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Development and Evaluation of Oral Gastroretentive Floating Matrix Tablet of Famotidine

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ABSTRACT

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents drug is released slowly at the desired rate from the system. The present study mainly focuses on the development and evaluation effervescent based floating matrix tablet of famotidine. This oral drug delivery offers several advantages over the standard conventional oral dosage forms. Effervescent based floating matrix tablet of famotidine was prepared using sodium bicarbonate as effervescent agent and by incorporating hydrophobic agent stearic acid which retards the drug release and allow the dosage form to float on gastric fluid for several hrs. Then the tablet was evaluated for hardness, friability, drug content and *in vitro* drug release. On the basis of the preliminary trials, a 3^2 full factorial design was employed to study the effect of independent variables, HPMC K4M: Carbopol 934P ratio (X_1) and concentration of effervescent agent (X_2) on dependent variables like floating lag time, Q_4 and Q_8. The best batch (F3) exhibited optimum floating lag time (16 sec), drug content (98.94%), Q_4 (54.36 %), Q_8 (93.98%) and similarity factor (83.92). The controlled release of famotidine was observed and good fit to the zero order was demonstrated.

Keywords: Famotidine; floating drug delivery system; Floating lag time; *In vitro* drug release.

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INTRODUCTION

The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate. The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required[1-2] Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a long time[3]. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3 hrs through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem[4.] Gastro retentive dosage form can remain in the gastric region for several hrs and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients[5]. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the

fluctuations in plasma drug concentration[6-9]. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids due to the incorporation of at least one porous structural element such as foam or hollow body and remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time[10]. While the system is floating on the gastric contents drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach.

Famotidine inhibits acid production by reversibly competing with histamine for binding to H_2 receptor on the basolateral membrane of parietal cells. Famotidine is incompletely absorbed[11]. The bioavailability of oral doses is 40 to 45%. Famotidine undergoes minimal first-pass metabolism. The only metabolite identified in man is the S-oxide. There is a close relationship between creatinine clearance values & elimination half-life of famotidine 25 to 30% of an oral dose & 65 to 70% of an i.v. dose are recovered in urine as unchanged compound. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 ml/min, elimination halflife of famotidine may exceed 20 hrs. Degrades rapidly in acid and is more stable under alkaline conditions. Famotidine at a concentration of 2 mg per ml, diluted with glucose 5%, sodium chloride 0.9%, or sterile water was stable in PVP syringes stored at 4^0C for 14 days[12, 13].

MATERIALS AND METHODS:

Famotidine is procured from Torrent Pharmaceuticals, Mumbai, India. All other materials, excipients, solvents and reagents were either analytical or Pharmacopoeial grade and they were procured from S.D.Fine Chemicals Mumbai.

Here, in present work famotidine was selected as drug candidate which is highly soluble in acidic pH so stearic acid as hydrophobic agent was used to achieve the controlled drug release. HPMC K4M and carbopol 934P were used as matrix forming and release rate controlling agent. Sodium bicarbonate was used as effervescent agent and dicalcium phosphate as diluents was used. Acryflow L which acts as lubricant and glidant was used to improve the flow property.

Drug excipients compatibility study

Differential scanning calorimetric (DSC) study

Drug excipients compatibility study was carried out by Shimadzu DSC-60 in dry N_2 atmosphere (flow rate 50 ml/min) and temperature scanning rate was 10^0C/min up to 300^0C. About 2 mg of each sample were weighed using closed aluminium pans.

FTIR study:

Drug excipients interaction was checked by comparing the FTIR spectra of pure drug famotidine and FTIR spectra of the physical mixture of drug and excipients. The IR spectra were taken from FTIR-8400S (Shimadzu Corporation, Tokyo, Japan). In the present study, Potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered KBr crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded.

Method of preparation of effervescent based floating matrix tablet

Weighed quantity of stearic acid and famotidine was mixed and melted up to 70^0C. The molten mass was then cooled to room temperature and this solidify mass was crushed, ground gently with a mortar and pestle and passed through sieve of 60 mesh size. To this mixture appropriate weighed quantity of HPMC K4M, carbopol 934P, dicalcium phosphate, acryflow L were added and mixed properly. This mixture was compressed (8.4 mm diameter, concave punches) using multi punch tablet compression machine (Rimek mini press-I).

Formulation of Famotidine floating matrix tablet.

To determine effect of stearic acid and stearic acid concentration on the drug release the formulation batches P1 without stearic acid and P2, P3, P4 containing drug: stearic acid ratio 1:0.5, 1:0.75 and 1:1 were prepared respectively. Dissolution of all the tablets were carried out using 900ml of pH 1.2 buffer at 37^0C$\pm$0.5^{0}C (900 ml using USP apparatus II at 50 rpm.) The drug release up to 8 hrs was measured. Formulation of preliminary trial batch was shown in Table 1.

Table 1: Formulation of batches for Famotidine floating matrix tablet

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine	40	40	40	40	40	40	40	40	40
Stearic acid	-	20	30	40	30	30	30	30	30
HPMC K4M	20	20	20	20	10	20	30	30	30
Carbopol 934P	20	20	20	20	10	20	30	30	30
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Dicalcium phosphate	30	30	30	30	30	30	30	30	30
Acryflow L	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

Determination effect of drug: polymer ratio on drug release profile and Floating lag time (FLT)

In an attempt to determine drug: polymer ratio the formulation batches P5, P6 and P7 containing drug: polymer ratio 1:0.5, 1:1 and 1:1.5 were prepared and shown a drug release profile and FLT. The drug release studies were carried out using 900ml of pH 1.2 buffer at 37 ^{0}C$\pm$ 0.5^{0}C (900 ml using USP apparatus II at 50 rpm.) The drug release up to 8 hrs was measured

Optimization of effervescent floating tablet by 3^2 full factorial designs

On the basis of the preliminary trials in the present study 3^2 full factorial designs was employed to study the effect of independent variables, i.e. HPMC K4M: Carbopol 934P ratio (X_1) and Amount of sodium bicarbonate (X_2) on dependent variables floating lag time, Q_4 and Q_8. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses as

$$\mathbf{Y = b_0 + b_1X_1+b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2}$$

Where,

Y is the dependent variables,

b_0 is the arithmetic mean response of the nine runs,

b1 is the estimated coefficient for the factor X_1

The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. The Floating Lag Time (Y_3), Q_4, Q_8 values for the 9 batches (F1 to F9) showed a wide variation. The 3^2 full design layout and transformed value and formula of 3^2 factorial batches were shown in table 2 and table 3 respectively.

$$Y_3 = 30.31 - 4.16\ X_1 - 4.82\ X_2 + 0.928\ X_1^2 - 2.475\ X_2^2 + 4.48\ X_1X_2$$

$$Q_4 = 48.31 - 4.22\ X_1 + 0.662\ X_2 + 1.248\ X_1^2 - 0.439\ X_2^2 - 0.515\ X_1X_2$$

$$Q_8 = 89.68 - 8.66\ X_1 + 0.978\ X_2 - 0.478\ X_1^2 + 0.021\ X_2^2 - 0.006\ X_1X_2$$

Table 2: 3^2 full factorial design with transformed value

Batch No.	Variables level in coded form				
	X_1	X_2	X_1X_1	X_2X_2	X_1X_2
F1	-1	-1	+1	+1	+1
F2	-1	0	+1	0	0
F3	-1	+1	+1	+1	-1
F4	0	-1	0	+1	0
F5	0	0	0	0	0
F6	0	+1	0	+1	0
F7	+1	-1	+1	+1	-1
F8	+1	0	+1	0	0
F9	+1	+1	+1	+1	+1

Translation of coded levels in actual units

Variables level	Low (-1)	Medium (0)	High (+1)
HPMC K4M :Carbopol 934P(X_1)	25:15	20 :20	15:25
Amount of sodium bicarbonate(X_2)	10mg	15mg	20mg

Note: All the batches contained the constant amount of famotidine as 40 mg, stearic acid as 30 mg, dicalcium phosphate 30 mg and drug : polymer ratio is 1:1

Table 3: Formulation of factorial batches of Famotidine floating matrix tablet

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine	40	40	40	40	40	40	40	40	40
HPMC K4M	25	25	25	20	20	20	15	15	15
Carbopol	15	15	15	20	20	20	25	25	25
Sodium bicarbonate	10	15	20	10	15	20	10	15	20
Steraric acid	30	30	30	30	30	30	30	30	30
Dicalcium phosphate	20	20	20	20	20	20	20	20	20
Acryflow L	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

Evaluation of Famotidine floating matrix tablet:

1. Evaluation of powder blend[18, 17]

Angle of repose

The angle of repose of powder blend was determined by the funnel method. Angle of repose was calculated using the equation

$$\tan \theta = h/r$$

Bulk density[17]

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk density (ρb) was calculated using following equation

$$\rho b = M/Vb$$

Tapped density[18]

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The tapped density (ρt) was calculated using following equation

$$\rho t = M/Vt$$

Compressibility Index (CI) [18]

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle Size distribution of the powder. Tapped (ρt) and Apparent (ρb) Bulk density measurements can be used to estimate the compressibility of a material.

$$Cl = \frac{\rho t - \rho b}{\rho t} \times 100$$

Drug Content[14]

An accurately weighed amount of powder blend containing famotidine (40 mg) was extracted with pH 1.2 buffer .The absorbance was measured at 265 nm after suitable dilution.

2. Evaluation of Famotidine floating matrix tablet

Thickness [18]

The thickness of the tablets was determined by using vernier calipers.

Weight variation test[18]

To study weight variation 20 tablets of each formulation were weighed using a reputed micro system (Reptech) electronic balance and the test was performed according to the official method.

Hardness and friability[14, 15]

The hardness was tablets were determined using the Monsanto hardness tester and Roche Friabilator respectively.

Content uniformity[15]

Ten tablets were finely powdered; quantities of the powder equivalent to 40 mg of famotidine were accurately weighed and transferred to a 100ml of volumetric flask containing 1.2 pH buffer and mixed thoroughly. The solution was made up to volume and filtered. Appropriate dilutions were done using 1.2 pH buffer and absorbance of the resulting solution was measured at the maximum at 265 nm using a UV-Visible spectrophotometer.

***In vitro* buoyancy studies**[15]

Floating behaviour studies were carried out in a USP XXIII dissolution apparatus type II at a speed 50 rpm in 900 ml 1.2 pH buffer at 37±0.5^{0}C for 8 hrs. The time required for the tablets to rise to the surface and float was taken as floating lag time. The following parameters were determined: Floating lag time, floating duration.

***In vitro* dissolution studies**[15, 16]

The release rate of famotidine from floating matrix tablets was determined using the USP XXIII dissolution testing apparatus II (Paddle). The dissolution test was performed using 900ml of 1.2 pH buffer at 37±0.5^{0}C and 50 rpm to simulate *in vivo* conditions. Drug content in the sample was determined spectrophotometrically at 265 nm using Simadzu-1800 UV-Visible double beam Spectrophotometer.

Comparison of *in vitro* release profile[19]

The *in vitro* drug release profile of all batches with theoretical drug release profile was compared using similarity factor (f2).

$$f_2 = 50\mathrm{X}\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5}\mathrm{X}100\right\}$$

Where, Rt, Tt are the percentage release of the reference and test profile, respectively, at the t time point. n is total number of sample times.

Kinetic modelling and Mechanism of drug release[16]

Data obtained form *in vitro* drug release studies were fitted to various kinetic equations. The kinetic models used are zero order kinetic, korsmeyer kinetic, Hixon Crowel kinetic and Higuchi kinetics.

RESULTS AND DISCUSSION:

Differential scanning calorimetric (DSC) study

Drug excipients compatibility study was carried out by Shimadzu DSC-60 in dry N_2 atmosphere (flow rate 50 ml/min) and temperature scanning rate was 10^0C/min up to 300^0C. About 2 mg of each sample were weighed using closed aluminium pans. Sharp melting transition of famotidine was observed at 164.48^0C. In the physical mixture of drug and excipients melting endotherm at 164.98^0C. The DSC thermogram of drug and drug and physical mixture of drug and excipients were shown in figure 1 and figure 2 respectively.

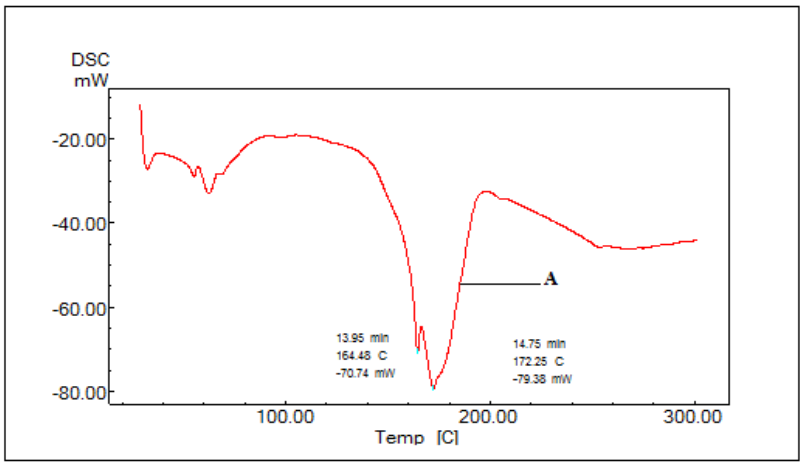

Figure 1: DSC thermogram of drug famotidine

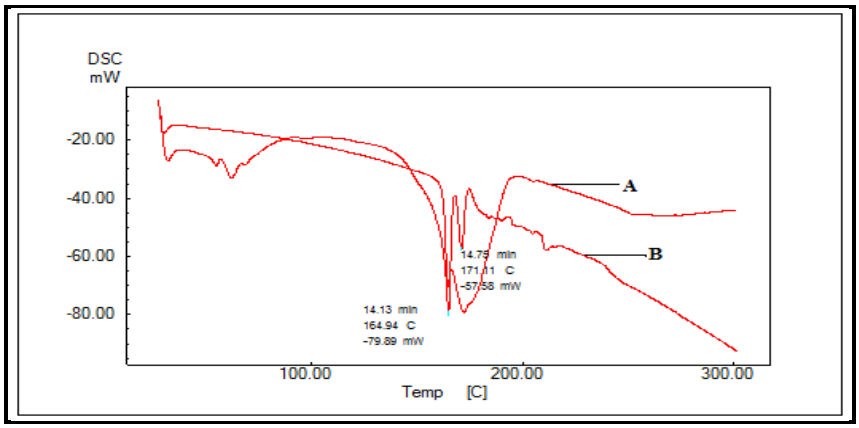

Figure 2: The DSC thermogram of physical mixture of drug and excipients

Results of DSC study showed that there was no change in melting point of drug in physical mixture of drug and excipients. Thus drug and excipients are compatible.

FTIR study

FTIR spectra of drug famotidine and of physical mixture of drug and excipients were shown in figure 3 and figure 4 respectively and result of FTIR spectra tabulated in table 4.occurs between drug and excipients. Drug and all excipients used are physically compatible.

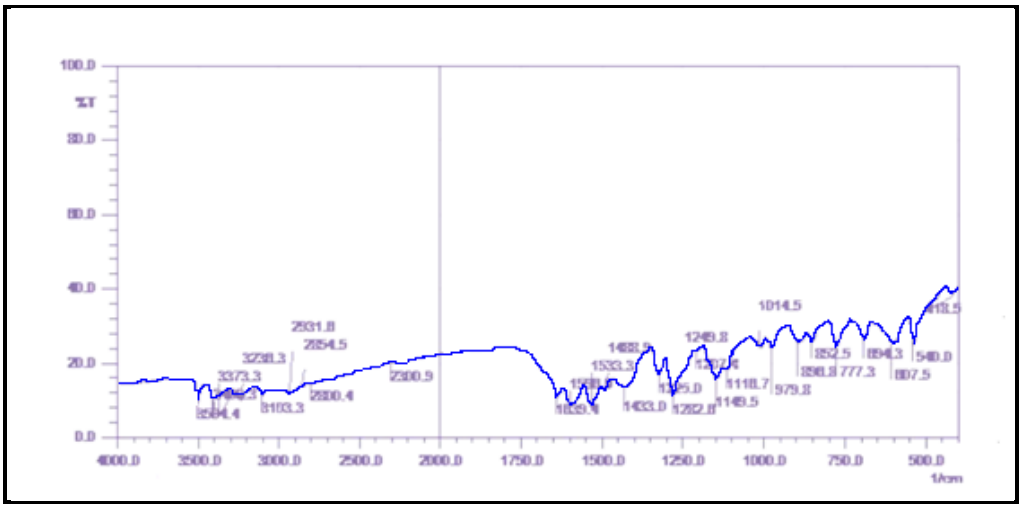

Figure 3: FTIR Spectrum of famotidine

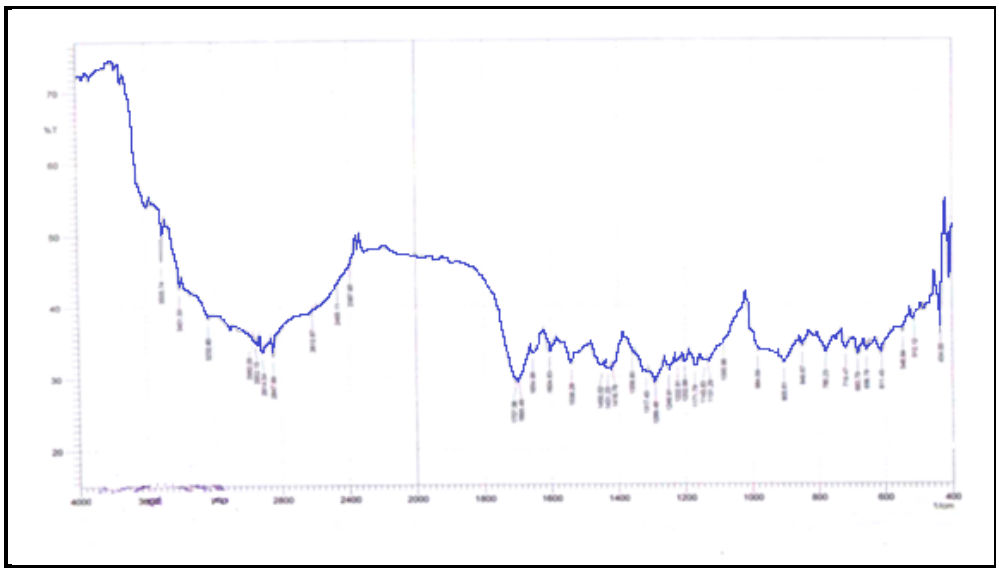

Figure 4: FTIR Spectrum for physical mixture of drug and Excipients

Table 4: Results of FTIR study

Vibration	Range (cm^{-1})	Drug (cm^{-1})	Physical mixture	
N-H Stretch	3300-3600	3400.3	3401.58	No interaction
=C-H	3100-300	3103.3	3104.58	
C=N	1650-1590	1639.4	1641.48	
C=C	1600-1500	1596.4	1604.36	
S=O	1550-1500	1533.3	1534.42	
C-S	1250-1350	1282.6	1289.53	
C-N	1070-1170	1149.5	1145.76	

Evaluation of Famotidine powder blend

Factorial batches taken by 3^2 full factorial designs of Famotidine floating matrix tablets. Powders of different formulation were evaluated for angle of repose, bulk density, tapped density, % compressibility and drug content. Here in all batches angle of repose vary from 24.29 to 26.94 means less than 30 which indicate good flow property of powder blend. Compressibility index up to 16% indicates good flow property and here values obtained vary from 12.82% to 16.67% showed satisfied flow property. Drug content of tablets of batches F1-F9 vary from 97.48% to 101.73% indicates good drug content (Table 5).

Table 5: Results of evaluation Famotidine powder blend of F1-F9 batch

Batch No	Angle of repose	Bulk density	Tapped density	% Compressibility	Drug content
F1	24.82± 1.38	0.36± 0.04	0.42± 0.02	14.28	98.27± 0.998
F2	24.73± 1.47	0.34± 0.03	0.39± 0.03	12.82	97.48± 0.973
F3	25.29± 1.42	0.33± 0.03	0.39± 0.02	15.38	100.42± 0.999
F4	24.42± 1.02	0.37± 0.04	0.43± 0.04	13.95	101.27± 0.977
F5	25.82± 1.68	0.37± 0.03	0.44± 0.04	15.90	101.73± 0.987
F6	25.54± 1.04	0.36± 0.04	0.42± 0.04	14.28	99.67± 0.927
F7	25.02± 1.28	0.35± 0.04	0.41± 0.02	14.63	99.39± 0.889
F8	25.82± 1.24	0.35± 0.03	0.42± 0.03	16.67	97.28± 0.899
F9	26.94± 1.05	0.36± 0.02	0.42± 0.03	14.28	98.63± 0.9 17

Evaluation of Famotidine floating matrix tablets

The Famotidine floating matrix tablet formulations were evaluated for different parameter like hardness, thickness, friability, average weight and assay.

The hardness value of tablet formulations was within the range of 3.5-4.5 kg/cm^2. Friability value of all formulations and commercial tablets were less than 1%. Small values in friability imply much less friability during transportation, which is important in terms of sustained release of tablets. The result was shown in table 6.

Table 6: Results of physical evaluation of Famotidine tablets of F1-F9 batch

Batches	Average Weight ((mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	260±0.68	3.50±0.2	4.3±0.46	0.72	93.22
F2	262±0.45	3.49±0.5	4.5±0.60	0.91	96.45
F3	261±0.89	3.49±0.3	4.9±0.43	0.87	94.16
F4	259±0.23	3.5 1±0.1	4.1±0.53	0.79	95.78
F5	256±0.77	3.49±0.1	4.8±0.62	0.90	93.95
F6	260±0.56	3.52±0.3	4.2±0.53	0.76	94.46
F7	259±0.98	3.50±0.2	3.7±0.70	0.94	93.22
F8	258±0.84	3.57±0.4	3.6±0.53	0.86	96.45
F9	263±0.51	3.47±0.5	4.0±0.70	0.77	94.16

Table 7: *In vitro* drug release of F1 - F9 batches of famotidine floating matrix tablet

Time (hr)	*In vitro* drug release (mean ± SD)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	**0**
1	17.18±2.13	18.11±1.79	18.97±1.12	13.57±2.51	14.63±1.45	15.11±3.34	9.21±1.56	10.34±2.11	**08.52±2.61**
2	17.18±2.13	29.44±2.83	30.19±2.37	13.57±2.51	14.63±1.45	25.02±2.26	15.01±4.51	15.18±4.79	**16.47±3.59**
3	39.78±4.9	41.07±1.77	41.97±1.84	35.01±5.34	35.67±2.17	35.91±4.15	28.43±2.89	29.04±2.89	**29.18±2.11**
4	52.33±3.11	53.78±3.21	54.36±3.25	47.34±1.98	48.05±4.23	49.18±1.93	44.98±5.12	45.61±5.12	**48.56±4.90**
5	65.49±1.46	65.22±2.34	65.91±4.48	60.13±2.88	59.84±1.22	59.99±2.59	51.19±3.98	52.29±3.98	**53.79±2.98**
6	78.53±5.10	79.83±1.91	65.91±4.48	72.03±4.46	72.35±5.12	73.19±3.78	64.04±2.29	64.34±2.29	**65.19±2.61**
7	92.32±2.21	93.09±1.63	93.98±2.99	81.41±2.23	80.36±1.81	82.78±4.98	71.91±1.09	72.97±1.09	**73.49±4.98**
8	96.68±3.94	98.12±1.78	98.97±1.31	89.08±1.17	89.57±3.09	90.46±1.90	79.49±2.61	80.52±2.61	**81.75±1.64**

***In vitro* drug release profile**

The in vitro dissolution of Famotidine floating matrix tablet was carried out in 1.2 pH buffer at 50 rpm for 8 hrs. The result was shown in Table 07 and figure 5.

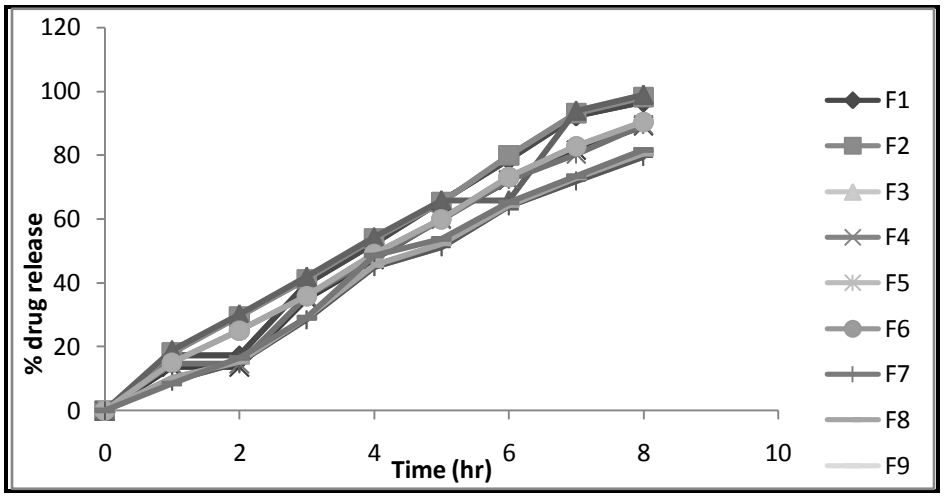

Figure 5: Comparative dissolution profile of Famotidine batches F1-F9

From the above data, the dissolution profile Famotidine floating matrix tablet of F3 batch meet the theoretical standard (figure 6).

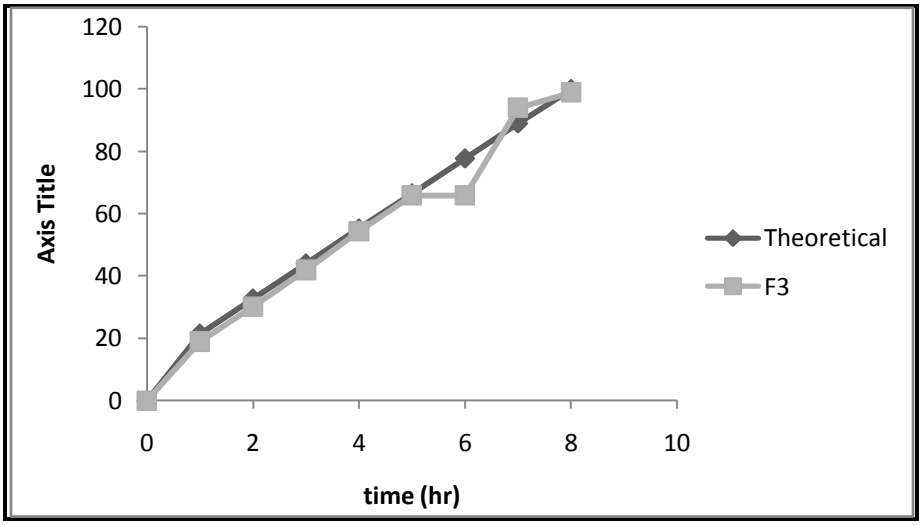

Figure 6: Comparison of dissolution profile of Theoretical & batch F3

Kinetic Modelling and Mechanism of drug release

The *in vitro* release data obtained were fitted in to various kinetic Equations. Correlations of individual batch with applied equation and result are shown in table 8. The release rates were calculated from the slope of the appropriate plots.

All batches showed higher correlation with zero order kinetics, Higuchi kinetics and korsmeyer Peppas kinetics. To find out release mechanism the *in vitro* release data were fitted in Korsmeyer Peppas equation where n is a factor, which indicates the mechanism of the release. For all

batches it was found that n value was greater than 0.5 and less than 1.0 which indicates anomalous transport mechanism (Table 8).

Table 8: Release kinetics for Famotidine floating tablet formulation batches F1-F9

Batch	Regression				
	Zero order kinetic R^2	Higuchi kinetics	Hixon Crowel	Korsmeyer R^2	n value
F1	0.9940	0.9791	0.9506	0.9775	0.804
F2	0.9951	0.9792	0.9397	0.9767	0.778
F3	0.9949	0.9786	0.9307	0.9757	0.754
F4	0.9962	0.9838	0.9816	0.9843	0.922
F5	0.9970	0.9836	0.9785	0.9845	0.878
F6	0.9967	0.9822	0.9767	0.9835	0.862
F7	0.9879	0.9793	0.9894	0.9990	0.930
F8	0.9884	0.9812	0.9901	0.9903	0.970
F9	0.9920	0.9813	0.9858	0.9901	0.942

Result of 3^2 full factorial design with evaluation parameter of Famotidine floating matrix tablet of Famotidine

Result of Box Behnken design layout, Coded variable form and evaluation parameter like Drug content, % drug release at Q_4 and Q_8 hrs, FLT were shown in Table 9.

Table 9: 3^2 full factorial design layouts with result of evaluation parameter for floating matrix tablet of Famotidine

Batch No	Variables level in coded		Drug content (%)	% Drug release (Q_4)	% Drug release (Q_8)	FLT (sec)	Similarity Factor (F_2)
	X1	X2					
F1	-1	-1	99.67	52.33	92.32	43	80.78
F2	-1	0	98.23	53.78	93.09	21	82.82
F3	-1	+1	98.94	54.36	93.98	16	83.92
F4	0	-1	92.78	47.34	81.80	49	61.55
F5	0	0	93.95	48.05	80.36	31	62.65
F6	0	+1	94.46	49.19	82.78	19	65.09
F7	+1	-1	91.22	44.98	71.91	51	48.27
F8	1	0	93.45	45.61	72.97	34	49.09
F9	+1	+1	94.46	44.56	73.49	20	49.99

1. Factorial equation for floating lag time

The floating lag time for all the batches F1 to F9 varied from 16 to 51 sec and showed good correlation coefficient as 0.9961 (table 10). Results of the regression equation indicated that the effect of X_2 (concentration of sodium bicarbonate) was more significant ($P < 0.05$) than X_1 (HPMC K4M : Carbopol 934P ratio). Hence as the concentration of sodium bicarbonate increase

the floating lag time decreases and as the concentration of polymer increases the floating lag time increases.

$Y3 = 30.31 - 4.16\ X_1 - 4.82\ X_2 + 0.928\ X_1^2 - 2.475\ X_2^2 + 4.48\ X_1X_2$

$R^2 = 0.9961$

2. Factorial equation for Q_4

The amount of drug released is an important parameter for controlled release action of the floating matrix tablet of famotidine. The amount of drug released at 4 hrs from the matrix tablet varied from 44.56 % to 54.36 % (table 09) and showed good correlation coefficient as 0.9968 (table 10). Results of the regression equation indicated that effect of X_1 (polymer: polymer ratio that is HPMC K4M: Carbopol 934P ratio) was more significant ($P<0.05$) as compared to the effect of X_2 (concentration of sodium bicarbonate).

$Q_4 = 48.31 - 4.22\ X_1 + 0.662\ X_2 + 1.248\ X_1^2 - 0.439\ X_2^2 - 0.515\ X_1X_2$

$R^2 = 0.9968$

3. Factorial equation for Q_8

The amount of drug released is an important parameter for controlled release action of the floating matrix tablet of famotidine. The amount of drug released at 8 hrs from the matrix tablet varied from 71.91% to 93.98% (table 09) and showed good correlation coefficient as 0.9971 (table 10). Results of the equation indicated that the effect of X_1 (polymer: polymer ratio that is HPMC K4M: Carbopol 934P) was more significant ($P < 0.05$) than effect of X_2 (concentration of sodium bicarbonate).

$Q_8 = 89.68 - 8.66\ X_1 + 0.978\ X_2 - 0.478\ X_1^2 + 0.021\ X_2^2 - 0.006\ X_1X_2$

$R^2 = 0.9971$

Table 10: Summary of results of regression analysis

Coefficient	B0	B1	B2	B11	B22	B12	Multiple R
FLT (sec)	30.31	-4.16	-4.82	0.928	-2.475	4.48	0.9961
Q_4 (%)	48.31	-4.22	0.662	1.248	-0.439	-0.5 15	0.9968
Q_8 (%)	89.68	-8.66	0.978	-0.478	0.021	-0.006	0.9971

Selection of the best batch

The selection of the best batch depends on Floating lag time, Q_4, Q_8, drug content and similarity factor. The FLT of batch F3 is 16 sec (figure 7) which is good because of less chances of gastric emptying. Drug content for the batch F3 is 98.97 % which is highest instead of other batches. Dissolution data and graph are recorded in Table 07 and Figure 5 respectively. The amount of drug released for the batch F3 at 4 hrs was 54.36 % which was nearly similar to theoretical release profile and the 93.98 % drug release from the formulation within 8 hrs means it is a

prominent batch for sustained release formulation. The similarity factor of the batch F3 was 83.92 which was nearer to the hundred instead of other batches so, the batch F3 is selected as final optimized batch. All these criteria were matched with formulation batch F3 so it was considered as the best batch among other formulation batches.

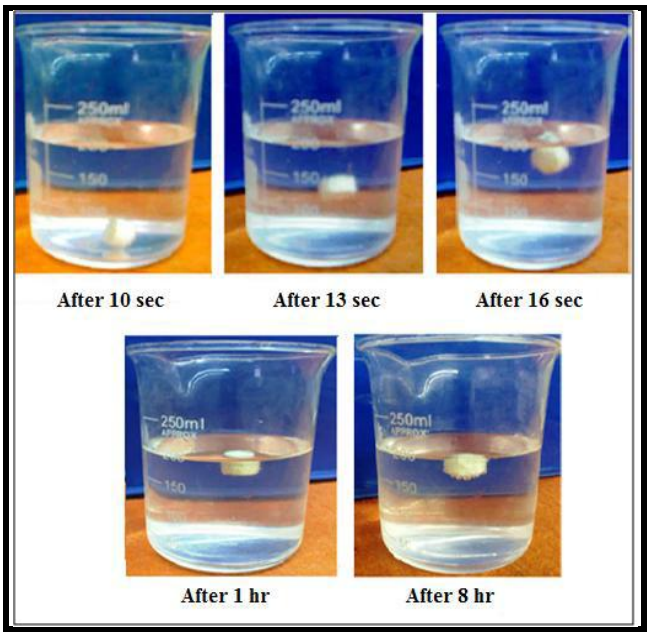

Figure 7: Floating behaviour of Famotidine tablet of optimized batch F3

CONCLUSION:

The present investigation deals with the formulation, optimization and evaluation of effervescent based floating matrix tablet of famotidine. To minimize critical process parameter direct compression method was selected for the formulation of the tablets. The evaluation study shows that formulation F3 batch was ideally suited to be sustained release formulation. The promising formulations F3 have displayed good drug content and a sustain release action of 8 hrs and minimum FLT of tablet. The controlled release of famotidine was observed and good fit to the zero order.

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REFERENCE

1. Lee TW, Robinson JR. Remington. The Science and Practice of Pharmacy. 19th ed. Bal Lippincott Williams and Wilkins; 2000:903-929.

2. Swarbrick J, Boylan JC. Encyclopaedia of Pharmaceutical Technology. 1990:281-286.
3. Nayak A, Maji R, Das B. Gastroretentive drug delivery systems. Asian J Pharm Sci 2010; 3:2-10.
4. Garg R, Gupta G. Progress in Controlled Gastroretentive Delivery Systems. Trop J Pharm Res 2008; 3: 1055-1066.
5. Arora S, Ali J, Ahuja A, Khar R. Floating drug delivery System. AAPS Pharm Sci Tech 2005; 3: E372-E390.
6. Brahma, Singh N, Kwon, Kim H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release 2000; 63:235–259.
7. Gangadharappa V, Pramod kumar T. Gastric Floating Drug Delivery Systems: A Review. Indian J Pharm Edu 2007; 41(4): 295-305.
8. Patel G, Patel H, Patel M. Floating Drug Delivery System: An Innovative Approach to Prolong Gastric Retention. Pharmaceutical review 2007; 5(6):22-29.
9. Shah S, Patel J, Patel N. Stomach Specific Floating Drug Delivery System. Int J Pharm Tech Res 2009; 3: 623-633.
10. Müller W, Anders E. Floating system for oral therapy. 1989; WO Patent 89/06956.
11. http://en.wikipedia.org/wiki/famotidine#History and development.
12. Yunqi W, Reza F. Stability of metronidazole, tetracycline HCl and famotidine alone and in combination. Int J Pharm 2005; 290:1–13.
13. Bullock A. Stability of famotidine 20 and 50 mg/L in total nutrient admixtures. Am J Hosp Pharm 1989; 46: 2326-2329.
14. Jain A, Jain C,Tanwar Y, Narka P. formulation, characterization and *in vitro* evaluation of floating microspheres of famotidine as a gastroretentive dosage form. Asian J Pharm 2009: 222-226.
15. Fujiwara M, Miyazaki S, Kubo W, Itoh K, Konno Y, Dairaku M, et al. The effect of taste masking agents on *in situ* gelling pectin formulations for oral sustained delivery of paracetamol and ambroxol. Int J Pharm 2005; 297: 38-49.
16. Tadros M. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro–in vivo* evaluation in healthy human volunteers. Eur J Pharm Biopharm 2010; 74:332–33.
17. Costa P, Lobo J M S. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 12: 123-133.

18. Cooper J, Gun C. Powder Flow and Compaction. Inc Carter SJ, Eds. Tutorial Pharmacy. New Delhi, hidix CBS Publishers and Distributors; 1986:211-233.
19. Lachman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy, 3rd ed., Varghese Publishing House; 1987:297-300.