Research Article

Formulation Development, Optimization and Evaluation of Famotidine Floating Matrix Tablets

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ABSTRACT

The purpose of this research work was to prepare a gastroretentive drug delivery system of Famotidine. This study investigated utility of a 3-factor, 3-level Box-Behnken design and optimization process for floating tablet of famotidine with 5 replicates of center points. Amount of HPMC K4 (Hydroxy Propyl Methyl cellulose), amount of $NaHCO_3$ and amount of citric acid were selected as the independent variables whereas total floating time (TFT), half life, % cumulative drug release at 10 hrs, and diffusion coefficients (n) were selected as dependent variables. The prepared tablets of famotidine were evaluated for dissolution study and found to follow zero order release kinetic. The responses were analyzed using ANOVA and the individual response parameters were evaluated using F test and polynomial equation was generated for each response using MLRA. The amount of HPMC K4 and amount of citric acid were found to significantly influence all response parameters selected whereas the amount of $NaHCO_3$ has significant effect on TFT. Optimum amount of HPMC K4, $NaHCO_3$, and citric acid is important in achieving good floating time and minimum floating lag time. It was clear from dissolution profiles that the tablets of batch F3, F7, and F12 exhibits initial burst phase during the first hour of dissolution. The burst phase was followed by a limited drug release for the rest of the period. The produced tablets exhibited good floating time and controlled drug release over a period of 12 h. The resultant data were critically analyzed to locate the composition of optimum formulations. All predicted values of response variables of optimized formulation demonstrated close agreement with the experimental data during optimization procedure.

Keywords: Famotidine, Gastroretentive floating tablet, Box-Behnken Design, Controlled release, Hydroxy Propyl Methyl Cellulose.

INTRODUCTION

The objective of the present study was to develop single unit gastroretentive drug delivery system of Famotidine. Famotidine is a histamine H_2-receptor antagonist. It is prescribed widely in Active Duodenal ulcers, Gastric ulcers, Zollinger-Ellison syndrome, Gastro Esophageal Reflux Disease (GERD) and Erosive Esophagitis. It has a low biological half-life of 2.5-4.0 h. The current recommended adult oral dosage of famotidine is 20 mg twice daily or 40 mg once daily. [1] The low bioavailability (40-45 %) and short biological half-life (2.5-4.0 hrs) of Famotidine following oral administration favors development of a sustained release formulation. The gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral

sustained delivery of drugs. The aim of research work is to formulate and evaluate controlled release floating tablet of Famotidine in view to enhance bioavailability and therapeutic action. The specific objective of research includes: Formulation of GRDDS containing Famotidine, which would remain in stomach and/or upper part of GIT for prolonged period of time in view to maximize the drug release in the upper part of GIT. Employment of Box-Behnken design for formulation of GRDDS. Evaluation of the formulation for their hardness, friability, drug content, floating lag time, total floating time, i*n vitro* dissolution study, i*n vitro* buoyancy study, i*n vivo* buoyancy study and stability study. Mathematical optimization of the variable of formulation using response surface methodology and their evaluation to obtained reliable and reproducible product. Comparison of observed values of optimized formulation with predicted values.

The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained

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delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. [2] It has been reported that the oral treatment of gastric disorders with an H_2 receptor antagonist like Famotidine or Ranitidine used in combination with antacids promotes local delivery of these drugs to the receptor of parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases efficacy of drugs to reduce acid secretion. Hence this principle may be applied for improving systemic as well as local delivery of Famotidine, which would efficiently reduced gastric acid secretion. [3]

MATERIALS AND METHODS

Famotidine was obtained as gift sample from Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat. HPMC K4 was obtained as gift sample from Zydus-Cadila Healthcare Ltd, Ahmedabad, Gujarat. Sodium bicarbonate, citric acid and Magnesium stearate were received from S. D. Fine-Chem. Limited, India. All other chemicals used were of analytical reagent grade, available commercially and used as such without further processing.

Preparation of Famotidine floating tablets:
The ingredients were weighed accurately and mixed thoroughly as per Table 3. The granules were dried in conventional hot air oven at 45°C. Drying of the granules was stopped when the sample taken from the oven reached a loss on drying (LOD) value of 1 to 3 %, as measured by a moisture balance at 105°C. The dried granules were sized through 20 meshes. The mixture was blended with magnesium stearate for 2-3 min to improve flow property. The powder was compressed into tablet weighing 250 mg using 8.75 mm shallow biconcave punches in a single punch tablet machine to a hardness of 2-4 kg/cm^2.

Formulation Design (BOX-BEHNKEN DESIGN) [4]
A 3-factor 3-level Box-Behnken design was used for the formulation of tablets. This design is suitable for exploring quadratic response surface and constructing second order polynomial models. The design consists of replicated center points and the set of points lying at the midpoint of the multidimensional cube that defines the region of interest. The non linear quadratic model generated by the design in the form:

$$Y = X_0 + X_1A + X_2B + X_3C + X_4A^2 + X_5B^2 + X_6C^2 + X_7AB + X_8BC + X_9AC + E$$

Where, Y is the measure response associated with each factor level combination: X_0 is an intercept: X_1 - X_9 are the regression coefficient: A, B, C are the factor studied and E is the associated error term. The independent factors used in the design are listed in Table 1.

Table 1: Independent factors

Independent variable	Levels		
	Low	Middle	High
A = Amount of HPMC K4 (mg)	50	70	90
B = Amount of NaHCO3 (mg)	20	35	50
C = Amount of Citric Acid (mg)	0	5	10

Box-Behnken designs are response surface designs, specially made to require only 3 levels, coded as -1, 0, and +1. Box-Behnken designs are available for 3 to 10 factors. Box-Behnken design is formed by combining two-level factorial designs with incomplete block designs. This procedure creates designs with desirable statistical properties but, most importantly, with only a fraction of the experimental trials required for a three-level factorial. Because there are only three levels, the quadratic model was found to be appropriate.

Table 2: Constraints for Optimized formulation

Name	Goal	Lower Limit	Upper Limit
Amt of HPMC K4	minimize	50	90
Amt of NaHCO$_3$	minimize	20	50
Amt of CA	maximize	0	10
TFT	maximize	3.17	12
%CR 10 hr	Maximize	57.35	80
T 50 %	Is target = 6.00	0.6	8.6
Diffusion coefficient (n)	Is target = 1.00	0.066	1.558

Drug content and physical evaluation
Compressed tablets were evaluated for assay, weight variation and friability according USP 24. 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 min. 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. Amount of drug present in one tablet is calculated. The results are shown in Table 4.

Swelling Index [12]
The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900 ml rotated at 50 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as

W U (%) the tablet= Weight of the swollen tablet −Initial weight of / Initial weight of the tablet × 100

***In vitro* buoyancy study** [5]
The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT).The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.* The tablets were placed in a 200 ml beaker containing 0.1 N hydrochloric acid. The time required for the 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 results are shown in Table 4.

***In vitro* drug release study**
Dissolution of the tablet of each batch was carried out using USP type II apparatus using paddle.[6-7] 900 ml of 0.1 N HCl was filled in a dissolution vessel and the temperature of the medium were set at 37 ± 0.5º C. One tablet was placed in each dissolution vessel and the paddle rotational speed was set at 50 rpm. 10 ml of sample was withdrawn at every hour for 12 hrs and same volume of fresh medium was replaced

Table 3: Composition of formulations of floating tablets of Famotidine (Box-Behnken Design)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Famotidine	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K4	50	90	50	90	50	90	50	90	70	70	70	70	70	70	70	70	70
NaHCO$_3$	20	20	50	50	35	35	35	35	20	50	20	50	35	35	35	35	35
Citric Acid	5	5	5	5	0	0	10	10	0	0	10	10	5	5	5	5	5
PVP K 30	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Mg. Stearate	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Lactose	103	63	73	33	93	53	83	43	88	58	78	48	68	68	68	68	68
Total	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250

Table 4: Results of evaluation of tablets for Box-Behnken design batches

Batch	Floating Lag Time (seconds) ± SD	Total Floating Time (hrs) ± SD	Drug Content (mg) ± SD
F1	19.67 ± 1.53	4.83 ±0.29	39.43 ± 0.15
F2	1346.67 ± 128.58	12.00 ± 0.00	39.65 ± 0.22
F3	13.67 ± 1.53	3.73 ± 0.25	39.25 ± 0.36
F4	22.33 ± 2.52	12.00 ± 0.00	39.35 ± 0.46
F5	37.00 ± 2.65	12.00 ± 0.00	39.65 ± 0.22
F6	86.67 ± 7.64	12.00 ± 0.00	39.15 ± 0.33
F7	11.67 ± 1.53	03.17 ± 0.29	40.36 ± 0.33
F8	16.00 ± 2.00	12.00 ± 0.00	40.46 ± 0.35
F9	80.33 ± 3.06	12.00 ± 0.00	40.42 ± 0.64
F10	36.00 ± 3.61	12.00 ± 0.00	40.27 ± 0.30
F11	25.67 ± 2.08	12.00 ± 0.00	39.00 ± 0.28
F12	15.33 ± 1.53	04.83 ± 0.29	39.55 ± 0.45
F13	15.33 ± 0.58	12.00 ± 0.00	39.16 ± 0.51
F14	15.00 ± 1.00	12.00 ± 0.00	40.05 ± 0.14
F15	15.00 ± 1.00	12.00 ± 0.00	39.12 ± 0.37
F16	14.67 ± 0.58	12.00 ± 0.00	40.11 ± 0.47
F17	15.33 ± 0.58	12.00 ± 0.00	40.02 ± 0.41

Table 5: The Design and Response summary data

Std.	Factors			Response			
	A: Amt of HPMC K4	B: Amt of NaHCO$_3$	C: Amt of Citric Acid	TFT (h)	%CR 10 h	$t_{50\%}$ (h)	n
1	50.00	20.00	05.00	5.81	99.52	1.2	0.324
2	90.00	20.00	05.00	12	69.23	4.4	0.856
3	50.00	50.00	05.00	4.71	99.89	0.7	0.138
4	90.00	50.00	05.00	12	67.44	7.1	1.285
5	50.00	35.00	00.00	12	69.88	7.1	1.243
6	90.00	35.00	00.00	12	59.17	8.1	1.166
7	50.00	35.00	10.00	4.15	99.69	0.6	0.066
8	90.00	35.00	10.00	12	63.72	7.5	1.328
9	70.00	20.00	00.00	12	67.91	6.5	0.989
10	70.00	50.00	00.00	12	57.33	8.3	1.558
11	70.00	20.00	10.00	12	66.87	8.3	0.751
12	70.00	50.00	10.00	5.81	99.89	0.7	0.146
13	70.00	35.00	05.00	12	67.84	7.2	0.857
14	70.00	35.00	05.00	12	67.91	7.1	0.806
15	70.00	35.00	05.00	12	68.47	7.2	1.000
16	70.00	35.00	05.00	12	70.88	7.0	0.975
17	70.00	35.00	05.00	12	70.11	7.0	0.814

Table 6: Dissolution data treatments of tablets of batch F1 to batch F17

Batch	Zero order		Higuchi			Korsmeyer Peppas		
	K_0	r^2	K_H	r^2	n	r^2	Km	
F1	12.789	0.3335	35.193	0.9258	0.324	0.9952	48.65	
F2	7.376	0.9880	19.331	0.9133	0.856	0.9992	9.84	
F3	13.187	0.6216	39.456	0.5383	0.138	0.8341	76.09	
F4	6.765	0.9951	17.450	0.8356	1.285	0.9842	3.96	
F5	6.695	0.9859	17.148	0.7977	1.243	0.9966	4.10	
F6	6.051	0.9957	15.710	0.8674	1.166	0.9791	4.50	
F7	13.971	0.9879	36.660	0.3385	0.066	0.8534	86.66	
F8	6.417	0.9925	16.520	0.8261	1.328	0.9875	3.45	
F9	7.130	0.9903	18.690	0.9015	0.989	0.9907	7.45	
F10	5.393	0.9586	13.650	0.7377	1.558	0.9977	1.76	
F11	7.130	0.9730	18.789	0.9376	0.751	0.9965	11.65	
F12	13.947	0.5441	39.256	0.5770	0.146	0.8911	74.59	
F13	6.801	0.9963	17.684	0.8716	0.857	0.9873	8.83	
F14	6.913	0.9929	18.033	0.8859	0.806	0.9816	9.92	
F15	6.473	0.9896	16.640	0.8134	1.000	0.9778	6.24	
F16	7.040	0.9974	18.228	0.8468	0.975	0.9875	7.26	
F17	7.282	0.9923	19.015	0.8926	0.814	0.9827	10.33	

every time. The samples were filtered through a 0.45 μ membrane filter and diluted to a suitable concentration with 0.1 N hydrochloric acid. The samples were analyzed for drug release against 0.1 N HCl as a blank at wavelength of 265 nm using double beam UV visible spectrophotometer. The drug release was calculated using the equation generated from

standard curve. The % cumulative drug release was calculated. The plot of cumulative percentage drug release Vs time is shown in figure 1-5.

Statistical analysis

The response surface methodology is a collection of mathematical and statistical techniques used for modeling and analysis of problems in which a response of interest is influenced by several variable and the objectives is to optimize this response. The run or formulation, which are designed based on Box-Behnken design are evaluated for the response. The response values are subjected to multiple regression analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis are Total floating time, T50%, % CR10 hrs and Diffusion coefficient (n). The Diffusion coefficient (n) obtained after fitting the release rate to Korsmeyer and Peppas model. The curve fitting results of the release rate profiles of the formulation are given in Table 6. The multiple regression analysis was done using DESIGN EXPERT 6.0.11 (STAT-EASE) demo version software, which specially meant for this optimization process. Analysis of data was carried out using ANOVA and the individual parameter was evaluated with F-test. Using the regression coefficient of factor, the polynomial equation for the each response is generated. [8]

Drug-Polymer interaction studies

The IR analysis of the sample was carried out for qualitative compound identification. The pellet of approximately 1 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of Potassium Bromide in pressure compression machine. The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm^{-1} – 600 cm^{-1}. The IR spectrum is depicted in figure 6.

Kinetic treatment of dissolution profiles

The *in vitro* release data of all formulations were also subjected to model fitting analysis to know the mechanism of drug release from the formulations by treating the data according to zero order,[9] Higuchi[10] and Korsemeyer-Peppas equation.

Optimization [4], [11]

The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). Constraints for responses and factors are shown in Table 2. By utilizing DESIGN EXPERT 6.0.11 (STAT-EASE) demo version software, we got one solution for optimized formulation. The optimized formulation is prepared and evaluated for total floating time, T50%, % CR 10 hrs, diffusion coefficient (n). Observe response value of the optimized formulation is compared with predicted value.

RESULTS AND DISCUSSION

On the basis of preliminary identification test it was concluded that the drug complied the preliminary identification. There was no drug polymer interaction, which was confirmed by the IR spectra of drug and physical mixture. The IR spectrum is depicted in figure 6. The physical parameters of tablets showed that the tablets of all batches had desirable physical characteristics. All the batches of tablet produced (except batch F2) were found to exhibit short floating lag times (maximum floating lag time recorded was 87.67 ± 6 second). The short floating lag time can be due to presence of sodium bicarbonate and citric acid. Sodium bicarbonate and citric acid were used in combine to minimize
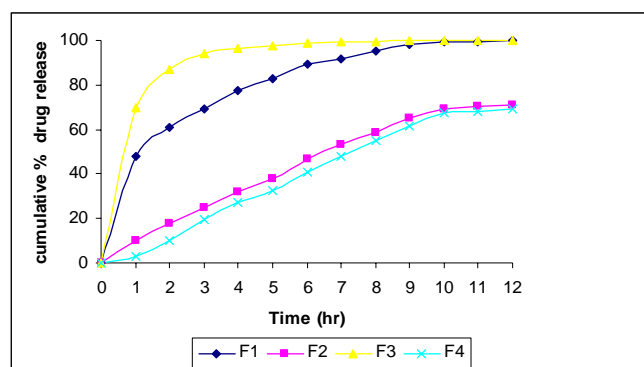

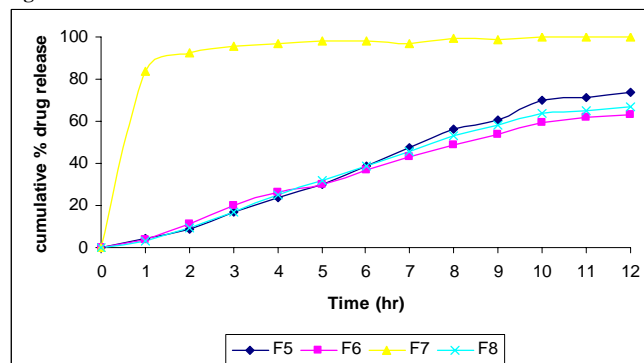Fig. 1: Dissolution Profile of Batch F1 to F4
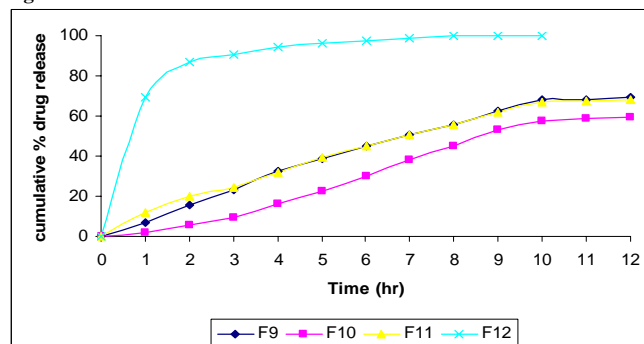

Fig. 2: Dissolution Profile of Batch F5 to F8

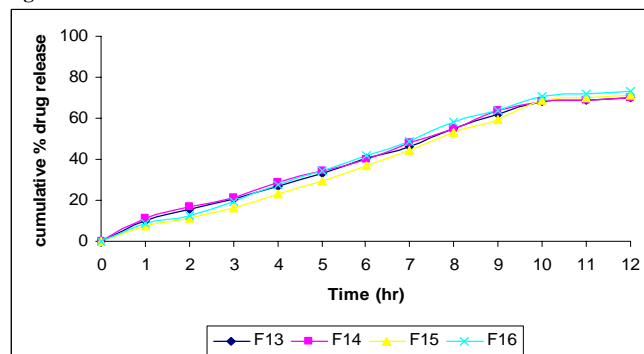Fig. 3: Dissolution Profile of Batch F9 to F12
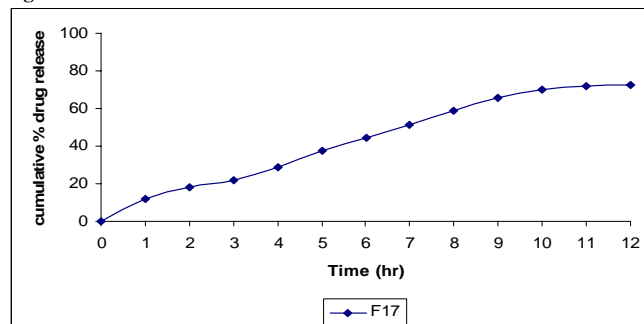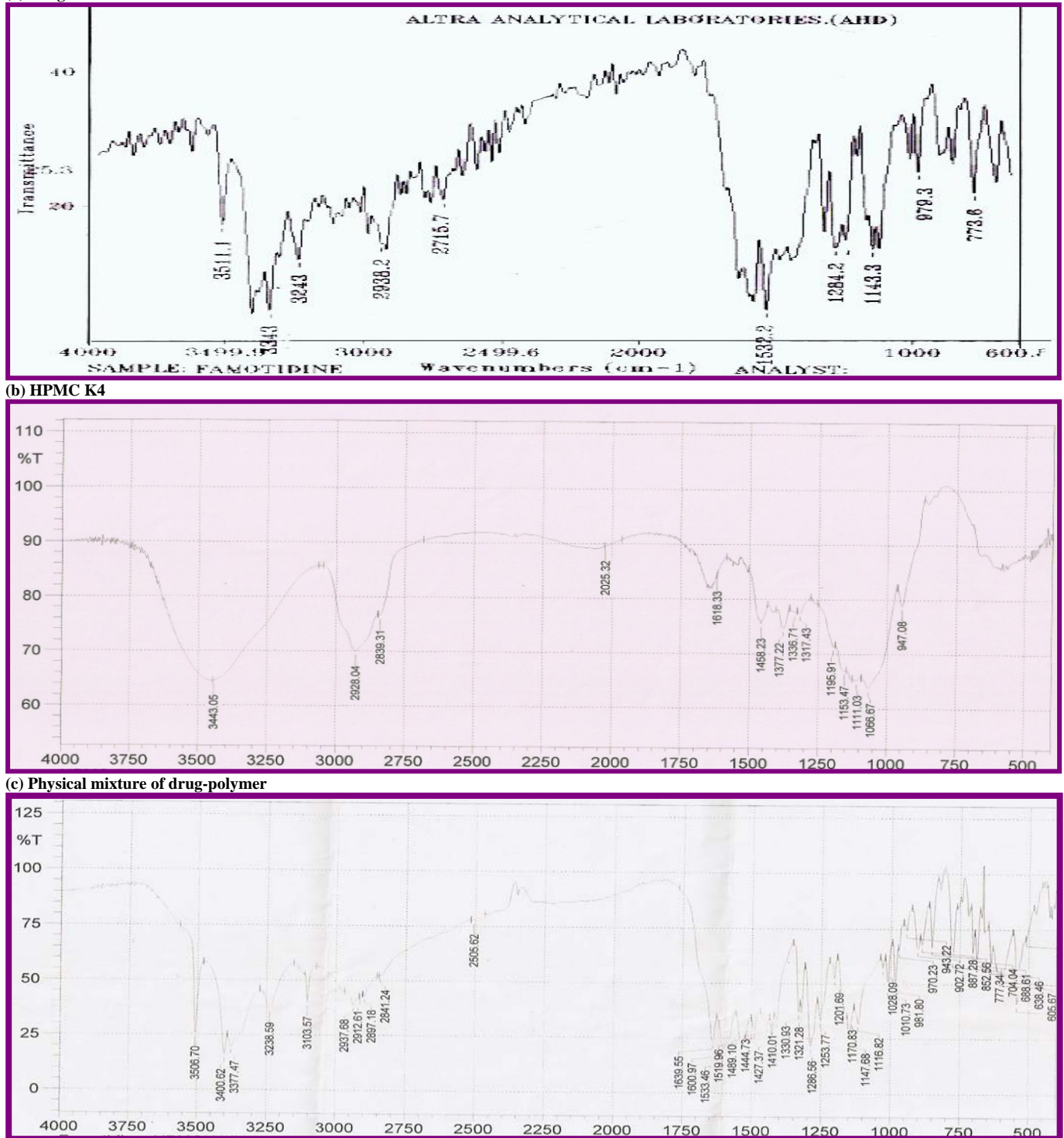

Fig. 4: Dissolution Profile of Batch F13 to F16

Fig. 5: Dissolution Profile of Batch F17

Figure 6: FT-IR spectra of (a) Drug (b) HPMC K4 and (c) Physical mixture
(a) Drug

(b) HPMC K4

(c) Physical mixture of drug-polymer

the lag time in fabrication of GRDDS. The tablet of batch F2 exhibited a longer floating lag time of 22 min. This can be due to the presence of NaHCO3 at low level and HPMC K4 at high level. The high level of HPMC K4 would possibly prevents the entry of media into the tablet matrix and prolong the floating lag time. All batches of tablet were found to exhibit maximum floating time i.e. 12 hrs. Tablets of batch F1, F3, F7 and F12 exhibited short floating time i.e. 3-5 hrs because they eroded faster in media due to high amount of NaHCO3 and citric acid in coupled with less amount of HPMC K4. Value of "Prob > F" less than 0.05 indicate factor A, B, C, AC, BC had significant effect on total floating time.

One factor plot shows that amount of HPMC K4 increased, TFT increased due to increased matrix integrity at high amt of HPMC K4 while amt of NaHCO3 and citric acid increases TFT decrease because $NaHCO_3$ and citric acid promote faster erosion of tablets. From the results of swelling index it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the

dosage form. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

So the presence of optimum amount of HPMC K4, $NaHCO_3$, and citric acid is important in achieving good floating time and minimum floating lag time. Incorporation of sodium bicarbonate helps to produce carbon dioxide gas which entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float. The relationship between the dependent and independent variables was further elucidated using contour and response surface plots. Contour plot shows that at a fixed level of $NaHCO_3$ (35 mg), TFT decrease at low level of A (amount of HPMC K4) and high level of C (citric acid). However at high level of A (amount of HPMC K4) TFT remains unaffected with change in amount of citric acid. These might be due to at low level of HPMC K4 (50 mg), matrix unable to remain intact with increase in citric acid.

It was clear from dissolution profiles that the tablets of batch F3, F7, and F12 exhibits initial burst phase during the first hour of dissolution. The burst phase was followed by a limited drug release for the rest of the period. The initial burst release can be attributed to low levels of HPMC K4 combined with high levels of $NaHCO_3$ and citric acid. It was observed during the dissolution studies that tablets of all three batches eroded quickly with increased effervescence. Other formulation showed a linear pattern of Famotidine release from floating tablet. However simultaneous increasing amount of HPMC K4 and amount of citric acid had no significant effect on % CR10 hrs and T 50 %. The interaction effect of B and C at a fixed levels of A indicated that % CR10 hrs increases whereas T 0.5 decrease at high levels of both B and C. This can be attributed to formation of compact matrix with increasing level of HPMC K4 and porous matrix with increasing level of $NaHCO_3$ and citric acid. The dissolution data of most of formulation fitted well into zero order release kinetics. The data fitment of the dissolution profiles done according to Korsmeyer-Peppas model (Table 1) indicating the values of diffusion coefficients obtained range from 0.06 to 1.55. The formulation F1, F3, F7 and F12 which exhibited an initial burst phase showed a low value of diffusion coefficients ranging from 0.06 to 0.32. Low level of HPMC K4 coupled with high amount of $NaHCO_3$ and citric acid for these formulations was responsible for the incompatibility of the system to control the release of Famotidine from the GRDDS. Other tablet formulations gave relatively higher n value for diffusion coefficient ranging from 0.75 to 1.55. The mechanism of drug release in these cases was known to follow case II transport mechanism i.e. characterized by both erosion and diffusion.

For the optimization of floating tablets of Famotidine constraints was fixed for all factors and response. Constraints were set according to formulation of floating tablets using minimum amount of excipients, which will give desired response values. In the present study the aim was zero order drug release from the tablets and so that the diffusion coefficient was targeted to 1. The dissolution data of optimized formulation fitted well into zero order release kinetics (r^2 = 0.9942). The diffusion coefficient (n) value

0.93 i.e. nearest to 1 indicated that floating tablets follow zero order kinetics of drug release. The mechanism of drug release in these cases was known to follow case II transport mechanism i.e. characterized by both erosion and diffusion. Stability studies were performed for optimized formulation and it was found that formulation was stable for 3 months at 40 ° C/ 75 % RH. The formulation was found to be stable in terms of morphology, drug content and drug release. Gastric retention time of Famotidine can be increased by formulating it in a floating dosage form using optimum amount of HPMC K4, $NaHCO_3$ and citric acid. The produced tablets exhibited good floating time and controlled drug release over a period of 12 hrs. It was concluded that the floating tablets released drug in stomach in view to enhance bioavailability of Famotidine. It can be concluded that by the application of experimental design (Box-Behnken design) and optimization technique, optimized formulation can be obtained with minimum expenditure time and money. Floating tablets of Famotidine were formulated according to Box-Behnken design. It can be concluded that a floating tablet with good floating and controlled release property can be obtained by optimizing amount of HPMC K4, $NaHCO_3$ and citric acid. The number of experimental trials carried out to produce the optimized formulation was considerably reduced thereby substantially cutting down the expenditure on time and money.

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