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Research Article

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Formulation and *in-vitro* evaluation of effervescent floating tablets of an antiulcer agent

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ABSTRACT

Floating drug delivery systems are utilized to target drug release in the stomach or to the upper parts of intestine. Oral delivery of an anti-ulcer agent, famotidine was facilitated by preparing various floating dosage forms which can increase its absorption in the stomach by enhancing gastric residence time. Polymers utilized were hydroxypropyl methylcellulose K15M (HPMC K15M) and hydroxypropyl methylcellulose K100M (HPMC K100M) as gel forming agents along with sodium bicarbonate and citric acid as gas generating agents. Formulated tablets were evaluated for their physicochemical properties as well as drug release profile. Effect of effervescent agents and polymeric substances were also investigated for floating properties and drug release characteristics. Drug release pattern of all formulations followed non-fickian diffusion or anomalous diffusion.

Keywords: Floating drug delivery systems, Anti-ulcer agent, Gastric residence time, Effervescent agents**.**

INTRODUCTION

The primary objective of an oral controlled drug delivery system is to release the drug in a very predictable manner and to enhance its bioavailability [1]. However, the developmental 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 (GRT) of drugs, gastroretentive dosage forms (GRDFs) are developed which can remain in the gastric region for several hours [3]. Prolonged residence time in the stomach is highly desirable for drugs that are locally active in the stomach, or are unstable in the intestinal or colonic environment, and/or have low solubility at higher pH values [4]. Incorporation of the drug in gastroretentive floating dosage form provides a mean to utilize all the pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms [5].

The main approaches for gastric retention that have been examined thus far includes: floating system, mucoadhesion or bioadhesion system, high density system, magnetic system, super porous hydrogels, raft forming system, low density system, and floating ion exchange resins, unfoldable, extendable or expandable systems etc [6]. Among the various approaches employed to increase the retention of an oral dosage form, effervescent floating drug delivery system is a considerably easy and logical approach in the development of GRDFs. [7]

Gastroesophageal reflux disease (GERD) results from inflammation of the esophageal mucosa caused by the reflux of gastric contents into the esophagus. In patients with GERD, the reflux of acid and other gastric contents occurs

frequently and leads to prolonged, painful inflammation of the esophageal mucosa. Strategies for treatment of GERD include measures that decrease secretion of gastric acid, neutralize acid, improve esophageal clearance, protect the esophageal mucosa, or increase the competence of lower esophageal sphincter to prevent reflux [8]. The histamine H_2 receptor antagonists are among the most effective antisecretory drugs available for management of acid peptic diseases. Famotidine is one of the histamine H_2 receptor antagonists. The objective of the current study was to formulate and evaluate floating tablets of famotidine for the treatment of gastric ulcers and to increase the efficiency of drug; thus providing sustained action at specific site of gastrointestinal tract.

EXPERIMENTAL SECTION

Materials and methods:

Famotidine was received as a gift sample from Oyster Labs Ltd., Ambala, India. Methocel K15M (15000 cPs) and methocel K100M (1, 00,000 cPs) apparent viscosity as a 2% solution) were received as gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Sodium bicarbonate and citric acid anhydrous were obtained from S.D. Fine Chem Ltd., Mumbai, India. Polyvinyl pyrrolidone K-30 (PVP K-30), magnesium stearate, and talc were procured from HiMedia Labs Pvt. Ltd., Mumbai, India. Isopropyl alcohol was obtained from Qualigens Fine Chemicals, Mumbai, India. All other chemicals and reagents used were of analytical grade.

Flow properties of granules:

The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose (θ), the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of funnel. The $\tan^{-1}$ of (height of the pile / radius of its base) provided the angle of repose. Bulk density, Tapped density, Carr's index and Hausner's ratio were calculated using tap density apparatus [9]. The cylinder was raised and dropped under its own weight by a fixed drop height of 3 mm ± 10 % at a nominal rate of 250 drops per minute using tap density apparatus [Electrolab, USP].

Formulation of tablets:

The composition of different formulations of famotidine floating tablets is shown in table 1. Tablets were prepared using wet granulation technique. The ingredients were weighed accurately and mixed thoroughly. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol. The granules (18 mesh) were dried in a conventional hot air oven at 45^0C. The dried granules were sized through 18/22 mesh, lubricated with magnesium stearate (1% w/w) and purified talc (2% w/w) and then compressed on a mini rotary punching tablet machine (Fluid Pack Machinery, Ahmedabad, India) with punches of 7 mm.

Table 1: Formulation of floating tablets using different ratio of polymers and effervescent agents

Ingredients (mg)	Formulation Code									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Famotidine	40	40	40	40	40	40	40	40	40	40
HPMC K15 M	40	50	60	60	60	-	-	-	-	-
HPMC K100 M	-	-	-	-	-	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 tablets:

Weight variation:

Twenty tablets from each batch were selected randomly and their average weight was calculated. Then individual weight of each tablet was determined using digital electronic balance and was compared with average weight. The mean ± standard deviation values of weight variation were calculated [10].

Thickness:

Three tablets were taken from each formulation randomly and their thickness was examined with vernier caliper. The mean ± standard deviation values of thickness were calculated [11].

Hardness:

Hardness or tablet crushing strength (the force required to break a tablet in a diametric compression) was measured using a Pfizer type tester. The test was performed on three tablets from each formulation and the average reading

was noted. The mean ± standard deviation values of hardness were calculated [12, 13].

Friability:
Friability of tablets was determined using a Roche friabilator. Ten preweighed tablets were placed in the friabilator, operated for 4 min at 25 rpm. The tablets were taken out, dedusted and reweighed [14]. Percentage friability of tablets was measured as per the following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The mean ± standard deviation values of friability were calculated.

Drug content uniformity:
Twenty tablets of each formulation were weighed and average weight was calculated. The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 mL of 0.1 N hydrochloric acid, followed by stirring for 30 minutes [10]. The solution was filtered through a 0.45 µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 265 nm using 0.1 N hydrochloric acid as blank.

***In vitro* buoyancy studies:**
In vitro buoyancy was determined by measurement of floating lag time. Tablets were placed in a 100 mL beaker containing 0.1 N hydrochloric acid. Time required for tablet to rise to the surface and float was determined as *"floating lag time"*. The duration of time the dosage form constantly remained on the surface of medium was determined as the *"total floating time"*. The mean ± standard deviation values of buoyancy were calculated [10].

Swelling characteristics:
The swelling properties of HPMC matrices containing drug were determined by placing the weighed tablet matrices (w_1) in the basket of dissolution apparatus, in 900 mL of 0.1 N hydrochloric acid at 37 ± 0.5°C [15]. The tablets were removed periodically from the dissolution medium and, after removing free water, the swollen weight (w_2) was measured [16]. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation:

$$\mathbf{WU\%} = \frac{\mathbf{w_2 - w_1}}{\mathbf{w_1}} \times \mathbf{100}$$

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.

***In vitro* dissolution study:**
In vitro dissolution study was performed in USP dissolution apparatus type II, in 900 mL 0.1 N hydrochloric acid (pH 1.2), maintained at 37± 0.5ºC at a speed of 50 rpm. At suitable time intervals, aliquots (10 mL) were withdrawn and immediately replaced with equal volume of fresh dissolution medium to maintain a constant volume for drug dissolution. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable concentration with 0.1 N hydrochloric acid. Absorbance of these solutions was measured at 265 nm using a systronic UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard calibration curve [17].

Mathematical modeling of drug release profile:
The cumulative amount of famotidine release from formulated tablets at different time intervals were fitted to zero order kinetics, first order kinetics, Higuchi model and Korsmeyer–Peppas model to characterize mechanism of drug release [18-20].

RESULTS AND DISCUSSION

Evaluation of granules:
The granules prepared for compression were evaluated for their flow properties. Bulk density was found between 0.364-0.421 gm/cm^3 with HPMC K15M and 0.365-0.395 gm/cm^3 with HPMC K100M. Tapped density ranged

between 0.419-0.486 gm/cm^3 with granules containing HPMC K15M and 0.427-0.452 gm/cm^3 with HPMC K100M. Results are shown in table 2. Carr's index (%) and Hausner's ratio were also calculated. Carr's index was found to be in the range of 11.59-14.80, 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. Powders with low interparticle friction have ratio of approximately 1.2, whereas more cohesive, less flowing powders have ratio >1.6. Hausner's ratio values for all the formulations were found to be near about 1.2 indicating low interparticle friction. Angle of repose was found to be in the range of 25.10-29.30º with HPMC K15M and 23.70-25.40º with HPMC K100M. The values of angle of repose were less than 30, indicating good flowability. All these values indicate that the prepared granules exhibited good flow properties.

Table 2: Characterization of granules

S. No.	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index (%)	Hausner Ratio (H_R)	Angle of repose (ɵ)
F1	0.421	0.486	13.63	1.157	25.10
F2	0.412	0.478	13.80	1.160	25.20
F3	0.364	0.419	13.12	1.151	29.30
F4	0.376	0.440	14.54	1.170	27.10
F5	0.378	0.432	12.50	1.142	27.07
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

Evaluation of tablets:

Weight variation:

Since the powder material was free flowing, tablets obtained were of uniform weight due to uniform die fill, with acceptable weight variations as per pharmacopoeial specifications. Average weights of floating tablets in all the batches varied in between 198.35 mg to 199.65 mg. Variation was determined less than 7.5 % which is found to be within limits as prescribed in USP. Results of weight variation are shown in table 3.

Thickness:

Thickness of tablets of all batches was observed in between 3.28-3.38 mm which is found to be satisfactory. Findings are shown in table 3.

Hardness:

A difference in tablet hardness may reflect differences in tablet density and porosity, which are supposed to vary in release patterns of drug by affecting the rate of penetration of the dissolution fluid at the surface of tablet and formation of gel barrier. Hardness of tablets was measured and found in the range of 5.13-6.06 kg/cm^2, sufficient to withstand shock. Results are shown in table 3.

Friability:

Friability was found to be less than 1% indicating good mechanical resistance. Results are shown in table 3.

Drug content uniformity:

Drug content varied in between 97.95% to 98.29 % in different formulations, indicating good content uniformity in prepared batches. Results of drug content uniformity are shown in table 3.

***In vitro* buoyancy studies:**

All the tablets were prepared by effervescent approach. Sodium bicarbonate and citric acid were added as gas generating agents. Sodium bicarbonate induced the carbon dioxide generation in presence of dissolution media (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore; this combination was selected for the formulation of floating tablets. Buoyancy of tablets is governed by both swelling of hydrocolloid particles on the tablet surface when it contacts the gastric fluids, which in turn results in an increase in the bulk volume and the presence of internal voids in the dry centre of the tablet (porosity). These two factors are essential for the tablet to acquire bulk density less than 1 and so remain buoyant on gastric fluid. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of tablet less than 1 and tablet becomes buoyant. Results of floating lag time and total floating time are shown in table 3.

All the formulations constantly floated on dissolution medium for more than 12 h. Swelling polymers (HPMC

K15M and HPMC K100M) appeared to prolong the lag time while effervescent agents appeared to reduce the lag time. However, the influence of effervescent agents was found to be more significant. All the batches were found to exhibit short floating lag time due to presence of sodium bicarbonate and citric acid. It was observed that decrease in citric acid level increased the floating lag time and tablets were found to float for longer duration. The tablets with low-viscosity grade HPMC K15M exhibited short floating lag time as compared with formulations containing high viscosity grade HPMC K100M. This indicated that the molecular weight distribution or viscosity of the gel-forming polymer influenced the *in vitro* buoyancy.

Swelling characteristics:

HPMC is a hydrophilic polymer. It swells on contact with water. 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 K15M than that of tablets containing HPMC K100M. The hydrodynamic volume occupied by the hydrated polymer chains is larger in high viscosity grade polymer. Consequently, greater swollen mass of matrices were formed. Moreover, with the increase in citric acid concentration in formulations containing HPMC K15M and 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 F3-F5 containing HPMC K15M and F8-F10 containing HPMC K100M, swelling index was also increased. Formulations containing low concentration of polymer, swelling index was found to be less. Results of swelling index are shown in table 3.

Table 3: Various physicochemical characteristics of floating tablets

S. No.	Evaluation Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Average weight (mg) ±SD	198.90 ± 1.77	199.65 ± 2.88	199.40 ± 1.87	198.35 ± 1.26	198.55 ± 1.70	198.50 ± 1.60	199.15 ± 1.69	198.75 ± 1.71	199.05 ± 1.60	198.40 ± 1.66
2	Thickness (mm)	3.28 ± 0.083	3.38 ± 0.083	3.32 ± 0.083	3.30 ± 0.070	3.28 ± 0.083	3.30 ± 0.070	3.28 ± 0.083	3.34 ± 0.114	3.28 ± 0.083	3.28 ± 0.083
3	Hardness (kg/cm^2)	6.06 ± 0.11	5.36 ± 0.15	5.83 ± 0.15	5.53 ± 0.05	5.40 ± 0.10	5.13 ± 0.15	5.50 ± 0.10	5.46 ± 0.15	5.36 ± 0.15	5.46 ± 0.15
4	Friability (%)	0.41	0.37	0.60	0.49	0.35	0.57	0.43	0.48	0.35	0.39
5	Drug Content (%)	98.08 ± 0.54	98.16 ± 0.60	98.04 ± 0.79	98.08 ± 0.54	98.08 ± 0.54	97.95 ± 0.65	98.20 ± 0.69	98.16 ± 0.68	98.29 ± 0.57	98.25 ± 0.65
6	Swelling Index (%)	102.50 ± 2.50	135.80 ± 3.81	160.80 ± 3.81	169.10 ± 3.81	180.80 ± 5.20	155.00 ± 5.00	205.10 ± 5.00	220.10 ± 5.25	235.00 ± 2.50	254.10 ± 3.68
7	Floating lag time (sec.)	39.00 ± 1.00	41.66 ± 1.52	43.33 ± 1.52	37.00 ± 1.00	32.66 ± 2.08	40.00 ± 1.52	43.66 ± 2.00	48.33 ± 1.52	39.00 ± 2.00	33.66 ± 1.52
8	Total floating time (hr.)	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr	>12hr

Data are expressed as mean ±SD (n=3)

***In vitro* dissolution studies:**

Since the pH of stomach is elevated under fed condition (~3.5), therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate. Moreover, citric acid has a stabilizing effect on famotidine formulation. The effect of different grades and amount of HPMC in the tablet with varying proportion of citric acid was studied on the release characteristics.

It was observed that the release of drug from such formulations decreased on increasing the proportion of HPMC in the formulations. 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. The drug release from formulations containing HPMC K15M (F1 to F3) varied between 90.30% to 84.07% and that prepared from HPMC K100M (F6 to F8) varied from 88.03% to 83.80%.

It is evident from the *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, disturbing the monolithic tablet. The citric acid level in the formulations greatly influenced the drug release, irrespective of HPMC grade. The prepared formulations sustained the drug release for a period of 10 h**.** The cumulative percentage drug release versus time plots for different formulations are presented in figure 1-2.

Mathematical modeling 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 4. To confirm the exact mechanism of drug release from these tablets, the data were fitted to various models. The 'n' value of Korsemeyer-Peppas model for the different formulations was found in between 0.527 and 0.764 which lies with in 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. Hence, the *in vitro* release observed for various formulation of famotidine floating tablets showed well controlled and sustained release.

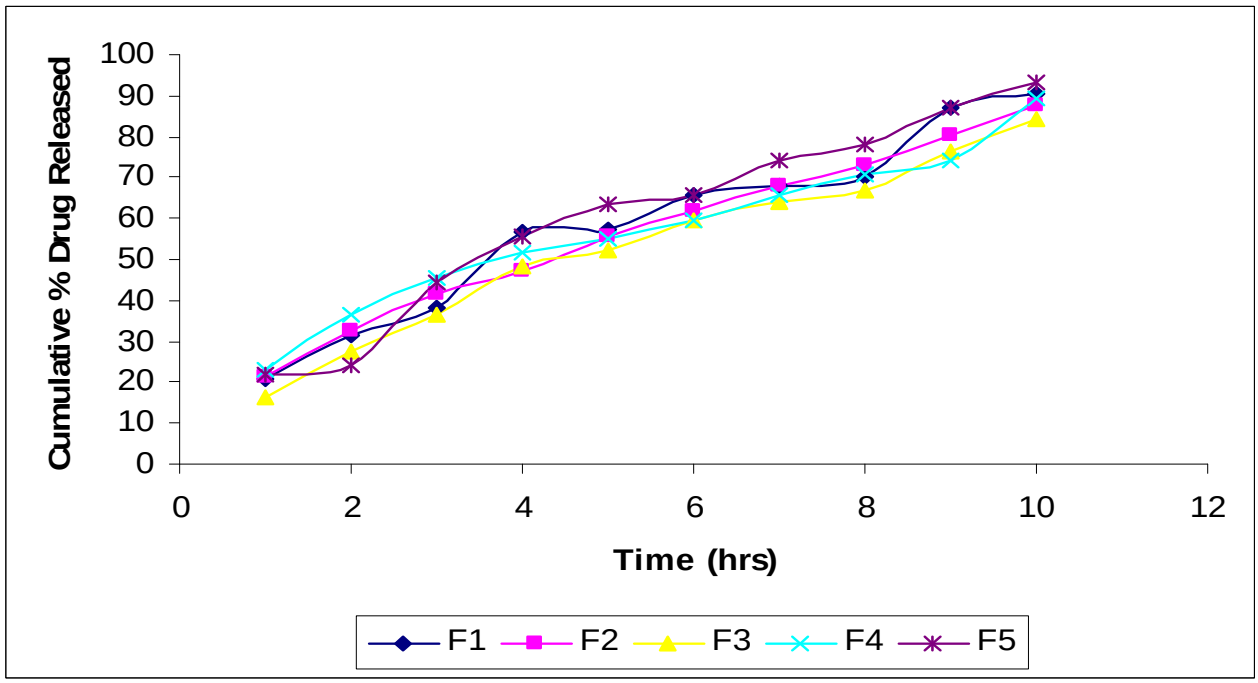

Fig. 1: *In-vitro* dissolution profile of formulations F1-F5

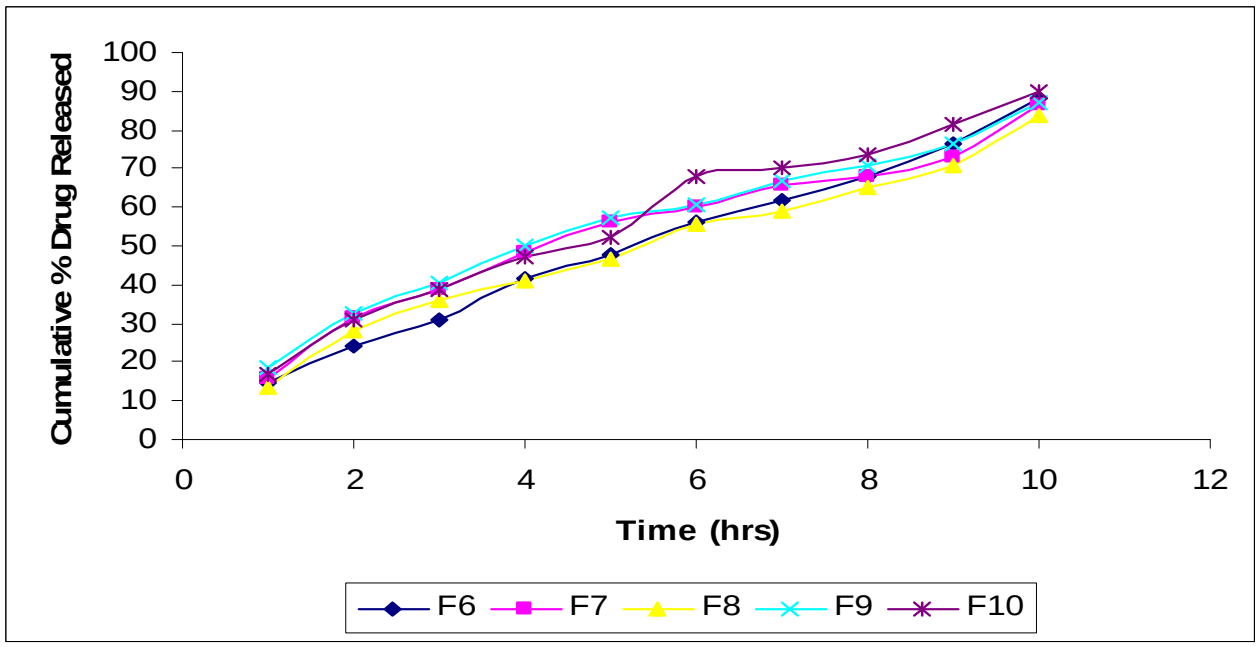

Fig. 2: *In-vitro* dissolution profile of formulations F6-F10

Table 4: 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_o	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	n
F1	0.9583	7.375	0.9173	0.212	0.9687	31.69	0.9937	0.616
F2	0.9921	6.984	0.9424	0.181	0.9841	29.88	0.9824	0.618
F3	0.9774	6.933	0.9575	0.164	0.9714	30.10	0.9937	0.686
F4	0.9674	6.246	0.8666	0.170	0.9717	26.75	0.9853	0.527
F5	0.9614	7.900	0.9270	0.239	0.9796	34.08	0.9960	0.617
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

Effect of grade and amount of HPMC on the release rate of drug and floating characteristics:

It is suggested that the hydrophilic polymer such as HPMC when comes in contact with the water, it absorbs water and swells to form a gel layer which serves as a barrier to drug diffusion. The drug release process from a HPMC matrix involves water penetration into the dry matrix, hydration and gelation of the polymer, dissolution of the drug and diffusion of the dissolved drug through the resultant gel layer. From the results, it was concluded that grade of HPMC polymer affect the drug release. Formulations prepared with HPMC K15M showed higher drug release than that of prepared with HPMC K100M. It may be attributed due to high viscosity of HPMC K100M than from HPMC K15M. Amount of polymer also affects the drug release. Higher concentration of polymer cause less drug release than lower concentration of polymer in the formulation. It was observed that *in vitro* drug release for formulation F1 prepared with HPMC K15M was found to be 90.30%, which was decreased to 87.40% for batch F2 and was further decreased to 84.07% for formulation F3. Drug release for batch F6 containing HPMC K100M was found to be 88.03%, which was decreased to 86.60% for batch F7 and was further decreased to 83.80% for formulation F8.

Amount and grade of polymer also affects the floating characteristics. It was examined that as the concentration as well as grade of polymer increases, floating lag time increases and vice-versa. It might be due to slow carbon dioxide generation. It was observed that floating lag time for batch F1 containing HPMC K15M was 39 sec, which was increased for formulation F2 (41.66 sec) containing HPMC K15M and that was further increased for formulation F3 (43.33 sec) containing HPMC K15M. Floating lag time for batch F6 containing HPMC K100M was found to be 40 sec, which was more than F7 (43.66 sec) containing HPMC K100M and that for F8 containing HPMC K100M was 48.33 sec.

Effect of effervescent agents on floating lag time and release rate:

Rapid expansion and formation of a low density system with in minutes after contact with gastric fluid are required to obtain a suitable floating dosage form. Citric acid and sodium bicarbonate as effervescent agents were utilized in the formulation. In contact with dissolution medium, these agents generate carbon dioxide, which accumulates under the surrounding polymer.

On increasing the concentration of effervescent agents, floating lag time was found to be decreased. It was observed that floating lag time for batch F3 was 43.33 sec, which was decreased for formulation F4 (37 sec) and that was further decreased for formulation F5 (32.66 sec). Floating lag time for batch F10 was found to be 33.66 sec, which was less than F9 (39 sec) and that for F8 was 48.33 sec. Release rate of drug from batch F5 (93.15%) containing HPMC K15M was found to be increased as compared to F4 (89.10%) after 10 h and release rate of drug from F4 was more than F3 (84.07%). Release rate of drug from batch F10 (90.10%) containing HPMC K100M was found to be increased as compared to F9 (87.20%) after 10 h and release rate of drug from F9 was more than F8 (83.80%). It was concluded that faster and higher carbon dioxide generation caused by increasing the concentration of effervescent agents resulted in higher swelling of polymeric membrane according to a higher gas pressure and subsequent faster drug release as well as decrease in floating lag time.

CONCLUSION

In the present investigational work, effervescent floating tablets of famotidine were formulated to provide controlled release of drug with an effective and safe therapy for stomach ulcers in a reduced dose manner. From the observation, it was concluded that the addition of gel-forming polymers, methocel (K15M and K100M) and gas-generating agent, sodium bicarbonate along with citric acid were essential to achieve *in vitro* buoyancy profile. Drug release from the tablets was sufficiently sustained and non-fickian transport was also confirmed. In order to examine

the actual floating ability of prepared formulations on gastric content and their usefulness in extending gastric residence time, such formulations can be surely selected for *in vivo* evaluation. Moreover, it is hoped that further research with a variety of gas-forming agents and new preparation methods will lead to the development of more effective effervescent floating drug delivery systems.

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