Research Article

Formulation and Evaluation of Floating Beads Of Famotidine

S. M. Deepak Vallamsetti*, Ms. Nimisha
Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University, Lucknow, Uttar Pradesh, India.
***Corresponding author's E-mail:** deepak17pharma@gmail.com

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ABSTRACT

The purpose of this research was to prepare a floating drug delivery system of famotidine. In the present study, preparation of famotidine floating beads, evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of polymers ratio to match target release profile was investigated. Floating beads were prepared by Emulsion Gelation Method using hydroxyl propyl methylcellulose (HK), Polycarbophil (PC) and Carbopol (CP) as the rate controlling polymers with Sodium alginate (SA) as thickening agent. Particle size analysis, drug entrapment efficiency, surface topography, buoyancy percentage and release studies were performed. Beads formulated with mixture of SA and PC showed the highest drug content and entrapment compared to other formulations. The beads did not swell or erode in the dissolution media, which suggested that drug release was dependent on the dissolution and diffusion of the drug through the polymer matrix. The buoyancy studies on the beads proved that a minimum of 20% w/w of cod liver oil was required to impart satisfactory buoyancy to the beads. The results showed that beads formulated with mixture of SA and PC (F4) showed the highest drug release compared to other formulations. So the formulation F4 was selected for stability studies according to ICH guidelines for a period of three months and the formulation (F4) formulated with a mixture of SA and PC in 9:1 ratio was proved to be effective.

Keywords: Floating drug delivery system (FDDS), Gastroesophageal reflux disease (GERD), Carbopol, Modified flow through dissolution apparatus, Polycarbophil.

INTRODUCTION

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. Several approaches are currently used to prolong gastric retention time.[1-6] These include floating drug delivery systems, also known as hydro dynamically balanced systems, swelling and expanding systems, polymeric bio adhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices.

Floating drug delivery system[2] (FDDS) promises to be a potential approach for gastric retention. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying.[7]

Famotidine[1, 20] is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease.[3, 4, 16-18] In the management of benign gastric and duodenal ulceration the dose is 40 mg daily by mouth at bedtime, for 4 to 8 weeks. In gastroesophageal reflux disease the recommended dose is 20 mg by mouth twice daily for 6 to 12 weeks; where gastroesophageal reflux disease is associated with esophageal ulceration, the recommended dosage is 40 mg twice daily for a similar period[8]. For the short term symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 10 mg up to twice daily is suggested. In the Zollinger-Ellision syndrome the initial dose by mouth is 20 mg every 6 hours, increased as necessary; dose up to 80 mg daily have been employed.[19] The low bioavailability (40-45%) and short biological half-life (2.5-4.0 hours) of famotidine following oral administration favours development of a sustained release formulation.[9]

The objective of research work is formulation and evaluation of floating drug delivery systems containing famotidine, which would remain in stomach for prolonged period of time in view to maximize bioavailability of the drug.[10]

MATERIALS AND METHODS

Materials

Famotidine was obtained as a gift sample from Lee Pharma, Hyderabad (India). Sodium Alginate (SA) Molychem- Mumbai, Hydroxypropyl Methyl Cellulose K15M (HK), Calcium Chloride and Hydrochloric acid from Merck- Mumbai, Carbopol 934P (CP) and Polycarbophil (PC) were obtained from Lobachemie- Mumbai, and Cod Liver Oil from Universal Medicare Pvt. Ltd, Mumbai. All other chemicals/reagents used were of analytical grade, available commercially and used as such without further processing. A UV/Vis spectrophotometer (Elico, Double beam UV-VIS Spectrophotometer: SL 218) was used for drug analysis.

Preparation of floating famotidine beads

Famotidine, SA, HK, CP and PC were passed through sieve no 80 separately. Famotidine (20% w/w of dry polymer weight) was dissolved in distilled water. SA (3% w/v) alone and polymer mixtures (3% w/v) containing SA and HK, SA and CP and SA and PC in 3 different ratios were dissolved in above dispersion. To the above mixture cod liver oil (20%w/w) was added and stirred to form a homogeneous emulsion. The drug-loaded emulsion was extruded through a 23G syringe needle into calcium chloride solution (2% w/v) maintained under gentle agitation. The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight. Table 1 lists the formulation variables for different formulations of famotidine loaded floating beads. Blank beads without famotidine were also prepared using the same technique.[11]

Table 1: Formulation variables of various famotidine bead formulations

Formulation Code	SA : HK (3% w/v)	SA : PC (3% w/v)	SA : CP (3% w/v)	Oil (% w/w)
F Blank	10:0	10:0	10:0	-
F	10:0	10:0	10:0	10
	10:0	10:0	10:0	15
	10:0	10:0	10:0	20
F1	9:1	-	-	20
F2	8:2	-	-	20
F3	7:3	-	-	20
F4	-	9:1	-	20
F5	-	8:2	-	20
F6	-	7:3	-	20
F7	-	-	9:1	20
F8	-	-	8:2	20
F9	-	-	7:3	20

Characterization of floating beads of famotidine

Determination of bead diameter

The diameter of a sample of gel beads (20 beads) of each formulation was determined using a dial thickness meter. Measurement for each sample was repeated ten times. Mean diameter and standard deviations were recorded.[12]

Drug Content

An accurately weighed sample of beads (200mg) was crushed in a mortar and added to 100 ml of 0.1N hydrochloric acid buffer (pH 1.2). This mixture was kept overnight under stirring to elute complete drug from the polymer matrix. The mixture was filtered and analysed spectrophotometrically at a wavelength of 265nm against blank bead mixture, which was treated similarly. The drug content of each formulation was recorded as mg / 200 mg of gel beads.[13]

Drug Entrapment Efficiency

The percentage drug entrapment efficiency (%EE) of each bead formulation was calculated using the following equation:

$$EE\ (\%) = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Determination of swelling index

The swelling behaviour of the famotidine beads was studied in 0.1 N HCl (pH 1.2) buffer. Approximately 100mg of beads were taken in a dissolution basket and weighed (W1), the baskets along with the beads were immersed in 0.1N HCl buffer. The weight (W2) of the basket along with the beads was determined for 8 h: every 30 minutes for the first 2 h, and then every h after that. The swelling index (SI) of each formulation was calculated using the following equation:

$$\%\ SI = \frac{W2 - W1}{W1} \times 100$$

Buoyancy studies

The time between the introduction of the FDDS into the medium and its buoyancy to the upper one third of the dissolution vessel (floating lag time) and the time for which the formulation constantly floated on the surface of the medium (floating duration) were measured simultaneously as a part of dissolution studies by visual observation.[14]

In-vitro drug release studies

In Vitro Drug Release Studies by Conventional Method

In vitro release characteristics of famotidine floating beads (n=3) were evaluated employing USP XIV dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 500 ml of 0.1 N HCl buffer as dissolution medium maintained at 37±0.5 ºC. The contents were stirred at 50 rpm. A 5 ml aliquot of the solution was withdrawn at predetermined time intervals for 8 h and fresh 5ml dissolution media was replaced to maintain sink condition. The sample aliquots were analysed spectrophotometrically at a wavelength of 265nm.[15]

In Vitro Drug Release Studies by Modified Flow through Dissolution Method

In vitro release characteristics of famotidine floating gel beads (n=3) were evaluated in 0.1N HCl (pH 1.2). Dissolution of floating beads was carried out in a modified flow through dissolution by further modifying the modified Rosette Rice test apparatus with an outer hot water glass jacket. A glass beaker of 100 ml was modified at the base by adding a tapped glass tube outlet to collect samples. This apparatus was housed inside an outer glass

jacket through which hot water at 37±2ºC was circulated continuously. The medium was stirred at 75 rpm on a magnetic stirrer. A burette connected to a reservoir was mounted above the beaker to deliver fresh dissolution medium at a flow rate of 10ml 30min-1. Sampling was done at every 30 min till 8 h. The sample aliquots were analysed spectrophotometrically at a wavelength of 265nm.

Stability Studies

Stability studies were carried out according to ICH guidelines by storing the formulations at different temperatures and humidity conditions for a period of three months in a programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). The samples were withdrawn at 30, 60 and 90 days and analysed for the drug content, floating behaviour and *in vitro* drug release.

Mechanism of release

The mechanism of release was determined by fitting the release data to the various 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.

RESULTS AND DISCUSSION

Compatibility study

The DSC thermo grams of physical mixture of famotidine and the polymers showed no characteristic peaks of the polymers and famotidine peaks were still present but slightly shifted from their original positions which could be possibly due to an ionic interaction and this characteristic features of drug melting suggested that no problem of incompatibility. Some modification of drug peak, such as changes in area, shape or peak temperature were found, but they arose simply from mixing the components.

Compatibility studies by FT-IR

The physical mixture showed identical spectrum with respect to the spectrum of the pure drug, indicating there is no chemical interaction between the drug molecule and polymers. (Figure 1).

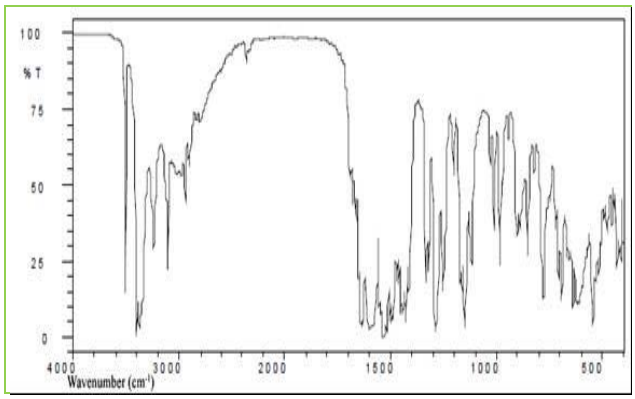

Figure 1: FT-IR spectra of optimized formulation F4

Micrometrics

The angle of repose, porosity, bulk density, tapped density and the compressibility index of the formulations was found to be in the good range indicating the excellent flow properties of the formulated formulations F1-F9. (Table 2)

Table 2: Micrometric properties of the Famotidine formulations

Formulation	Angle of Repose θ	Loose bulk Density (gm/ml)	Tapped Bulk Density (gm/ml)	Compressability Index (%)	Porosity %
F	22.30	0.126	0.131	16.10	14.78
F1	26.55	0.112	0.115	13.46	22.10
F2	25.18	0.104	0.109	14.50	31.30
F3	26.12	0.100	0.105	16.12	28.45
F4	27.10	0.125	0.134	10.05	27.20
F5	24.28	0.116	0.121	10.39	20.12
F6	25.35	0.112	0.118	11.30	17.85
F7	26.55	0.090	0.102	13.30	20.12
F8	29.88	0.085	0.105	15.24	19.56
F9	24.30	0.110	0.115	15.50	21.34

Particle size analysis

The prepared beads were almost spherical and translucent. The mean surface diameter of 10 formulations was between 1.576±0.012 (SD) and 1.612±0.015 (SD). (Table 3). The mean particle diameter of the blank oil entrapped famotidine beads containing no drug were found to be 1.424±0.012 (SD), but the drug loading to the beads increases the size of the beads of, e. g. it was found that the mean diameter of formulation F was increased to 1.526±0.015 (SD) upon drug loading. It was found that incorporation of copolymers such as CP, HK and PC to the bead formulations result in further increasing of the bead diameter as in case of formulations to F9. As the process parameters were kept constant, the

added materials were responsible for the change in the size of the famotidine beads.

Table 3: Characterization of floating Famotidine beads

Formulation Code	Mean Diameter ± SD (mm)	Drug content (mg)	% EE
F Blank	1.424±0.008	-	-
F	1.512±0.015	2.294±0.034	38.24
F1	1.516±0.012	4.456±0.031	74.26
F2	1.522±0.022	4.159±0.142	69.31
F3	1.498±0.015	4.087±0.098	68.11
F4	1.504±0.032	5.814±0.041	96.90
F5	1.514±0.015	5.386±0.121	89.78
F6	1.524±0.015	4.777±0.049	79.62
F7	1.520±0.012	5.088±0.092	84.80
F8	1.517±0.030	4.953±0.087	82.55
F9	1.526±0.015	4.887±0.074	81.45

Drug entrapment efficiency

The percent drug entrapment efficiency for various famotidine floating bead formulations was found to vary between 38.24% and 89.81%. Formulation F4 showed the highest drug entrapment and formulation F showed the lowest entrapment of drug. The low drug entrapment efficiency of the F formulation may be attributed to the highly porous nature of the calcium alginate matrix, due to which the drug may diffuse back into the cross linking solution from the bead matrix during cross linking period. The drug entrapment also increases with addition of the copolymers into the bead formulation.

Floating Properties

The floating ability was found to be directly related to the amount of oil entrapped in the polymer matrix. The beads remained afloat throughout the study period (12hrs) and the beads continued to float till 24h. It was found that varying the polymer and copolymer concentrations in the bead formulations did not affect the floating lag time or the floating duration of the beads in the dissolution media.

Swelling index

The beads were also not swollen or eroded during the dissolution studies in 0.1 N HCl. Thus, from these results, it could be assumed that the drug release was not under the control of the swelling behaviour but rather was controlled by the dissolution of the famotidine in the dissolution medium and diffusion of the famotidine through polymer matrix.

***In-vitro* release profile**

Conventional method

In-vitro drug release study of famotidine floating beads was carried in 0.1N HCl (pH 1.2), for a period of 12 hrs. In the 0.1N HCl, the beads exhibited a biphasic release profile as an initial rapid drug release phase (burst effect) was followed by a sustained, gradually increasing drug release phase after 1h extending up to 12hrs. Formulation F contained only SA could not sustain the famotidine release up to 12hrs. It released complete drug at the end of 04 hrs. Whereas formulations contained HK; F1, F2 and F3 released 68.42%, 63.12% and 61.00% of drug respectively at the end of 12hrs. Whereas formulations contained PC; F4 (table 4), F5 and F6 released 99.74%, 94.29% and 91.01% of drug respectively at the end of 12hrs and the release profile is shown in figure 2. The formulations contained CP; F7, F8 and F9 released 83.52%, 79.72% and 74.47% of the drug at the end of 12hrs respectively. The results show that incorporation of rate controlling polymers such as HK, PC and CP to the bead formulations can sustain the drug release from the oil entrapped famotidine beads. Incorporation of these copolymers into the calcium matrix increases the viscosity of the polymers matrix and correspondingly decreases the drug release. Results also show that as the concentration of the copolymers increases in the formulation, the drug release is further decreased and more sustaining of drug release is observed because as the concentration of copolymers is increased the viscosity of the polymer matrix is further enhanced.

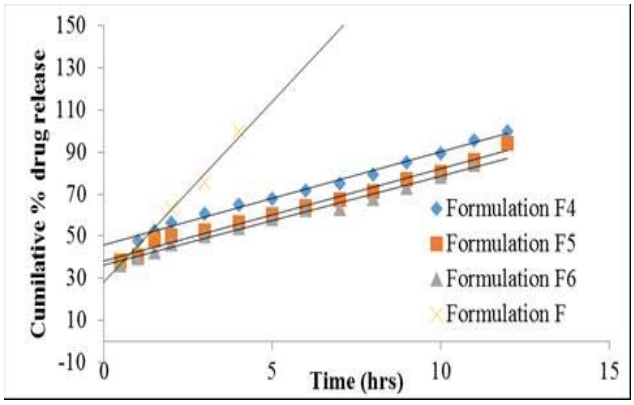

Figure 2: Comparison of *in vitro* dissolution characteristics of F, F4, F5, and F6.

The in vitro release data of all the batches were fitted to zero order, first order, Higuchi and Korsemeyer and Peppas equations. All the formulations, F1 to F9 followed Higuchi model. As the n values of the Korsemeyer-peppas model for all the formulations was found to be less than 0.5, it suggested that the drug release from the beads followed fickian diffusion.

Modified flow through dissolution method

In vitro drug release study of famotidine floating beads was carried in 0.1N HCl (pH 1.2), for a period of 12hrs. In the 0.1N HCl, the beads exhibited a biphasic release

profile as an initial rapid drug release phase (burst effect) was followed by a sustained, gradually increasing drug release phase after 1h extending up to 12hrs. Formulation F contained only SA could not sustain the famotidine release up to 12hrs. It released complete drug at the end of 5.0 hrs. Whereas formulations contained HK; F1, F2 and F3 released 69.69%, 66.37% and 60.22% of drug respectively at the end of 12hrs.

Table 4: *In vitro* release characteristics of formulation F4

Time (hrs)	SQRT	Log Time	Cum. % drug release	Log% drug release	Log% drug remaining
0	0	-	0	-	2.0000
0.5	0.7071	-0.3010	41.69±1.21	1.6201	1.7657
1.0	1.0000	0.0000	48.08±1.82	1.6820	1.7153
1.5	1.2247	0.1760	52.50±1.02	1.7202	1.6766
2.0	1.4142	0.3010	56.36±1.15	1.7510	1.6398
3.0	1.7320	0.4771	60.54±1.21	1.7821	1.5961
4.0	2.0000	0.6020	64.93±1.25	1.8125	1.5449
5.0	2.2360	0.6989	67.98±1.61	1.8324	1.5054
6.0	2.4494	0.7781	71.46±1.57	1.8541	1.4554
7.0	2.6457	0.8450	75.23±0.46	1.8764	1.3939
8.0	2.8284	0.9030	79.15±0.37	1.8985	1.3191
9.0	3.0000	0.9542	85.15±0.12	1.9302	1.1717
10.0	3.1622	1.0000	89.37±0.37	1.9512	1.0265
11.0	3.3166	1.0413	95.63±0.27	1.9806	0.6404
12.0	3.4641	1.0791	99.74±0.09	1.9989	-0.5850

Table 5: *In vitro* release characteristics of formulation F4 (Modified flow through method)

Time (hrs.)	SQRT	Log time	Cum.% drug release	Log% drug release	Log% drug remained
0	0	-	0	-	2.0000
0.5	0.7071	-0.3010	29.84±1.24	1.4749	1.8460
1.0	1.0000	0.0000	33.45±1.49	1.5245	1.8231
1.5	1.2247	0.1761	35.74±1.28	1.5532	1.8079
2.0	1.4142	0.3010	39.29±1.14	1.5943	1.7832
2.5	1.5811	0.3979	42.40±1.05	1.6274	1.7604
3.0	1.7321	0.4771	44.25±1.09	1.6460	1.7462
3.5	1.8708	0.5441	45.83±0.85	1.6612	1.7337
4.0	2.0000	0.6021	48.13±1.16	1.6825	1.7149
4.5	2.1213	0.6532	51.00±1.24	1.7076	1.6901
5.0	2.2361	0.6990	53.30±1.32	1.7268	1.6693
5.5	2.3452	0.7404	55.38±1.27	1.7434	1.6495
6.0	2.4495	0.7782	58.80±1.24	1.7694	1.6148
6.5	2.5495	0.8129	60.63±1.18	1.7827	1.5951
7.0	2.6458	0.8451	65.01±1.16	1.8130	1.5439
7.5	2.7386	0.8751	68.32±1.48	1.8346	1.5007
8.0	2.8284	0.9031	71.10±1.28	1.8519	1.4608
8.5	2.9154	0.9294	74.21±1.34	1.8705	1.4114
9.0	3.0000	0.9542	78.25±1.26	1.8935	1.3374
9.5	3.0822	0.9777	81.33±1.23	1.9103	1.2711
10.0	3.1622	1.000	85.58±1.24	1.9324	1.1589
10.5	3.2403	1.0211	87.72±1.22	1.9431	1.0891
11.0	3.3166	1.0413	89.47±1.17	1.9517	1.0224
11.5	3.3911	1.0606	93.56±1.15	1.9711	0.8088
12.0	3.4641	1.0791	99.47±1.10	1.9977	-0.2757

The formulations contained PC; F4 (Table 5), F5 and F6 released 99.47%, 93.62% and 90.63% of the drug at the end of 12hrs respectively. The formulations contained CP; F7, F8 and F9 released 84.48%, 75.19% and 72.39% of the drug at the end of 12hrs respectively. It appears that incorporation of CP decreased the famotidine release by many folds. CP is insoluble in 0.1N HCl (pH 1.2) and swelling behavior of the CP is attributed to the unchanged –COOH group that get hydrated by forming hydrogen bonds with the imbibing water and, therefore, extending the polymer chain. Formulation without CP (F1 to F6) exhibited a higher burst effect, likely due to the fact that CP is a cross linked polymer with high viscosity as compared with HK and PC.

It was found that a higher total amount of drug release was achieved with conventional method compared to the modified method. The higher drug release from the USP dissolution method could be due to the fact that the volume of dissolution medium is larger when compared to the modified method which offers more sink condition. Still the modified dissolution apparatus offers better simulation of in vivo conditions.

Stability studies

In view of potential utility of the formulation, stability studies were carried out on formulation F4 for three months according to ICH guidelines. At the end of each month, the formulations were subjected to drug assay, floating behaviour and in vitro release studies and the results are shown in Table 6. At various time intervals, samples were evaluated for the stability studies. There were no more difference in the drug content and the floating properties at the various sampling intervals. The in vitro drug release profiles were super imposable which confirms the stability of the product.

Table 6: Stability study of formulation F4

Time	Drug content	Floating FLT (min)	Behavior Duration (hrs.)	Drug release at 12 hrs.
First month	5.404±0.051	0	24hrs	99.46±1.21
Second month	5.397±0.084	0	24hrs	97.22±1.70
Third month	5.395±0.072	0	24hrs	97.18±1.12

CONCLUSION

Beads formulated with mixture of SA and PC showed the highest drug content and entrapment compared to other formulations. The beads did not swell or erode in the dissolution media, which suggested that drug release was dependent on the dissolution and diffusion of the drug through the polymer matrix. The buoyancy studies on the beads proved that a minimum of 20% w/w of cod liver oil was required to impart satisfactory buoyancy to the beads. The beads showed instantaneous and excellent buoyancy and remained afloat on the dissolution medium throughout the study period.

The in vitro drug release study showed that SA alone could not sustain the drug release for sufficient period of time whereas incorporation of rate controlling polymers such as HK, PC and CP as copolymers can effectively sustain the drug release from the bead formulations. Comparison of in vitro release profile from both the dissolution methods showed that the USP method gave the higher drug release profile compared to the modified dissolution method. The results showed that beads formulated with mixture of SA and PC (F4) showed the highest drug release compared to other formulations. So the formulation F4 was selected for stability studies. The selected formulation showed no more changes drug content, floatability or in vitro drug release profile after storage during stability study for three months. Thus, the objective of the present work of formulating a dosage form for famotidine by using a low density oil and different proportions and combinations of release rate controlling polymers has been achieved with success.

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