Nat. Volatiles & Essent. Oils, 2020;07(1):131-141

Formulation and Evaluation of Sustained Release FloatingTablets

Dr. Bharat V. Jain[1*], **Dr. Sandip R. Pawar**[1], **Dr. Tanvir Y. Shaikh**[1], **Dr. Md. Rageeb Md. Usman**[1]

[1*]Professor, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda-425107, M.S

***Corresponding Authors:** Dr. Bharat V. Jain,
*Professor, Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda-425107, M.S
bharatjain2006@gmail.com

Abstract
The purpose of the present study was to prolong the gastric residence time of famotidine by developing gastric floating drug delivery system (GFDDS). And to study influence of different polymers on its release rate using gas-forming agents, like sodium bicarbonate, citric acid. Floating tablets were prepared by wet granulation method using PVP K-30 as a binder and the other polymers include xanthan Gum, HPMC K100M, six different formulations with the varying concentrations of polymers were prepared and the tablets were evaluated in terms of their precompression parameters like bulk density, tapped density, haunsner ratio, angle of repose, compressibility index, post compression physical characteristics, *in-vitro* release, buoyancy, floating lag time (FLT), total floating time (TFT) and swelling index. All the formulations showed good floating lag time i.e. less than 3 mins. The batch containing combination of xanthan gum and HPMC 100M (i.e. F-6) showed total floating lag time more than 12 h, the highest swelling index among all the prepared batches (i.e. 230 %).The drug release was found to follow zero order kinetics.

INTRODUCTION

Floating drug delivery systems were firs 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. (v)Various dosage forms developed for gastric retentioninclude, floating tablets, (vi) floating beads, (vii) pellets, (viii) floating granules, (ix) floating microspheres. (x) Inthis investigation, an attempt was made to design floating tablets of famotidine using different release retarding polymers along with a gas-generating agent. [1]
Gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to stomach and upper parts of the gastrointestinal (GI) tract. These systems are designed to be retained in the stomach for longer period of time and hence significantly prolong the gastric residence time of drugs. Therefore, different approaches have been proposed to retain the dosage form in the stomach includingbioadhesive systems, swelling and expanding systems,floating systems and delayed gastric emptying devices. [2]

Famotidine is a H2-receptor antagonist and used orally for the treatment of active duodenal or gastric ulcer, gastro esophagel reflux disease, endoscopically diagnosed erosive esophageal reflux disease, endoscopically diagnosederosive esophagitis and as maintenance therapy for duodenal ulcer. Oral Famotidine also is used for themanagement of pathological GI hypersecretory conditions. IV Famotidine is used in hospitalized individuals with pathological GI hypersecretory conditions or intractable ulcers, or when oral therapy is not feasible. The plasma half–life following a single oral dose is 2.5-3.5 hrs. The success of therapy depends on

selection of appropriate delivery system as much as it depends on the drug itself. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicamentin order to achieve better selectivity and longer duration of action. Thus, Famotidine is chosen as a suitable candidate for sustained release drug delivery system. [3]

In the present investigation effervescent floating tablets of different formulation were developed with an objective of achieving 12 hrs floating and drug release time. Thisapproach also reduces the unwanted side effects of the drug, the tablet remain buoyant for a long period on the gastric contents, exhibiting a prolonged gastric residence time, resulting in sustained drug release and consistent blood levels of drug.

MATERIALS AND METHODS

Famotdine is an Active Ingredient received as gift sample from Mylon Laboratories, Sinner and Nasik. Xanthan Gum and HPMC K100M is used as a Polymers are obtained as giftsample from Cherly Laboratories Pvt. Ltd. 302, Mahape MIDC Mumbai, Sodium bi carbonate used as a Buoyancy Imparting agent, Citric acid used as a Stabilizing agent Lactose as a Diluent, Magnesium searate as a Lubricant, Purified talc as a Lubricant is purchased from S.D. fine chem. Ltd, Mumbai. All other ingredient, reagents and solvents are of analytical grade.

Methods for Characterization of Drug and Excipients

1. **Fourier Transform Infra-Red Spectroscopy (FTIR)** FTIR spectra of pure Famotidine and physical mixture ofdrug and excipients were recorded on Shimadzu corporation, (Tokyo, Japan) Model-1601 PC. Potassium bromide pellet method was employed and backgroundspectrum was collected under identical situation. Eachspectrum was derived from single average scans collectedin the region 400- 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra wereanalyzed by software supplied by Shimadzu.

2. **Differential Scanning Calorimetry (DSC)**

Thermal properties of the pure Famotidine and the physical mixture of drug and excipients were analyzed by Shimadzu DSC-60, Shimadzu Limited Japan. The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350°C at a heating rate of 10°C/ min, using nitrogen as blanket gas. [4]

Preparation of Tablets by Wet Granulation Technique Floating granules were prepared by using wet granulationtechnique. All the ingredients Xanthan Gum, hydroxylpropyl methylcellulose, lactose, sodium bicarbonate, citric acid and the active ingredients were mixed homogeneouslyand sieved through 40/60 meshes alcoholic solution of PVPK30 (5% W/V) in IPA was used as a granulating agent. Thegranules were dried in a conventional hot air oven at 40°Cfor 45 min. The dried granules were sieved through 40/60 meshes. Magnesium stearate and Talc was added as alubricant and the granules were compressed in to tabletsusing Single punch tablet machine. (Cadmach, Ahmedabad,India.) using 8 mm standard flat face punch, compressionforce was adjusted to obtain tablets with hardness in rangeof 4.1±0.51-5.1±0.23 kp. The tablet weights were 200±2 mgwith average diameter of 8.0±0.2 mm. Twelve formulationswere prepared and coded them from F1 to F6. The detail of composition of each formulation is given in Table 1. [5]

Evaluation of Granules

1. **Determination of Bulk Density and Tap Density**

Apparent bulk density (ρb) was determined by pouring theblend into a graduated cylinder. The bulk volume (Vb) andWeight of the powder (M) was determined. The bulk densitywas calculated using the formula:

$$\rho b = M/Vb$$

The measuring cylinder containing a known mass of powder or granules was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using the following formula:

$$\rho t = M/Vt$$

2. Compressibility Index

The measuring cylinder way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as:

$$I = (\rho t – \rho o/\rho t) x100$$

Where, ρt = tapped density and ρo = initial bulk density.

The value below 15% indicates a powder which usually gives rise to good flow characteristics whereas above 25% indelicate poor flow ability.

Haunsner ratio is an indirect index of ease of powder flow. It is calculated by the formula which is:

$$\text{Haunsner Ratio} = \rho t / \rho d$$

Where, ρt = tapped density and ρo = bulk density.

3. Angle of Repose

The frictional forces in a loose powder can be measured by the angle of repose (q). It was determined using funnelmethod. The powder or granules were poured through a funnel that can be raised vertically unit a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated (q). [5]

$$q = Tan\text{-}1(h/r)$$

Evaluation of Tablets

1. Appearance

The Tablets were observed visually and did not show any defect such as Capping, Chipping and Lamination.

2. Thickness and Diameter

The thickness and diameter of the tablet was carried out using vernier caliper. Five tablets were used for the above test from each batch and results were expressed in millimeter.

3. Hardness Test

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsanto hardness tester measured the hardness studies and results were expressed in kg/cm^2.

4. Weight Variation Test

Twenty tablets were selected at random, individuallyweighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. specification. As per I.P. not more than 5% and none deviate more than twice that percentage.

5. Friability Test

It was done in biological museum friability test apparatus where the tablets were subjected to combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre-weighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that loss less than 0.5 to 1.0% of their weight are generally considered acceptable.

$$\text{Friability (\%)} = W1 – W2/ W1 \ X\ 100$$

Where,

W1 = Weight of Tablets (Initial / Before Tumbling) &

W2 = Weight of Tablets (After Tumbling or friability)

Limit : Friability (%) = Not More Than 1.0 %

6. Drug Content Uniformity:

Ten tablets were weighed and taken in a mortar and crushed to powder from. A quantity of powder weighing equivalent to 40 mg of Famotidine was taken in a 100 ml volumetric flask and 0.1N HCl was added.

It was then heated at 60°C for 30 minute. The solution was filteredusing membrane filter (0.45 nm) and then its absorbance was measured at 266 nm. The amount of drug calculated using standard graph. [5]

Table 1: Formulation Batches of Floating Sustained Release Tablets of Famotidine

Ingredients (gm)	F1	F2	F3	F4	F5	F6
Famotidine	40	40	40	40	40	40
Xanthan Gum	40	80	-	-	20	40
HPMC K100M	-	-	40	80	20	40
NAHCO3	30	30	30	30	30	30
Citric acid	10	10	10	10	10	10
Talc	2	2	2	2	2	2
Lactose	66	26	66	26	66	26
Magnesium state	2	2	2	2	2	2
PVP K30	10	10	10	10	10	10
Total	200	200	200	200	200	200

Table 2: Characterization of Granules

Batch	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Carr's Index (%)	Hausner's Ratio (HR)	Angle of Repose (θ)
F1	0.547±0.02	0.660±0.01	24.24±0.11	1.32±0.24	27.54±1.2
F2	0.458±0.03	0.554±0.03	18.10±0.21	1.22±0.19	29.28±1.0
F3	0.384±0.05	0.531±0.08	24.38±0.31	1.31±0.17	25.64±1.6
F4	0.318±0.07	0.382±0.01	18.67±0.24	1.22±0.22	29.89±1.6
F5	0.417±0.05	0.529±0.05	21.42±0.12	1.26±0.16	25.76±1.3
F6	0.286±0.07	0.340±0.07	17.64±0.21	1.21±0.18	29.09±1.1

Table 3: Various Physicochemical Characterization of Famotidine Floating Tablets

Batch	Average weight (mg)±S.D.	Thickness (mm)*	Hardness (kg/cm2)*	Friability (%)*	Drug Content (%)*	Swelling Index (%)*
F1	198.45±0.02	3.18±0.12	4.1±0.23	0.28±0.01	99.92±1.2	169±5.32
F2	198.15±0.01	3.25±0.19	4.3±0.24	0.33±0.05	99.00±1.4	204±5.00
F3	198.50±0.03	3.09±0.05	4.5±0.67	0.31±0.07	98.85±0.5	111±2.51
F4	198.3±0.04	3.24±1.8	4.7±0.13	0.36±0.12	99.37±1.7	126±3.57
F5	198.65±0.12	3.19±1.5	4.9±0.12	0.27±0.10	99.12±1.1	214±5.00
F6	198.38±0.15	3.22±0.18	5.12±0.23	0.38±0.04	99.17±0.9	230±5.26

7. Floating Log Time

The floating log time for all the formulation was tested in dissolution vessel containing 900 ml of 0.1 N HCl solution. All the tablets showed floating log time between 1-2 minutes.

8. Total Floating Time

The floating time for all the formulation tested in dissolution vessel containing 900 ml of 0.1 N HCl solution. All the tablets showed floating time of more than 12 hrs.

9. Determination of Swelling Index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablet was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1 N HCL at 37±0.5°C. After every one hour up to 12 hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu BL-220H). The experiment was performed in triplicate for each time point. Swelling index (SI) was calculated by using the following formula: [1, 6]

Swelling Index = {(Wt-Wo)/ Wo} X 100

Where, Wt = weight of tablet at time t and Wo = weight of tablet before immersion.

10. *In-vitro* Buoyancy Studies

The time of tablet took to emerge on the water surface (floating lag time) and the time of tablet constantly float on the water surface (duration of floating) were evaluated in a dissolution vessel (dissolutions apparatus) were with 900 ml of 0.1N HCl previously set at 37°±0.5°C with paddle rotation at 50 rpm. The results for floating timeare presented in Table 4, from the study of floating properties it was observed that the floating lag time ranges from 56 to 101 s and tablets of each batchremained buoyant more than 12 hours, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced. [1, 7]

11. *In-vitro* Dissolution Studies

In-vitro drug release studies of famotidine were studied using dissolution apparatus USP type II paddle method with a stirring speed of 50 rpm at 37°C±0.5°C in 900 ml of (pH 0.1) simulated gastric fluids for 12 hours. The samples were taken at pre-selected gastric fluids for 12 hours. The samples were taken at one hr time intervals with replacement of equal volume of dissolution media. The collected samples were diluted (1:10) and the absorbance was measured spectrophotometrically at 266 nm. The percentage of famotidine released at various time intervals were calculated from the standard graph. In-vitro dissolution studies were carried out at in simulated gastric fluid (pH 0.1 buffers) for 12 hours. In order to find out the of order of release and the mechanism, which was predominately influences the drug release from the tablet, the in-vitro dissolution data was subjected to 3 different mode of graphical treatment. [8]

Kinetic Modeling of Drug Release

The release of drug from a polymeric matrix tablet dependson the gel layer around the tablet core. The dissolution profiles of all the batches were fitted to various kinetic models: zero order as cumulative amount of drug release vs. time, first order as log cumulative percentage of drug remaining vs. time and Higuchi's model as cumulative percentage of drug release vs. square root of time to ascertain the kinetics of drug release. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function. [9- 13]

The data obtained from *in-vitro* dissolution studies werefitted in different models viz. zero order, first order, Higuchi and Korsemeyer-Peppas equation, the results wereshown in Table 6. The first order plots were found to be fairly linear as indicated by their high regression values (r^2= 0.800 to 0.898) to confirm the exact mechanism of drug release from these tablets, the data were fitted according to Korsemeyer-Peppas equation. The n value of Korsemeyer- Peppas equation for different formulation was found to be 0.668 to 0.697 which was more than Slope values (n= >0.5) suggested that the release of Famotidine from the floating tablets followed the non-fickian transport mechanism. The dissolution data of optimized formulation F6 fitted well in zero order release kinetics (R^2=0.993), this means that water diffusion and also the polymer relaxation had an essential role in drug release. When n takes the value of > 0.5, it indicates diffusion sustained drug release. The value of n in case of optimized formulation F6 was 0.696 indicated that floating tablets were followed zero order kinetics of drug release. [17]

Table 4: *In-vitro* Buoyancy Studies of Famotidine Floating Tablets

Batch	Floating lag time (Sec)*	Total Floating Time (hrs)*
F1	89	>12
F2	72	>12
F3	101	>12
F4	95	>12
F5	80	>12
F6	56	>12

*All the values are expressed as mean± SE, n=3

Table 5: Cumulative % Release of Famotidine from Floating Tablets

Cumulative % Release of Famotidine (mean ±S.D., n= 3)						
Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	5.7825	6.9862	5.0851	5.3212	7.9985	8.0120
2	9.8212	12.6337	8.3587	8.9437	14.2875	13.4187
3	14.2762	18.6975	12.7237	13.1734	21.1162	19.6272
4	18.8775	25.1212	17.4825	18.4380	28.3505	26.3569
5	24.4687	31.7362	23.1391	24.0862	36.0615	33.8735
6	31.2385	39.2625	29.3856	30.3412	43.9434	41.8058
7	38.5987	47.3737	36.4387	36.9582	51.9567	50.1075
8	46.5345	55.8457	43.6952	44.5052	60.0925	58.7934
9	56.1262	64.6425	51.8062	53.5725	68.8956	67.9726
10	65.8912	73.7128	60.3765	63.1125	72.3864	78.2087
11	75.9632	83.8112	69.4687	72.9783	81.5962	86.5359
12	86.6258	92.1785	78.6375	83.0362	90.8550	96.0352

Table 6: Different Kinetic Models for Floating Tablets of Famotidine (F-1 to F-6)

Batch	Zero Order		First Order		Higuchi Model		Korsemeyer-Peppas		Best Fit
	K_O	R^2	K_1	R^2	Kh	R^2	N	R^2	
F1	7.087	0.973	-0.066	0.849	4.212	0.907	0.679	0.914	Zero order
F2	7.672	0.992	-0.083	0.852	4.532	0.944	0.696	0.946	Zero order
F3	6.509	0.979	-0.054	0.898	3.878	0.918	0.668	0.908	Zero order
F4	6.809	0.975	-0.060	0.870	4.053	0.910	0.676	0.906	Zero order
F5	7.517	0.998	-0.079	0.895	4.414	0.97	0.697	0.964	Zero order
F6	7.989	0.993	-0.1	0.800	4.711	0.946	0.696	0.953	Zero order

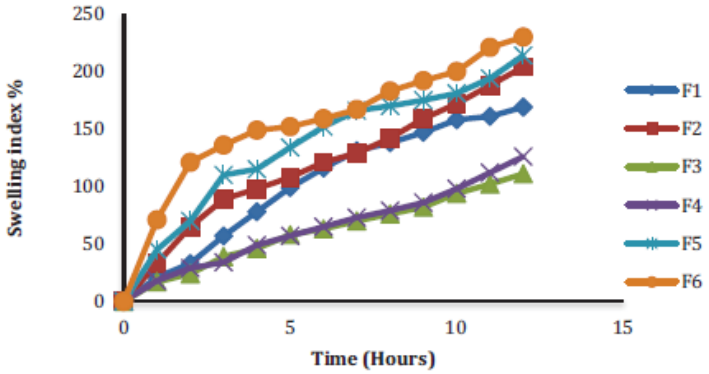

Figure 1: Swelling index of floating tablets of famotidine (F-1 to F-6)

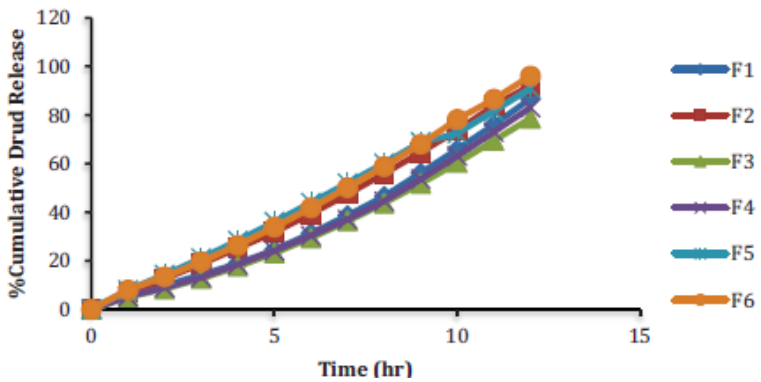

Figure 2: *In-vitro* drug release profile of floating tablets of Famotidine (F-1 to F-6)

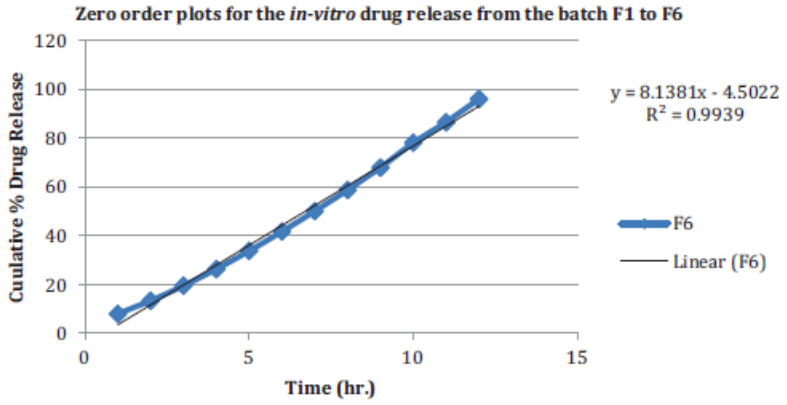

Figure 3: Zero order plots for the drug release from the optimized formulation F-6

RESULTS AND DISCUSSION

The oral bioavailability of Famotidine has been reported to be about 40% because of its rapid hepatic first pass metabolism. If the drug dosage form can retain the stomach as long as possible, to allow for maximum absorption, then the bioavailability could be improved. Gastric floating drug delivery is one approach were the gastro intestinal residence time is prolonged because of the floating behavior.

HPMC K100M was used as swellable polymers and chosen because it is widely used as a low density hydrocolloid system upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomachpH. Citric acid has stabilizing effect and sodium bicarbonateis used as a buoyancy-imparting agent. In the present study the formulations were prepared by using different polymers with proportions. The prepared formulations were evaluated for different physicochemical characteristics such as appearance, thickness and diameter,drug content, weight variation, hardness and friability. The release characteristic of the formulation was studied in *in- vitro* conditions.

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 2. Bulk density was found between 0.458-0.547 gm/cm^3 with Xanthan Gum and 0.318-0.384 gm/cm^3 with HPMC K100M. Tapped density ranged between 0.554-0.660 gm/cm^3 with granules containing Xanthan Gum, 0.382-0.531 gm/cm^3 with HPMC K100M. Carr's index was found to be in the range of 17.64-24.38 for both formulations, indicating goodflow.

Flowability of granules was found to be good as indicated by compressibility-flowability correlation data. Hausner's ratio is related to interparticle friction. Hausner'sratio values for all formulations were found to be near about 1.3 indicating low interparticle friction. Angle of repose was found to be in the range of 27.54°-29.28° with Xanthan gum and 25.64°-29.89° with HPMC K100M. The values of angle of repose were less than 30, indicating good flow ability.

Physicochemical Evaluation

Floating tablets of famotidine were prepared by using Xanthan Gum and HPMC K100M, sodium bicarbonate, citricacid and PVP K-30. The magnesium stearate and talc were used as lubricant and Guidant, respectively. Findings of the physicochemical characterization are shown in Table 3. Average weight of floating tablets in all the formulations varied between 198.15 mg to 199 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 3.09 mm to 3.25mm which is found to be satisfactory. The hardness fordifferent formulations was found to be between 4.1 to 5.1 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 98.85% to 99.92% for different formulations, indicating good content uniformity.

Swelling Index

Swelling study was performed on all the batches (F1 to F6) for 12 hours. The result of swelling index were shown in Figure 1, it shows the plot of swelling index as a function of time for different formulation. It was observed that the swelling indices were increased with increase in polymer concentration. Formulation containing Xanthan Gum showed higher swelling indices as compared with otherformulation containing the same amount of HPMC K100M. This is because during dissolution a tablet containing Xanthan Gum instantly forms a viscous gel layer that slows down in sweep of dissolution fluid towards the core of matrix tablet. Swelling was strong enough to avoid premature disintegration as well as burst effect and retarded the release of pure drug for a long period of time. Complete swelling was achieved by the end of seven to nine hours for different formulation. Swelling index values starts decreasing when polymer erosion starts in medium. The result of swelling index for optimized formulation F6 were shown in Table 3.

***In-vitro* Release Study**

In-vitro dissolution studies of all the formulations of floating tablets of Famotidine were carried out in 0.1 N HCl.The study was performed for 12 hours and percentage drug release was calculated at 1 hour time intervals. The results of *in-vitro* dissolution studies of all formulations were shown in Figure 5. The higher initial drug dissolution was observed in tablets containing Xantham Gum (F2) 92.17% and combination of Xanthan Gum and HPMC K100M (F6) 96.03 %. This showed that in combination with Xanthan Gum, HPMC hydrated more rapidly in thepresence of 0.1 N HCl. The variation in drug release was due to different types of polymers and different concentrations of polymer in all the six formulations.

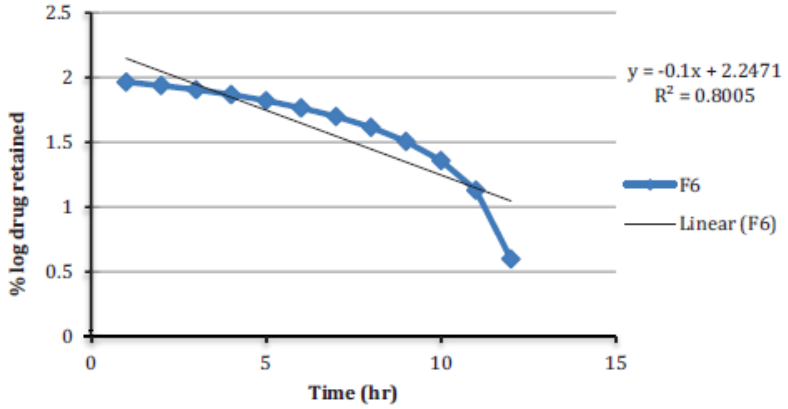

Figure 4: First order plots for the drug release from the optimized formulation F-6

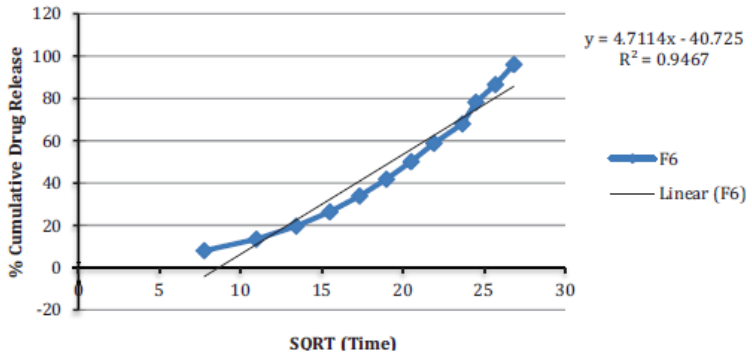

Figure 5: Higuchi matrix release optimized formulation F-6

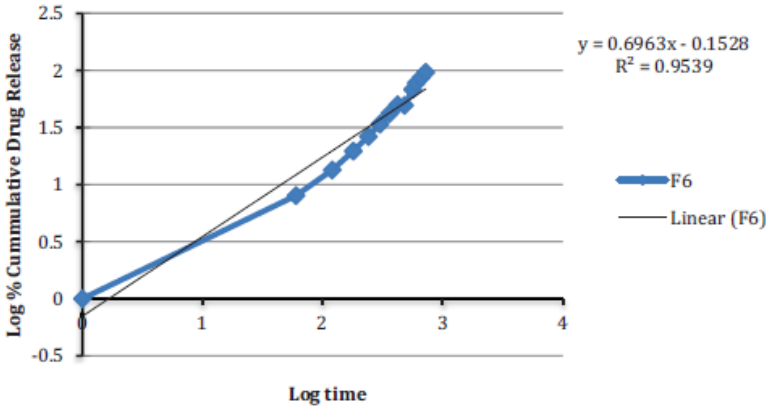

Figure 6: Korsmeyer and peppas release kinetics of optimized formulation F-6

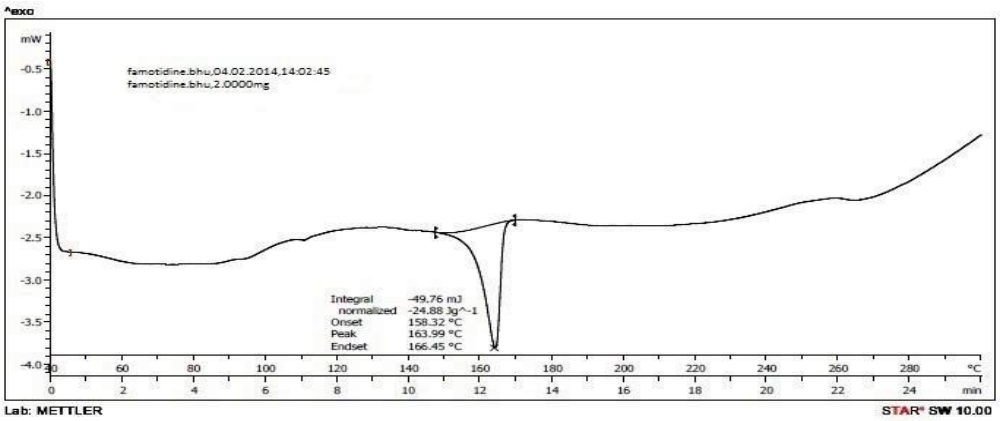

Figure 7: DSC thermal analysis of famotidine

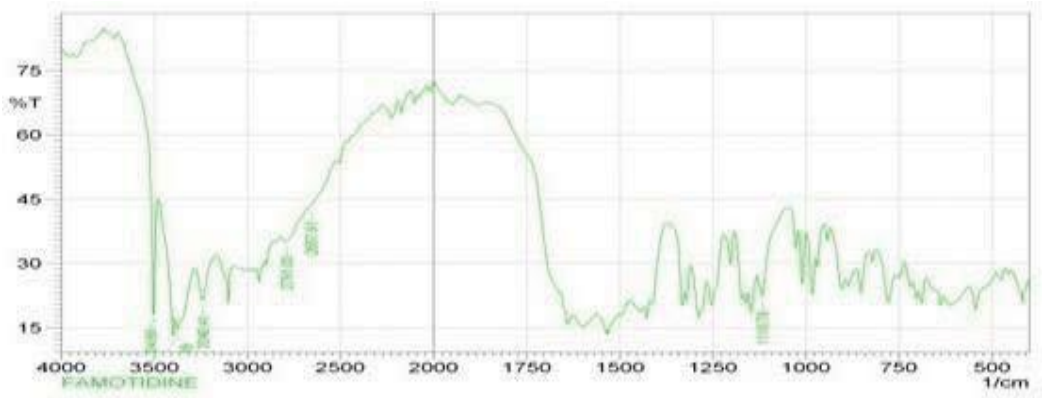

Figure 8: FTIR of famoidine

CONCLUSION

The aim of the present work was to study the effect ofpolymers with varying concentration on *in-vitro* release rate from gastric floating tablets of Famotidine based on low density polymer. The effervescent-based floating drug delivery was a promising approach to achieve *in-vitro* buoyancy. Different types of matrix forming polymers- Xanthan gum and HPMC K100M was studied. The use of gel-forming polymer methocel K100M and gas generating agentsodium bicarbonate was essential to achieve in vitrobuoyancy. Formulation F-VI showed controlled drug releaseand adequate floating properties. The kinetics of drug release was followed zero order drug release. The drug release from the tablets was sufficiently sustained and non-fickian transport of the drug from tablets was conformed.

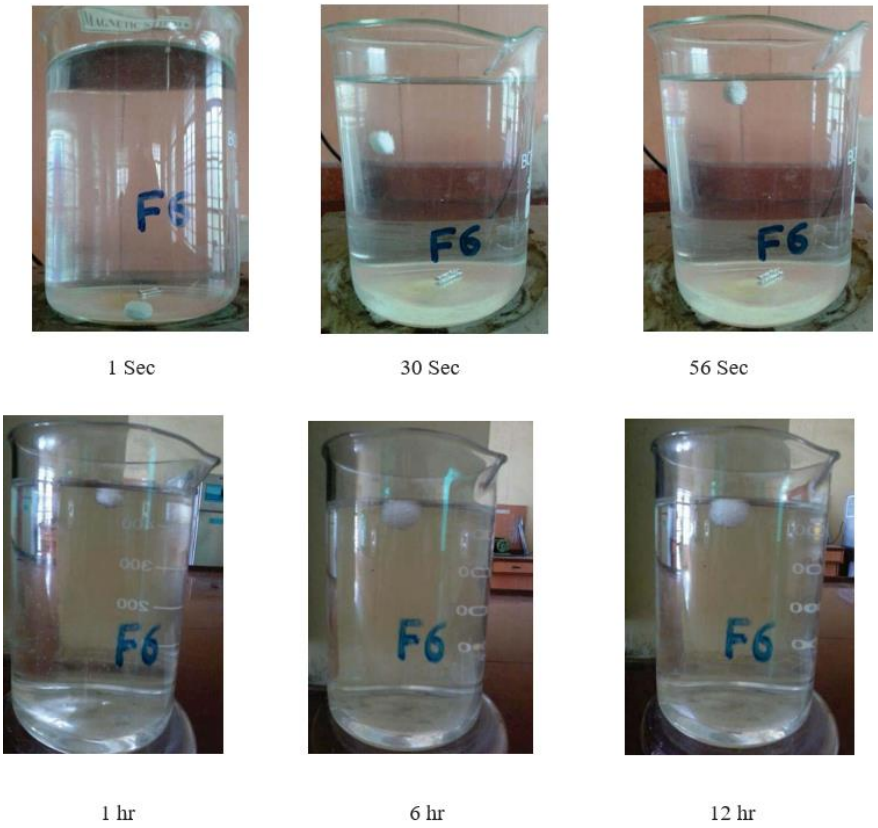

Figure 9: Floating Tablets

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