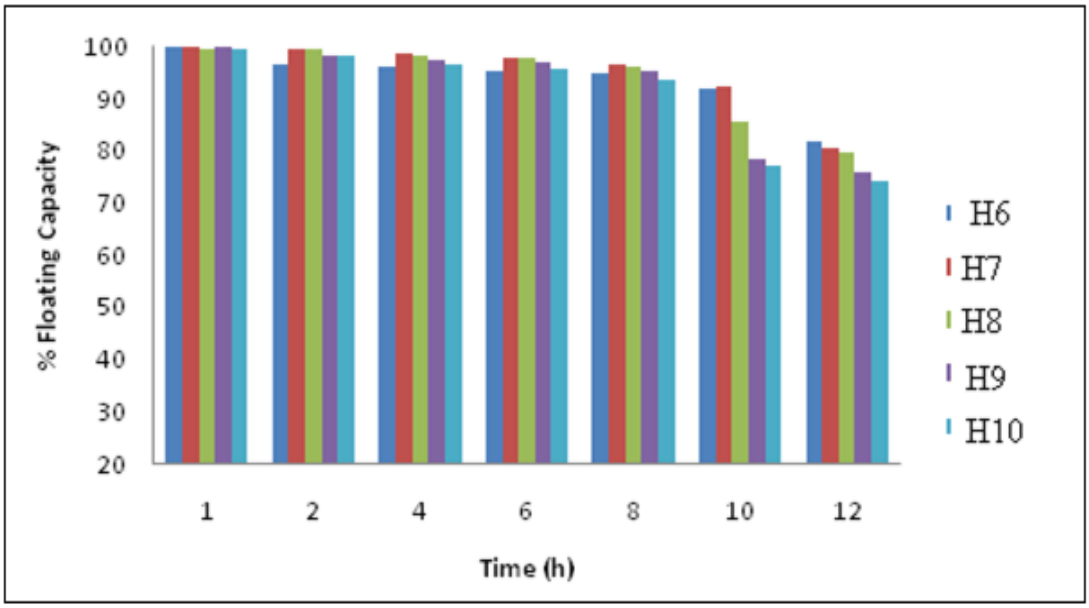

Figure 3. Results of Floating Capacity of Formulation H6 to H10

The formulation containing HPMC (K4M) with sodium bicarbonate shows the high percentage of floating capacity than the HPMC (K4M) with Calcium carbonate. The probable reason is HPMC (K4M) forms gel layer in contact with 0.1 N HCl, CO_2 gas which entrapped in gel network of HPMC (K4M) and help for floatation of microsphere. As the polymer ratio increases, the density of the microsphere increases with decreasing in floating ability of the microsphere

While gas-forming agent microsphere sinks The wet microsphere had better floating ability than dry microsphere. Floating ability is directly related to the gas kind of the polymer matrix. Wet microsphere can contain a greater proportion of CO_2 gas than dry ones and are thus more buoyant.

***In-vitro* drug release studies**

Effect of HPMC (K4M) and Sodium bicarbonate

In order to study the effect of HPMC (K4M) and sodium bicarbonate 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.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 microsphere containing the gelling agent forming a gelatinous barrier which controls the drug release rate. As the concentration of HPMC (K4M) increases with the constant amount of sodium bicarbonate in the formulation, the release rate was found to be decreases with increase in the floating ability.

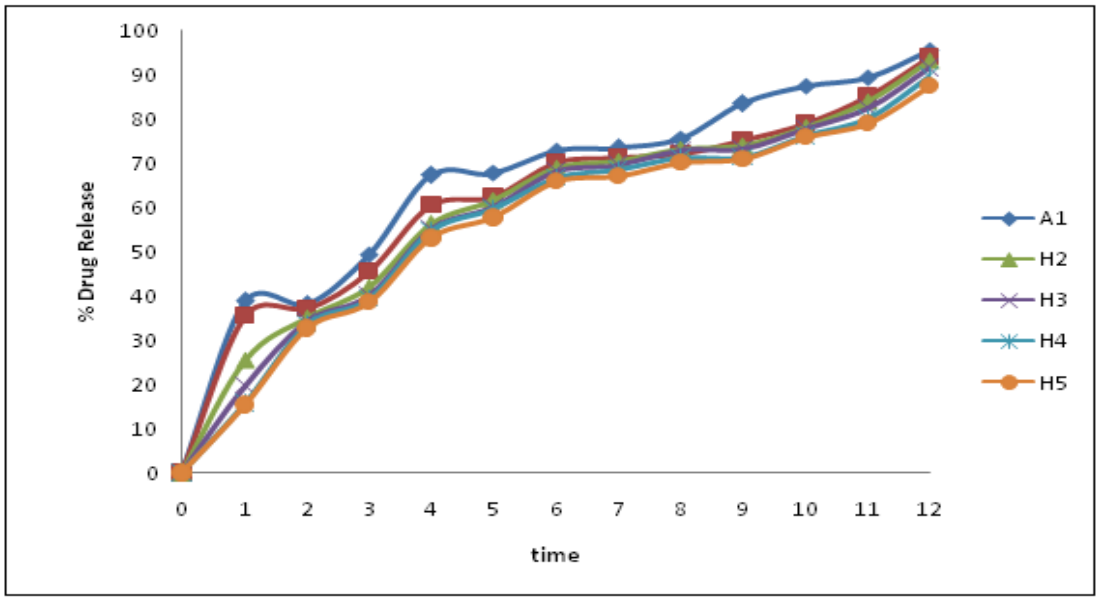

Figure 4. *In-vitro* Drug Release Study of Formulations A1 to H5

Effect of HPMCK4M and Calcium carbonate

In order to study the effect of HPMCK4M and Calcium carbonate on microsphere, the formulation prepared in the ratio of 1:1 to 1:5. The results are shown in Figure 5.

From the Figure 5, the HPMCK4M with calcium carbonate formulation showed slower drug release rate as compared to the HPMC (K4M) with sodium bicarbonate.

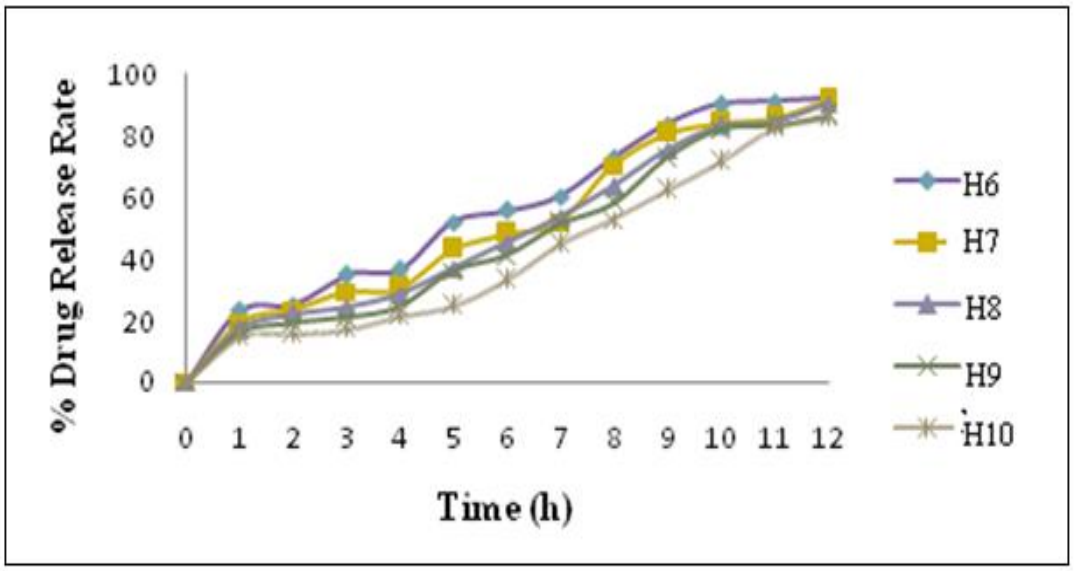

Figure 5. *In-vitro* Drug Release Study of Formulations H6 to H10

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. Criteria for selecting the most appropriate model was based on best goodness of fit with determination coefficient (r^2) nearer to 1.

Table 4: Results of Release Kinetic of Optimized Microsphere

Formulation Code	Regression Coefficient (r^2)				
	Zero order	First order	Matrix	Hixon Crowell	Korsemeyer-Peppas
H3	0.9764	0.9414	0.9385	0.9630	0.9665
H6	0.9656	0.8979	0.8675	0.9280	0.8426

6) Stability study

The optimized formulation was kept at room temperature and 75% relative humidity for 30 day. Then the microsphere 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 5: Results of Stability Study

Formulation code	Drug entrapment (%)	Drug release rate (%)
H3	66.79±1.44	91.62±0.34
H6	58.73±1.29	89.443±0.54

Mean ± S.D., n=3

CONCLUSION

The study has clearly shown that the kind of gas forming agent has a profound effect on size, floating ability, morphology, release rate and mechanical strength of floating microsphere In general, CaCO3 -formed smaller and stronger floating beads than NaHCO3. Consequently, microsphere formed with CaCO3 significantly extended drug release. Overall, it was demonstrated that although CaCO3 is a less effective gas-forming agent than NaHCO3. It is hoped that further research with a variety of gas-forming agents and new preparation methods for floating microspheres will lead to the development of more effective FDD Systems.

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