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DEVELOPMENT AND *IN-VITRO* CHARACTERIZATION OF EFFERVESCENT FLOATING DRUG DELIVERY SYSTEM OF FAMOTIDINE

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ABSTRACT

The objective of the present study was to prepare and evaluate gastroretentive floating drug delivery system containing famotidine as a model drug. Famotidine tablets were prepared by wet granulation method using two different grades of hydroxypropylmethyl cellulose- HPMC K4M and HPMC K100M by effervescent technique. Sodium bicarbonate (SB) and citric acid (CA) were incorporated as gas-generating agents. Floating tablets were evaluated for uniformity of weight, thickness, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The effect of effervescent agent on drug release profile and floating properties was also investigated. Prepared tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium. Non–Fickian diffusion was confirmed as the drug release mechanism from these tablets, indicating that water diffusion and polymer rearrangement played an essential role in drug release. All the prepared tablets showed good *in vitro* buoyancy.

INTRODUCTION: Oral controlled release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages and applications. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms [1].

However, the development process is precluded by several physiological difficulties, such as an inability to confine the dosage form within desired region of the gastrointestinal tract, fluctuation in the gastric emptying process etc. This variability may lead to an unpredictable bioavailability of an orally administered dosage form [2]. To increase the gastric retention time of drugs, gastroretentive floating dosage forms are developed which can remain in the gastric region for several hours [3]. Incorporation of the drug in these dosage forms prolong the retention time within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [4]. From the formulation and technological point of view, floating drug delivery system is considerably easy and logical approach in the development of gastroretentive dosage forms [5].

Gastroretentive floating drug delivery technology is one of the promising approach for enhancing the bioavailability and controlled delivery of drugs that exhibit narrow absorption window [6]. These drug delivery systems have been shown to possess better efficacy in controlling the release rate for drugs with site specific absorption [7].

Famotidine is a histamine H_2 receptor antagonist which is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. This drug completely antagonises the parietal

cell H_2 receptor. It inhibits histamine, gastrin and acetylcholine stimulated acid secretion; pepsin secretion also falls with the reduction in volume of gastric juice. It increases the incidence and rate of healing of peptic ulcers [8, 9].

In the present investigation, HPMC K4M and HPMC K100M were utilized along with gas generating agents such as sodium bicarbonate and citric acid for the formulation of floating tablets of famotidine which would increase the bioavailability, thereby improving the therapeutic efficacy and patient compliance.

MATERIALS AND METHODS: Famotidine was obtained from Oyster Labs Ltd., Ambala, India. HPMC K4M and HPMC K100M were procured from Colorcon Pvt. Ltd, Goa, India. Sodium bicarbonate and Citric acid were received as gift samples from S.D. Fine-Chem Ltd., Mumbai, India. Polyvinyl pyrrolidone K-30 (PVP K-30), Magnesium stearate and Talc were obtained from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Isopropyl alcohol was kindly provided by Qualigens Fine Chemicals, Mumbai, India.

Preparation of Floating Tablets: Tablets were prepared by wet granulation method. First of all, the ingredients were weighed and then mixed thoroughly. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol. After drying in conventional hot air oven at 45°C, the dried granules were passed through 18/22 mesh, then lubricated with magnesium stearate (1%w/v) and purified talc (2%w/v). Finally, the blend was compressed on a mini-rotary punching machine with punches of 7 mm [10]. The composition of different formulations of floating tablets is shown in **table 1**.

TABLE 1: FORMULATION OF FLOATING TABLETS USING DIFFERENT RATIO OF POLYMER AND EFFERVESCENT AGENTS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Famotidine	40	40	40	40	40	40	40	40	40	40
HPMC K4M	40	50	60	60	60	-	-	-	-	-
HPMC K100M	-	-	-	-	-	40	50	60	60	60
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20	20
Citric Acid	2	2	2	3	4	2	2	2	3	4
PVP K-30	20	20	20	20	20	20	20	20	20	20
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4

Evaluation of Granules: Prior to compression, granules were evaluated for their characteristic parameters, such as Bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The angle of repose was determined by the fixed funnel method. Bulk density, tapped density, Carr's index and Hausner's ratio were calculated using tap density apparatus (Electrolab, USP) [11].

Evaluation of Tablets: The prepared tablets were evaluated for uniformity of weight using 20 tablets. Hardness, thickness and friability were measured with Pfizer hardness tester, vernier calliper and Roche friabilator respectively. The results were expressed as mean ± Standard deviation [12-14].

Drug Content Uniformity: Twenty tablets were taken and powdered; powder equivalent to one tablet was accurately weighed and was allowed to dissolve in 100 mL of 0.1 N HCl, followed by stirring for 30 minutes. The solution was filtered through 0.45 µm membrane filter, diluted suitably and analysed using UV/Visible spectrophotometer at 265 nm using 0.1 N HCl as blank [12].

***In vitro* Buoyancy Studies:** The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 mL beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was taken as the floating lag time. The mean ± S.D. values of buoyancy were calculated [15].

Determination of Swelling Index: The swelling index of tablets was determined in 900 mL of 0.1 N HCl at 37±0.5°C. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = (w_2 - w_1)/w_1 \times 100$$

Where, w_1 = initial weight of tablet; w_2 = final weight after swelling of tablet.

The mean ± standard deviation values of swelling index were calculated [16].

***In vitro* Dissolution Studies:** *In vitro* dissolution studies were carried out using USP dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 900 mL of 0.1 N HCl, maintained at 37 ± 0.5°C. 10 mL of the sample was withdrawn at suitable time intervals and immediately replaced with an equal volume of 0.1 N HCl to maintain the volume constant. The samples were filtered through a 0.45 µm membrane filter, diluted sufficiently and analysed at 265 nm using UV/Visible double-beam spectrophotometer [17].

Kinetic Modelling of Drug Release: The suitability of several equations, which are reported in the literature to identify the mechanism(s) for the release of drug, was tested with respect to the release data [18-21]. Data were evaluated according to the following equations mentioned in **table 2**:

TABLE 2: KINETIC MODEL EQUATIONS

Model	Equation
Zero order	$F= K_0t$
First order	$\ln F=K_1t$
Higuchi	$F= K_Ht^{0.5}$
Korsmeyer and Peppas model	$F=Kt^n$

Where F is the fraction of drug release constant, t is the time, n diffusion coefficient

RESULTS AND DISCUSSION:

Characterization of Granules: Granules prepared for compression of floating tablets were evaluated for their flow properties like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results are shown in **table 3**. Bulk density was found between 0.370-0.391 gm/cm^3 with HPMC K4M and 0.365-0.395 gm/cm^3 with HPMC K100M. Tapped density ranged between 0.438-0.460 gm/cm^3 with granules containing HPMC K4M, 0.427-0.452 gm/cm^3 with HPMC K100M. Carr's index was found to be in the range of 11.33-15.52 for both formulations, indicating good flow.

Flowability of granules was found to be good as indicated by compressibility-flowability correlation data. Hausner's ratio is related to interparticle friction. Hausner's ratio values for all formulations were found to be near about 1.2 indicating low interparticle friction. Angle of repose was found to be in the range of 24.34°-29.40° with HPMC K4M and 23.70°-25.40° with HPMC K100M. The values of angle of repose were less than 30, indicating good flowability.

TABLE 3: CHARACTERIZATION OF GRANULES

S. No.	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's Ratio (H_R)	Angle of repose (θ)
F1	0.390	0.455	14.28	1.167	24.34
F2	0.390	0.460	15.21	1.179	26.30
F3	0.370	0.438	15.52	1.183	27.69
F4	0.385	0.445	13.48	1.155	29.40
F5	0.391	0.441	11.33	1.127	28.80
F6	0.374	0.439	14.80	1.173	23.70
F7	0.393	0.448	12.27	1.139	24.40
F8	0.365	0.427	14.51	1.169	24.69
F9	0.395	0.452	12.61	1.144	25.40
F10	0.389	0.440	11.59	1.131	23.96

Physicochemical Evaluation: Floating tablets of famotidine were prepared by effervescent technique using HPMC (K4M, K100M), sodium bicarbonate, citric acid and PVP K-30. The magnesium stearate and talc were used as lubricant and glidant, respectively. Findings of the physicochemical characterization are shown in **table 4**. Average weight of floating tablets in all the formulations varied between 198.15 mg to 199.15 mg. Variation was determined less than 7.5% which is found to be within limits as prescribed in USP. Thickness of tablets of all the formulations was observed in between 3.28 mm to 3.38 mm which is found to be satisfactory. The hardness for different formulations was found to be between 5.13 to 5.93 kg/cm^2 indicating satisfactory mechanical strength. The friability was below 1% for all formulations, which is an indication of good mechanical resistance of the tablets. Drug content varied in between 97.40% to 98.29% for different formulations, indicating good content uniformity.

TABLE 4: VARIOUS PHYSICOCHEMICAL CHARACTERISTICS OF FLOATING TABLETS

Evaluation Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Average weight (mg) ± S.D.	198.80±0.76	198.15±0.98	198.35±0.93	198.55±1.53	198.30±1.75	198.50±1.60	199.15±1.69	198.75±1.71	199.05±1.60	198.40±1.66
Thickness (mm)	3.34±0.054	3.38 ± 0.083	3.34 ± 0.054	3.34 ± 0.054	3.32±0.083	3.30±0.070	3.28±0.083	3.34±0.114	3.28 ± 0.083	3.28 ± 0.083
Hardness (kg/cm^2)	5.76±0.30	5.93±0.25	5.70 ± 0.10	5.50 ± 0.10	5.83±0.15	5.13±0.15	5.50±0.10	5.46±0.15	5.36±0.15	5.46±0.15
Friability (%)	0.43	0.47	0.31	0.45	0.56	0.57	0.43	0.48	0.35	0.39
Drug Content (%)	97.40	98.08	98.08	97.75	97.95	97.95	98.20	98.16	98.29	98.25
Swelling Index (%)	70.00±1.00	95.30±2.51	144.60±1.52	150.00±2.00	165.00±5.00	155.00±5.00	205.10±5.00	220.10±5.25	235.00±2.50	254.10±3.68
Floating lag time (sec.)	18.33±1.52	22.00 ± 1.00	39.66±1.52	35.66 ± 1.52	29.33 ± 1.52	40.00±1.52	43.66±2.00	48.33±1.52	39.00±2.00	33.66±1.52
Total floating time (hr.)	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr

***In vitro* Buoyancy Studies:** The combination of SB and CA is required for good floating ability and therefore, this combination was selected for the formulation of floating tablets. Buoyancy of the tablets is governed by both the swelling of hydrocolloid particles on the tablet surface and the presence of internal voids in the dry centre of tablet (porosity). These two factors are essential for the tablet to acquire bulk density less than 1 and so remain buoyant on gastric fluid.

Results of floating lag time and total floating time are shown in table 4. All the formulations constantly floated on dissolution medium for more than 12 hrs. All the batches were found to exhibit short floating lag times due to presence of SB and CA. Decrease in CA level increased the floating lag time and tablets were found to float for longer duration. The tablets with low-viscosity grade HPMC K4M exhibited short floating lag time as compared with formulations containing high viscosity grade HPMC K100M. Thus, a combination of SB and CA with HPMC was found to achieve *in vitro* buoyancy and floatability.

Swelling Indices: HPMC is a hydrophilic polymer. It swells on contact with water. The hydration ability of the formula is significant because it influences: (a) tablet buoyancy, (b) adhesion ability of swellable polymers as HPMC K4M and HPMC K100M, (c) drug release kinetics. The thickness of swollen layer formed around the matrix core was greater in matrices containing HPMC of higher viscosity grade. Thus, swelling index was comparatively less in tablets containing HPMC K4M than that of tablets containing HPMC K100M.

With the increase in citric acid concentration in formulations containing HPMC K4M and HPMC K100M, it was found that swelling of polymer increases due to higher gas pressure caused by faster and higher carbon dioxide generation.

It was evident from the results that as the citric acid concentration was increased in formulations i.e. F3-F5 containing HPMC K4M and F8-F10 of HPMC K100M, swelling index was also increased from 144.60%-165.00% and 220.10%-254.10% respectively. Results of swelling index are shown in table 4. **Fig. 1 and 2** depict graphical representations that were plotted with % swelling index versus time (hrs).

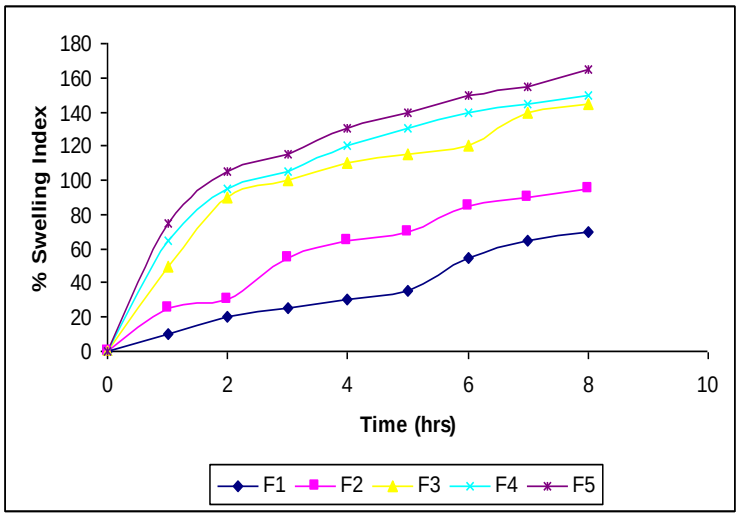

FIG. 1: SWELLING INDICES OF FORMULATION F1-F5 CONTAINING FAMOTIDINE

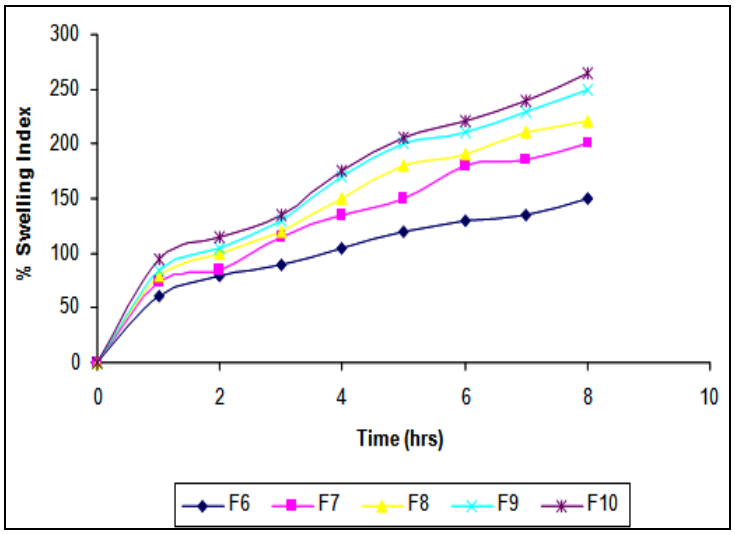

FIG. 2: SWELLING INDICES OF FORMULATION F6-F10 CONTAINING FAMOTIDINE

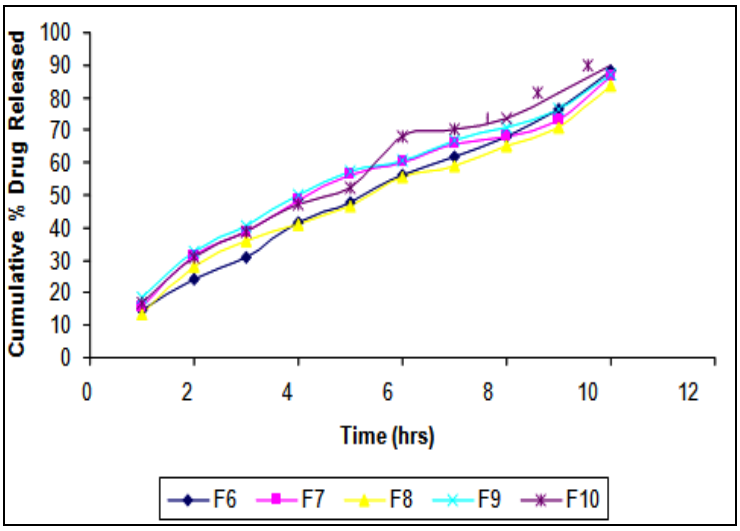

FIG. 4: *IN VITRO* DISSOLUTION PROFILE OF FORMULATION F6-F10

***In vitro* Dissolution Studies:** On increasing the proportion of HPMC in formulations, the release of drug was observed to be decreased. This might be due to increase in resistance of the gel layer to drug dissolution. At a high polymer level, formation of tightly swollen gel layer caused by more intimate contact between the particles of HPMC results in decrease mobility of drug particles in swollen matrices, which leads to decreased release rate. It is evident from *in-vitro* dissolution data that increase in citric acid concentration increased the release rate but reduced the floating time, probably due to the presence of excess carbon dioxide. Comparing different grades of HPMC, it was found that HPMC K100M provided better release characteristics with floating time of 10 hrs. The cumulative % drug release v/s time plots for different formulations are presented in **fig. 3 and 4**.

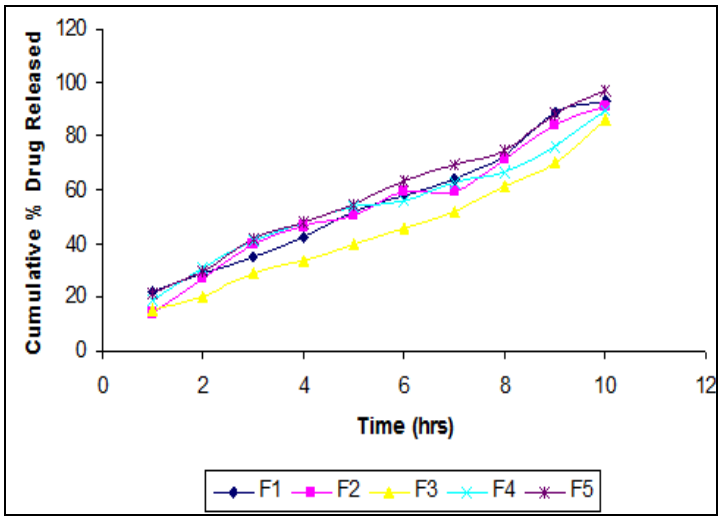

FIG. 3: *IN VITRO* DISSOLUTION PROFILE OF FORMULATION F1-F5

Mathematical Modelling of Drug Release: Data obtained from *in vitro* dissolution studies were fitted in different models viz. Zero order, First order, Korsemeyer-Peppas and Higuchi model. The data were processed for regression analysis using MS EXCEL statistical function. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined as shown in **table 5**.

To confirm the exact mechanism of drug release from these tablets, the data were fitted to Korsemeyer and Peppas model. The 'n' value of Korsemeyer- Peppas model for the different formulations was found between 0.615 and 0.764 which lies within the range of 0.5 and 1.0. Therefore, the most probable mechanism that the release pattern of all formulations followed was non-fickian diffusion or anomalous diffusion, where in the drug release mechanism is controlled by both diffusion as well as polymer relaxation process.

CONCLUSION: From the above studies, it has been observed that effervescent based floating drug delivery system is a promising approach to achieve controlled release behaviour and *in vitro* buoyancy profile. Floating tablets employing famotidine as a model drug can be prepared successfully using wet granulation technique. It was concluded that all formulations had acceptable physical parameters. The addition of gel-forming polymer HPMC (K4M and K100M) and gas-generating agents were essential to achieve *in vitro* buoyancy.

TABLE 5: FIT OF VARIOUS KINETIC MODELS FOR FLOATING DRUG DELIVERY SYSTEMS OF FAMOTIDINE

Formulation Code	Zero order		First order		Higuchi model		Peppas model	
	r^2	K_0	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	n
F1	0.9873	7.968	0.8500	2.445	0.9466	33.34	0.9631	0.638
F2	0.9769	7.831	0.7850	0.213	0.9710	33.37	0.9468	0.762
F3	0.9733	7.328	0.8990	0.167	0.9214	30.47	0.9800	0.722
F4	0.9727	6.835	0.8479	0.182	0.9665	29.12	0.9869	0.615
F5	0.9935	8.039	0.7989	0.286	0.9746	34.03	0.9880	0.648
F6	0.9954	7.746	0.9060	0.188	0.9790	32.91	0.9960	0.764
F7	0.9612	6.872	0.8893	0.169	0.9841	29.72	0.9858	0.733
F8	0.9811	6.897	0.9401	0.153	0.9795	29.45	0.9771	0.671
F9	0.9735	6.861	0.9386	0.174	0.9819	29.60	0.9910	0.633
F10	0.9786	7.691	0.9372	0.210	0.9880	33.03	0.9915	0.707

The type of polymer also affects the drug release rate. Polymer swelling is crucial in determining the drug release rate and is also important for floatation. Based on these findings, it has been revealed that floating type gastroretentive drug delivery system holds significant potential for better drug delivery and facilitates an enormous impact on health care. Moreover, it is anticipated that increased sophistication of this effervescent approach will ensure the successful delivery of therapeutic molecules in a more efficient manner.

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