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Original Article

FLOATING PULSATILE DRUG DELIVERY SYSTEM OF FAMOTIDINE: DESIGN, STATISTICAL OPTIMIZATION, AND *IN VITRO* EVALUATION

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ABSTRACT

Objective: Pulsatile systems are gaining a lot of significance as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The aim of the present research work was to design and optimize compression coated floating pulsatile drug delivery system of Famotidine. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release.

Methods: Floating pulsatile tablets were prepared by using press coated technology. The prepared system consisted of two parts: a core tablet containing the active ingredient and an erodible outer shell with gas generating agent. The burst release core tablet was prepared by using super disintegrants with the active ingredient. Press coating of optimized burst release core tablets was done by the polymer. A 3^2 full factorial design was used for optimization. The amount of HPMCE4M and Polyox WSRN60K was selected as independent variables. Lag period, drug release, buoyancy and swelling index were selected as dependent variables.

Results: Floating pulsatile release formulation (FPRF) F4 at level 0 (65 mg) for HPMC E4M and level-1 (75 mg) for Polyox WSR N60K showed lag time of 4 h with>90% drug release. The data were statistically analyzed using ANOVA, and $P<0.05$ was statistically significant.

Conclusion: The present research work demonstrates that famotidine could be successfully delivered to provide night-time relief of gastric acidity by formulating floating pulsatile drug delivery system. The press-coated formulation containing HPMCE4M and Polyox WSR N60K at 0,-1 level was in the optimum zone and has the potential for time-controlled pulsatile delivery of Famotidine.

Keywords: Floating pulsatile, Famotidine

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. In oral route, time and site specific modified release dosage forms are gaining interest as they are programmed release dosage forms or pulsatile release dosage forms [1, 2]. Recent studies reveal that the body's biological rhythm may affect normal physiological function, including gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow, renal blood flow, hepatic blood flow, urinary pH, cardiac output, drug-protein binding, and liver enzymatic activity, and biological functions such as heart rate, blood pressure, body temperature, blood plasma concentration, intraocular pressure, stroke volume, and platelet aggregation [3].

Most organ functions vary with the time of the day, particularly when there are rhythmic and temporal patterns in the manifestation of a given disease state. The symptoms of many diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, ulcers and rheumatic disease have followed the body's biological rhythm [4-6].

Pulsatile drug delivery system is attaining the highest interest in the field of pharmaceuticals, as this drug delivery system is helping in rapid release of drug at the particular site after a pre-determined off-release period (lag time) matching with circadian rhythm and support for patient compliance [7, 8]. The time controlled function of third generation DDSs currently under development is finding application in new and improved disease therapeutics. Biological rhythms may be applied to pharmacotherapy by adopting a dosage form that synchronizes drug concentrations to rhythms in disease activity [9, 13].

Conventional pulsatile release dosage forms release the drug after 5-6 h of lag period in lower part of gastrointestinal tract which is unfavourable for certain drugs which will degrade in higher pH conditions, which are undergo enzymatic degradation, which all leads to develop a gastro retentive drug delivery system which favours for retaining the drug at upper part of gastrointestinal tract, which won't affected by change in pH, gastric emptying rate. This technology also favours for the drugs which have absorption window at stomach [14-17]. These considerations led to the development of pulsatile release dosage forms possessing gastric retention capabilities. Of the numerous approaches to prolong gastric retention, floating drug delivery system is the most widely used technique and offers a simple, practical approach to increased gastric residence through inherent buoyancy.

Normal gastric acid secretion follows a circadian rhythm with a sudden surge of gastric acidity when the gastric pH level goes far below 4 for at least 1 h in the midnight. This pathophysiological condition is termed as a nocturnal acid breakthrough (NAB) and is even more prolonged and clinically critical for H. pylori-negative patients on proton pump inhibitor (PPI) therapy. It is demonstrated that adding a bed-time dose of H2 antagonist to an evening dose of proton pump inhibitor provides nocturnal recovery of gastric acid secretion. This limitation, however, can be overcome by a chrono therapeutic approach which will ensure that the highest blood levels of the drug coincide with the peak symptoms in early morning hours. Hence, a bedtime dosing of H2 antagonist from a pulsatile delivery system combined with normal twice a day PPI dosing would be a promising therapeutic regimen.

Famotidine is histamine H2-receptor antagonist used for duodenal ulcer, benign gastric ulcer, gastro-oesophageal reflux disease (GERD), and nocturnal acid breakthrough with half-life 2.5-3.5 h [18-22]. Polyox are water soluble resins. Polyox WSRN60K, HPMCE4M are highly water soluble polymers. Upon exposure to water or gastric juice, they hydrate and swell rapidly to form hydrogels with properties suited for controlled drug delivery. The current research work shows the development of specific technology, based on

combining floating and pulsatile principles. Floating pulsatile drug delivery system of famotidine was prepared by compression coating technology utilising design of experiments for optimization.

MATERIALS AND METHODS

Materials

Famotidine was generously gifted by Dr. Reddy's Lab. Hyderabad. HPMC E4M and Polyethylene Oxide (Polyox WSRN60K) were gifted by Colorcon Asia Pvt. Ltd., Goa, India. Croscarmellose sodium, Crospovidone, Sodium starch glycolate and microcrystalline cellulose were gifted by Dr. Reddy's Lab. Hyderabad, India.

Methods

Drug-excipient interaction

To investigate the chemical interaction, Fourier transformed infrared (FTIR) analysis of famotidine and the chosen excipients used in the formulation were carried out over the range of 400-4000 cm^{-1} using FTIR spectrometer (Bruker, Alpha-T, Ettlingen, Germany). The spectra obtained for pure drug alone and in combination with excipients were compared to confirm the interaction.

Preparation of burst releases core tablets

The core tablets were prepared by direct compression method. Required quantities of Famotidine, microcrystalline cellulose (MCC, Avicel PH-102) and super disintegrant were dispensed and sieved through #40 mesh and dry blended in a polybag for 10 min. The blend was lubricated for 5 min in a polybag with the addition of magnesium stearate. Different types of super disintegrants with concentrations of 5% and 10 % were used in the formulations. Then lubricated blend compressed into round-shaped tablets with table top pilot scale 10 stations rotary rimek mini press-I using 6 mm round punch (M/S Karnavati Engineering Ltd., Gujarat, India). Table 1 summarizes the composition of burst release core tablets.

Table 1: Composition details of core tablets

Ingredients	C1	C2	C3	C4	C5	C6
Famotidine (mg)	40	40	40	40	40	40
Croscarmellose sodium(mg)	3.75	7.5	-	-	-	-
Crospovidone(mg)	-	-	3.75	7.5	-	-
Sodium starch glycolate(mg)	-	-	-	-	3.75	7.5
Magnesium stearate(mg)	3	3	3	3	3	3
Microcrystalline cellulose (mg)	28.25	24.5	28.25	24.5	28.25	24.5
Total tablet weight (mg)	75	75	75	75	75	75

Formulation of floating pulsatile release tablets with individual polymers

Press coated technology [23] was used for preparing floating pulsatile drug release tablets using HPMC E4M, Polyox WSR N60K polymers, sodium bicarbonate, and citric acid as a gas generating agent in batch A1 to A7. Initial screening trials were taken to optimise the concentration of sodium bicarbonate. The concentration of gas generating agent was varied between 15% (56 mg) to 25% (95%) of sodium bicarbonate, the concentration of citric acid was fixed as 30 mg. After finalizing the optimum concentration of gas generating agents, the concentration of individual polymer was determined and used in designing the experiment of factorial design.

Press-coated tablets were prepared by keeping 50% barrier layer material into a 9 mm die; then the core tablet was placed at the centre. The remaining half of the barrier layer material was added into the die and compressed. Table 2 summarizes the composition of the floating pulsatile release tablet (FPRT) trial batches with individual polymers.

Table 2: Composition of the floating pulsatile release tablet (FPRT) trial batches with individual polymers

Ingredients	A1	A2	A3	A4	A5	A6	A7
Core tablet (mg)	75	75	75	75	75	75	75
HPMC E4M(mg)	75	75	75	140	180	-	-
Polyox-N60K(mg)	75	75	75	-	-	130	170
Sodium bicarbonate(mg)	56	75	95	75	75	75	75
Citric acid(mg)	30	30	30	30	30	30	30
Microcrystalline cellulose (mg)	64	45	25	55	15	45	25

Formulation of the floating-pulsatile release tablets (FPRT) using experimental design

A full factorial3^2 design was used for optimization procedure. It is suitable for investigating the quadratic response surfaces and for constructing a second order polynomial model, thus enabling optimization of the time-lagged coating process. Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert. A 3^2 randomized reduced factorial design was used in this study, and 2 factors were evaluated, each at 3 levels; experimental trials were performed at all 9 possible combinations prepared according to the formula. table 3 summarizes the independent and dependent variables along with their levels. The resulted formulations (testing runs) are listed in table 4.

Table 3: Variables and constraints in full factorial experimental design

Independent variable	Level			Constrains
	-1	0	1	
X1: HPMC E4M (mg)	55	65	75	In range
X2: Polyox WSR N60K (mg)	75	85	95	In range
Dependent variables				
Y1: Swelling Index				
Y2: Buoyancy lag time (Sec)				
Y3: Cumulative drug release at 4th h (%)				
Y4: Cumulative drug release at 6th h (%)				
Y5: Lag period (H)				

Table 4: Observed responses in full factorial design for famotidine floating pulsatile tablets

Formula code	Independent variables		Dependent variables				
	X1	X2	Swelling index (%)	Buoyancy lag time (Sec)	Y_{Q4}	Y_{Q6}	Lag period (H.)
F1`	-1	-1	122.11	112	97.02	99.89	2
F2	-1	0	127.4	113	97.1	99.56	3
F3	-1	+1	129	116	90.69	99.47	3
F4	0	-1	140	101	93.1	99.96	4
F5	0	0	156	118	3.48	89.27	5
F6	0	+1	167.4	113	3.87	80.94	6
F7	+1	-1	176.3	115	2.94	75.61	7
F8	+1	0	189.8	112	3.87	66.96	8
F9	+1	+1	206.1	120	5.35	59.94	8
Coded values	**Actual values**						
	X_1 (mg)		**X_2 (%)**				
-1	55		75				
0	65		85				
1	75		95				

X_1–Amount of HPMC E4M; X_2-amount of Polyox WSR N60K; Y_{Q4}-% Cumulative drug release at 4th h; Y_{Q6}-% Cumulative drug release at 6th h. In all the formulations, 75 mg of Sodium bicarbonate and 30 mg of citric acid was used. Final tablet weight was made up to 375 mg with microcrystalline cellulose

The percentage of HPMC E4M (*X1*) and Polyox WSR N60K (*X2*) were selected as independent variables. Initial screening studies provided a setting of the levels for each formulation variables. Lag period of 4 h, % drugs released at 4th hour and 6th hour, buoyancy and swelling index were selected as dependent variables. The batches were prepared as per the runs and evaluated the effect of individual variables on dependent variables according to response surface methodology

$$Y = b_0+P_1X_1+P_2X_2+P_{12}X_1X_2+P_{11}X_{21}+P_{22}X_{22} \quad (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and bi (P_1, P_2, P_{12}, P_{11}, and P_{22}) is the estimated coefficient for the corresponding factor Xi (X_1, X_2, X_1X_2, X_{12}, and X_{22}), which represents the average result of changing 1 factor at a time from its low to high value. The interaction term X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_{21} and X_{22}) are included to investigate nonlinearity.

Formulation of batches containing HPMC E4M and polyox WSR N60K as variables

The batches containing HPMC E4M and Polyox WSR N60K were prepared according to the factorial design. The concentration of sodium bicarbonate and citric acid were kept constant at the optimum level. The optimum level was finalised on the basis of the results of the evaluation of initial screening trials. In this factorial design, the concentration of HPMC E4M and the concentration of Polyox WSR N60K were varied keeping the values of other ingredients constant. The minimum and maximum levels of the variables were decided on the basis of the predicted individual batches. The concentration of both polymers was finalized in the range of 35 to 45%, so as to study the combined effect of HPMC E4M and Polyox WSR N60K on the lag period, release pattern, and swelling index. Tablet batches contain HPMC E4M and Polyox N60K as the variables (F1–F9) according to the factorial design. The effect of the variables on the response was also studied by using the response surface methodology and statistical study by analysis of variance (ANOVA) which was studied by using the Design Expert® Software (Version 8.0.7.1, StatEase Inc., Minneapolis). The mathematical modeling and mathematical relationships generated using multiple linear regressions for the studied response variables are expressed in the form of equations.

Manufacturing of compression coated tablets

Floating pulsatile release tablets were prepared as per below procedure. HPMC E4M, Polyox WSR N60K, gas generating agent sodium bicarbonate, and citric acid were weighed and passed through sieve number 40 separately. Powder mixing was carried out using polyethene bag for 15 min. mixing was continued for another, 10 min, and burst core release tablets were prepared according to the formula given in table-1. Press-coated tablets were prepared by keeping 50% barrier layer material into a 9 mm die; then the core tablet was placed at the centre. The remaining half of the barrier layer material was added into the die and compressed.

Evaluation of floating-pulsatile release tablets (FPRT)

Evaluation tests

The evaluation was performed to assess the physicochemical properties of powder mixture and developed formulations and also their release characteristics.

Physical properties of powder mixture

Angle of repose

It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal. Accurately weighed the quantity of powder is poured in the funnel and the height of funnel is adjusted to a height of 2.5 cm and the radius of the circle is measured by taking the diameter values of the average of four values and the half of the diameter is the radius. It can be calculated by using the formula,

$$\theta = \tan^{-1} (h/r)$$

Where, h = Height of the funnel

r =Radius of circle

Compressibility index

Tapped density and bulk density were measured, and the compressibility index was calculated by the using the formula,

$$\% \text{ Compressibility index} = [(\rho_t-\rho_o)/\rho_t] \text{ X100}$$

Where ρ_t = Tapped density

ρ_o = Bulk density.

Hausner's ratio

Tapped density and bulk density were measured, and the Hausner's ratio was calculated by using the formula,

Hausner's ratio = ρ_t/ρ_o

Where, ρ_t = Tapped density

ρ_o = Bulk density.

Physical characterization of the designed tablet

The properties of the compressed matrix tablets, such as hardness, friability, weight variation and content uniformity were determined using reported procedure.

Hardness

The hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage transformation and handling before usage depends on its hardness. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester.

Friability

Friability was determined by testing 10 tablets in a Roche friability tester. Accurately weighed ten tablets were placed in Roche Friabilator and rotated at 25 rpm for 4 min. The tablets were then de-dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

Percentage friability was calculated using the following equation.

$$\text{Friability} = ([W_0 - W]/W_0) \times 100$$

Where; W_0 = weight of the tablet at time zero before the revolution.

W = weight of the tablet after revolutions at 4 min.

Weight variation

The weight variation was determined by taking the weight of 20 tablets using an electronic balance (Electronic Balance). The average weight of all tablets was calculated. It passes the test for weight variation, if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown.

Determination of % drug content

The tablets were crushed in the mortar, and the powder equivalent to 20 mg of drug was dissolved in distilled water. The stock solutions were filtered through a membrane filter (0.45 mm). The solutions were then diluted suitably in 0.1N HCl. The drug content was analyzed at 266 nm by UV spectrophotometer (LABINDIA UV3200). Each sample was analyzed in triplicate.

Swelling index determination

Tablets were weighed individually (designated as W_1) and placed separately in glass beaker containing 200 ml of 0.1NHCl and incubated at 37 °C±1 °C. At regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed ($W2$) and swelling index (SI) was calculated using the following formula:

$$SI = W_2 - W_1/W_1 \times 100$$

Where $W_{1=}$ Initial weight; $W_{2=}$ Swollen tablet weight

***In vitro* buoyancy determination**

Floating behaviour of the tablet was determined by using USP dissolution apparatus-II in 900 ml of 0.1NHCl which is maintained at 37±0.5 °C, rotated at 50rpm. The floating lag time as well as total floating time is observed.

***In vitro* dissolution studies**

In vitro release of Famotidine from the prepared Matrix tablets was studied using USP XXIV dissolution rate test apparatus-II (Model: LAB INDIA UV3200) employing the paddle stirrer. 900 ml of 0.1N HCl was used as dissolution medium maintained at a temperature of 37±0.5 °C and the paddle was rotated at 50 rpm and is carried for 10 h. At each interval of 1 hour, 5 ml of samples were withdrawn by means of a syringe fitted with a prefilter and immediately replaced with 5 ml of fresh medium. The absorbance of the samples was measured at 266 nm after suitable dilution with the medium using UV Spectrophotometer, and the results are as follows.

Lag time

Lag time was considered as the time when the tablet burst and core tablet is out of press coating. This is considered as predetermined off-release period.

Stability testing of the best formulation

A short-term stability study on optimized FPRT was carried out by storing the tablets at 25 °C (±2 °C) and 60% RH (±5%) and 40 °C (±2 °C) and 75% RH (±5%) over a 3 mo period according to ICH guidelines. At the end of three months' time interval, the tablets were examined for drug content, and floating duration.

RESULTS AND DISCUSSION

Evaluation of burst releases tablets

The rapid increase in the disintegration of Famotidine with crospovidone at a concentration (5%) may be attributed to rapid swelling of the tablet. It was observed that disintegration time of tablet varies with different super disintegrants and at different concentration levels. Formulation C3 (5% crospovidone) showed lowest disintegration time (64 sec) with high drug release (99.8%). The results were captured in table 5, table 6 and fig. 1. For the development of pulsatile delivery, disintegration time must be short to obtain burst effect. The hardness was observed in the range of (2.4–2.7±0.18 Kg/cm^2), whereas friability was less than 1% which indicated that tablet had good mechanical resistance. Drug content was found to be high (>98.14%) and uniform in all tablet formulations. C3 was taken as core tablet for pulsatile release tablet, and it was taken for further studies.

Table 5: Physical properties of powder mixtures of burst release formulations

Formulation code	Angle of repose (°)	Compressibility index (%)	Hausner's ratio
C1	24.38±1.52	8.51±0.71	1.10±0.04
C2	29.20±1.86	9.61±1.19	1.09±0.09
C3	21.64±1.47	12.67±0.58	1.13±0.01
C4	21.80±1.19	15.02±0.81	1.14±0.08
C5	22.84±1.64	15.02±0.81	1.14±0.08
C6	27.35±1.32	14.92±1.12	1.17±0.03

Where *n* =3. Each value is mean±SD

Table 6: Evaluation parameters of burst release tablets

Formulation code	Disintegration time (sec)	Wetting time(sec)	% drug content
C1	78±0.57	98±0.84	98.43±0.54
C2	72±0.52	96±0.97	98.89±0.76
C3	64±0.51	84±0.86	99.52±0.58
C4	73±0.58	98±0.92	98.46±0.56
C5	69±0.62	90±0.94	99.36±0.62
C6	75±0.59	97±0.82	98.14±0.56

Where *n* =3. Each value is mean±SD

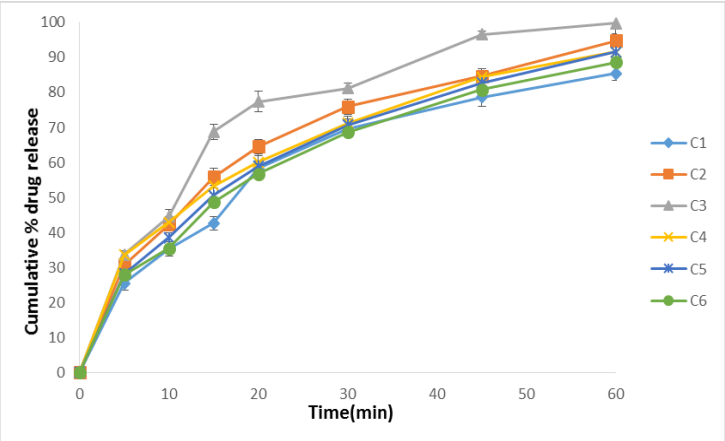


Fig. 1: *In vitro* drug release profile of core tablets. All values are represented as mean±SD (n=6)

Evaluation of batches with individual polymers

Drug release from the formulation was changed as the concentration of gas generating agent; $NaHCO_3$ was changed. The increase in concentration of sodium bicarbonate affects the release pattern; buoyancy lag time and hardness of the formulation. The concentration of gas generating agent, sodium bicarbonate was varied between 15% (56 mg) to 25% (95 mg) and 30 mg citric acid to achieve optimum floating without affecting the release pattern of the drug from formulation and to obtain proper lag period. The optimum gas generating agent concentration was 20% (75 mg) for sodium bicarbonate and 8% (30 mg) citric acid.

During the dissolution kinetics, the coating layer gradually starts to erode up to a limiting thickness of the coat. After this stage, a rupture of the shell was observed under the pressure which has applied by the swelling of the core tablet due to the presence of super disintegrant. This pressure was high due to the high swelling property of crospovidone, resulted in burst effect after 4 h along with complete and rapid drug release.

In formulations, A3 and A6 amount of coating polymer was too less which could not maintain the integrity of tablet for long and time is resulting in complete drug release within a short period of time. Individual polymer batches (A4 and A6) containing HPMC E4M and Polyox WSR N60K in the concentration of 37% and 34% respectively, show burst effect after 3 h after that constant drug release over the period of 6 h.

In batches A5 and A7 the amount of coating polymer was too high to achieve high lag time with minimum drug release. Individual polymer batches (A5 and A7) containing HPMC E4M and Polyox WSR N60K in the concentration of 48% and 45% respectively, show burst effect after 7 h. The drug release clearly depended on the kind and amount of hydrophilic polymers as that which was applied on the core. Hence, combination of these two polymers was used to get optimum floating ability and drug release. A formulation containing HPMC E4M (75 mg) and Polyox WSR N60K (75 mg) in combination showed optimum floating and released pattern. Hence this combination of polymers used for optimization study.

Evaluation parameters of batches with individual polymers showed in table-7. Tablet weight variation varied between 374±1.3 mg to 376±0.9 mg, the hardness of tablet varied between 6.1±0.57 kg/cm^2 to 8.9±0.68 kg/cm^2, drug content; buoyancy and lag time of different formulation was varied between 98.14±0.57% to 99.52±0.74%; 76±0.42 sec to 129±0.63 sec and 3 h to 7 h respectively.

Table 7: Evaluation parameters of batches with individual polymers

Trial batch code	Weight variation (mg) (*n* =10)	Hardness (Kg/cm^2) (*n* =3)	% Drug content (*n* =3)	Buoyancy lag time (sec) (*n* =3)	Lag period (Hr)
A1	375±1.5	6.1±0.57	98.43±0.52	129±0.63	3
A2	374±1.3	7.4±0.58	98.89±0.68	92±0.86	4
A3	375±1.9	8.9±0.68	99.52±0.74	76±0.42	5
A4	376±0.9	7.1±0.63	98.46±0.57	99±0.56	3
A5	375±1.4	7.9±0.57	99.36±1.00	102±0.68	7
A6	375±1.3	7.2±1.00	98.14±0.57	100±0.76	3
A7	374±1.3	7.6±1.01	99.23±0.49	109±0.28	7

Each value is mean±SD

Table 8: Physical properties of powder mixtures of floating-pulsatile release tablets

Formulation code	Angle of repose (°)	Compressibility index (%)	Hausner's ratio
F1	26.36±1.73	11.71±1.56	1.17±0.01
F2	24.38±1.52	10.71±0.84	1.13±0.02
F3	29.20±1.86	11.98±1.58	1.12±0.03
F4	21.64±1.47	8.51±0.71	1.10±0.04
F5	21.80±1.19	9.61±1.19	1.09±0.09
F6	21.80±1.19	12.67±0.58	1.13±0.01
F7	22.84±1.64	15.02±0.81	1.14±0.08
F8	27.35±1.32	14.92±1.12	1.17±0.03
F9	28.64±1.58	16.59±0.97	1.19±0.04

Where n=3, each value is mean±SD

Table 9: Evaluation of floating-pulsatile release tablets (F1–F9)

F. Code	Tablet weight (mg)	% Drug content (*n* =10)	Hardness (kg/cm2)	Swelling index (%)	Buoyancy lag time (sec)	%drug release (*n* =3)
F1	375±2.0	98.45±0.50	5±1.00	122.1±0.94	112±1.3	98.45±1.40
F2	376±2.4	97.27±1.00	7±1.40	127.4±0.67	113±1.7	98.92±1.30
F3	375±2.7	98.17±0.84	6±0.94	129.0±0.89	116±1.4	94.42±0.67
F4	375±1.0	97.96±0.50	8±0.84	140.0±0.57	101±1.0	99.00±0.48
F5	372±1.7	98.62±1.00	7±0.67	156.0±0.94	118±1.4	97.69±0.52
F6	374±1.3	97.39±0.67	7±0.43	167.4±0.74	113±1.7	92.00±1.40
F7	373±2.4	97.19±0.45	8±0.45	189.8±0.86	115±1.3	98.46±1.00
F8	375±1.5	98.82±0.84	7±0.54	190.4±0.57	112±1.0	91.00±0.68
F9	374±1.4	96.98±1.00	9±0.57	206.1±0.43	120±0.8	90.00±0.57

Each value is mean±SD

Evaluation of formulations with combination of polymers

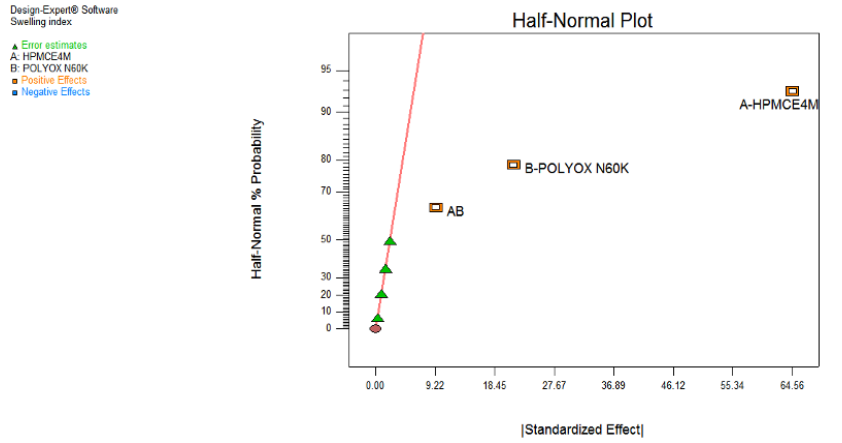
Most of the formulation blends showing good flow properties (table 8). Physical parameters of different floating pulsatile release formulations were evaluated and depicted in table 9. Tablet weight variation varied between 372±1.7 mg to 376±2.4 mg, the hardness of tablet varied between 5.0±1.00 kg/cm^2 to 9.0±0.57 kg/cm^2, drug content; buoyancy and swelling index of the different formulation were varied between 96.98±1.00% to 98.82±0.84%; 101±1.0 sec to 120±0.8 sec and 122.1±0.94% to 206.1±0.43% respectively.

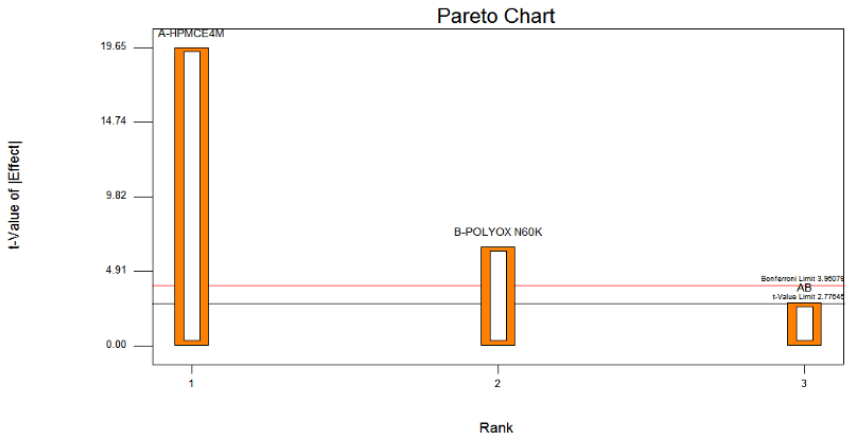
Swelling index

The swelling index plays an important role in determining the retention ability of the tablets in the stomach. In formulations, F1–F9 swelling index was in the range of 122.1±0.94% to 206.1±0.43%. In these formulations, maximum swelling index (206.1±0.43%) has been shown by F9 whereas minimum swelling index (122.1±0.94%) by F1. The effect of the variables on the swelling index and buoyancy in formulations F1–F9 are shown in below fig. 2 and fig. 3 respectively:

Swelling index =+157.12+32.28A+10.68B+5.73AB---------- (2)

All the polynomial equations were found to be statistically significant (P<0.01), as determined using ANOVA, as per the provision of Design Expert software. The combined effect of concentration of HPMC E4M and Polyox WSR N60K on swelling index was shown in Pareto chart and contour plots. From response surface plot and contour plot, it was observed that there is a positive impact of polymers on selling index. From the Pareto chat it can be concluded that selling index majorly governed by HPMCE4M compared to Polyox WSR N60K. As there is an increase in the concentration of HPMC E4M and Polyox WSR N60K up to intermediate concentration (level 0) there is increase in swelling index [24].





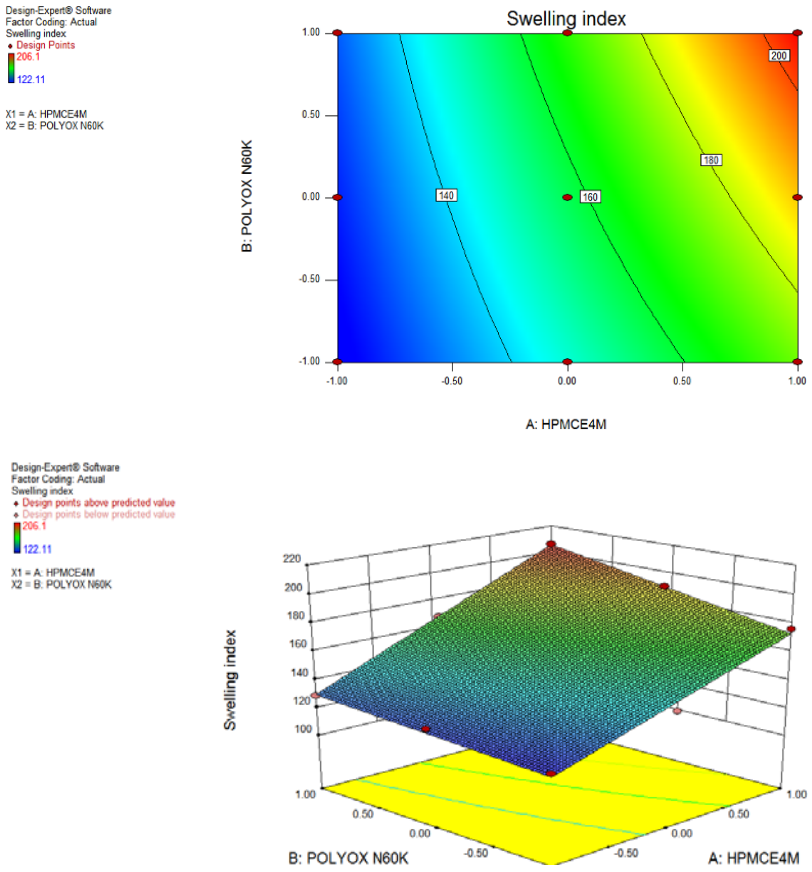
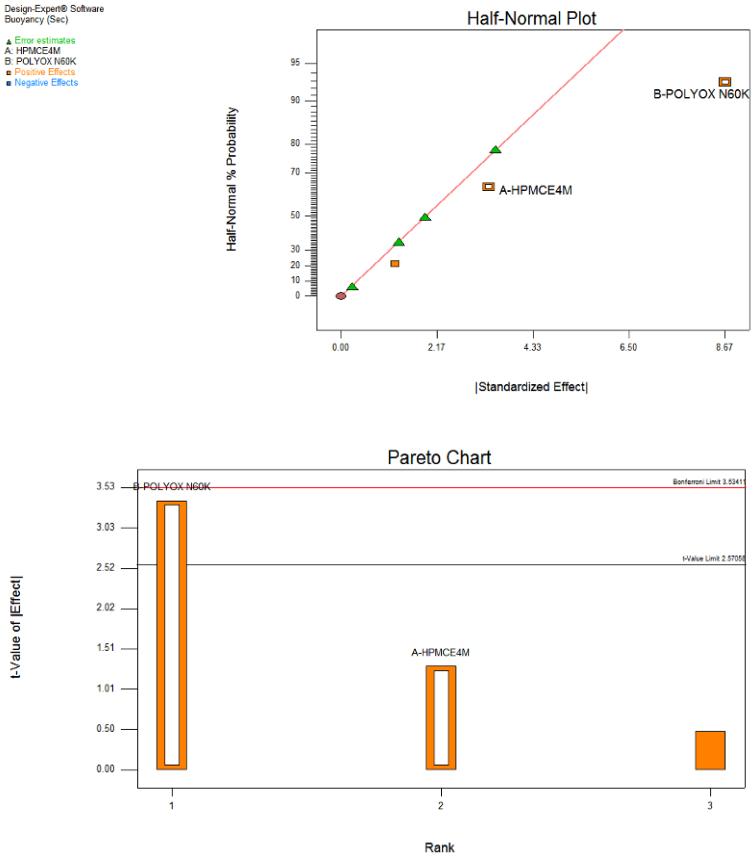


Fig. 2: (a) Half-normal plot showing the influence on swelling Index, (b) Pareto chart, (c) Response surface plot, and (d) Contour plot



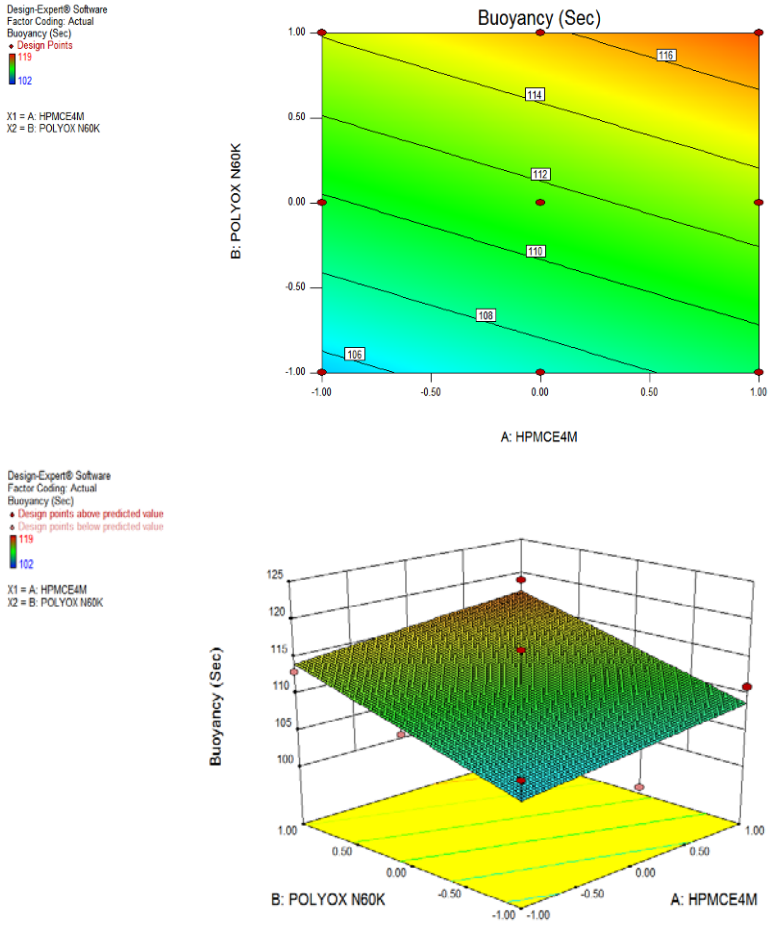


Fig. 3: (a) Half-normal plot showing the influence on buoyancy, (b) Pareto chart, (c) Response surface plot, and (d) Contour plot

Lag period

Lag period plays an important role in determining no or less amount drug releases of the tablets at a specific period. Nocturnal acid breakthrough typically appears in the second 6-hour period (2 to 4 am), after the evening dose of a PPI when patients are sleeping. The half-life of Famotidine is 2.5 to 3.5 hr. However for such cases, conventional drug delivery systems are inappropriate for the delivery of Famotidine, as they cannot be administered just before the symptoms are worsened, because during this time the patients are asleep. To follow this principle, it was necessary to design the dosage form so that it can be given at the bed time giving drug release in the morning. Using current release technology, it was possible to get the rapid and transient release of a certain amount of drugs within a short time period immediately after a predetermined off-release period, that is, lag time. Famotidine, which has a local activity for acidity in the stomach and better bioavailability showing, as compared with lower parts of GIT. Overall, these considerations led to the development of oral pulsatile release dosage forms possessing gastric retention capabilities. In designing floating-pulsatile system for Famotidine with a four-to-five-hour delay in a release after oral administration was considered as ideal. The dose administered at bedtime will give drug release in the early morning hours when the patient is most at risk.

In the formulations from F1 to F9 lag period was in the range of 2–8±0.2 h. In this set of formulation, optimum lag period (4.2±0.2) and drug release was observed in the formulation F4. Both polymers (HPMC E4M and Polyox WSR N60K) have shown a significant effect on lag period. As polymer concentration increase (level 1 to level 1) lag period was also get increased. The effect of the variables on the lag period in formulations F1–F9 are shown in Fig.4:

$$\text{Lag Period} = +5.11 + 2.50A + 0.67B - 0.17AB \quad \text{---------- (3)}$$

All the polynomial equations were found to be statistically significant ($P<0.01$), as determined using ANOVA, as per the provision of Design Expert software.

The combined effect of concentration of HPMC E4M and Polyox WSR N60K on lag period is shown in Fig.4. From response surface plot and contour plot in fig. 4, it was observed that both polymers have a significant effect on lag period. As concentration of HPMC E4M and Polyox WSRN60K increases (level+1, level+1) lag period is increased (>5 h) and uniformed[24]. At the maximum level of polymers, lag period was increased but did inhibit drug release.

***In vitro* drug release**

From the fig. 5 and fig. 6, it was observed that 65 mg HPMC E4M (level 0) and 75 mg Polyox WSR N60K (level-1) in F4 batch have shown lag time of 4.20 h, followed by sigmoidal release pattern giving 100% drug release at 6th hour. As the concentration of the Polyox changes from F1 to F9 the lag time and drug release also changes at the 6th hour.

$$\text{Cumulative \% Drug Release} = +85.73 - 16.07A - 5.85B - 3.81AB \quad \text{---------- (4)}$$

where A and B represent the variables used in the formulations. All the polynomial equations were found to be statistically significant ($P<0.01$), as determined using ANOVA, as per the provision of Design Expert software. The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The combined effect of concentration of HPMC E4M and Polyox WSR N60K on drug release was shown in fig. 5 and 6. As concentration of HPMC E4M and Polyox WSR N60K decreases (level 1, level −1) drug release is higher (>90%) and uniform [24, 25].

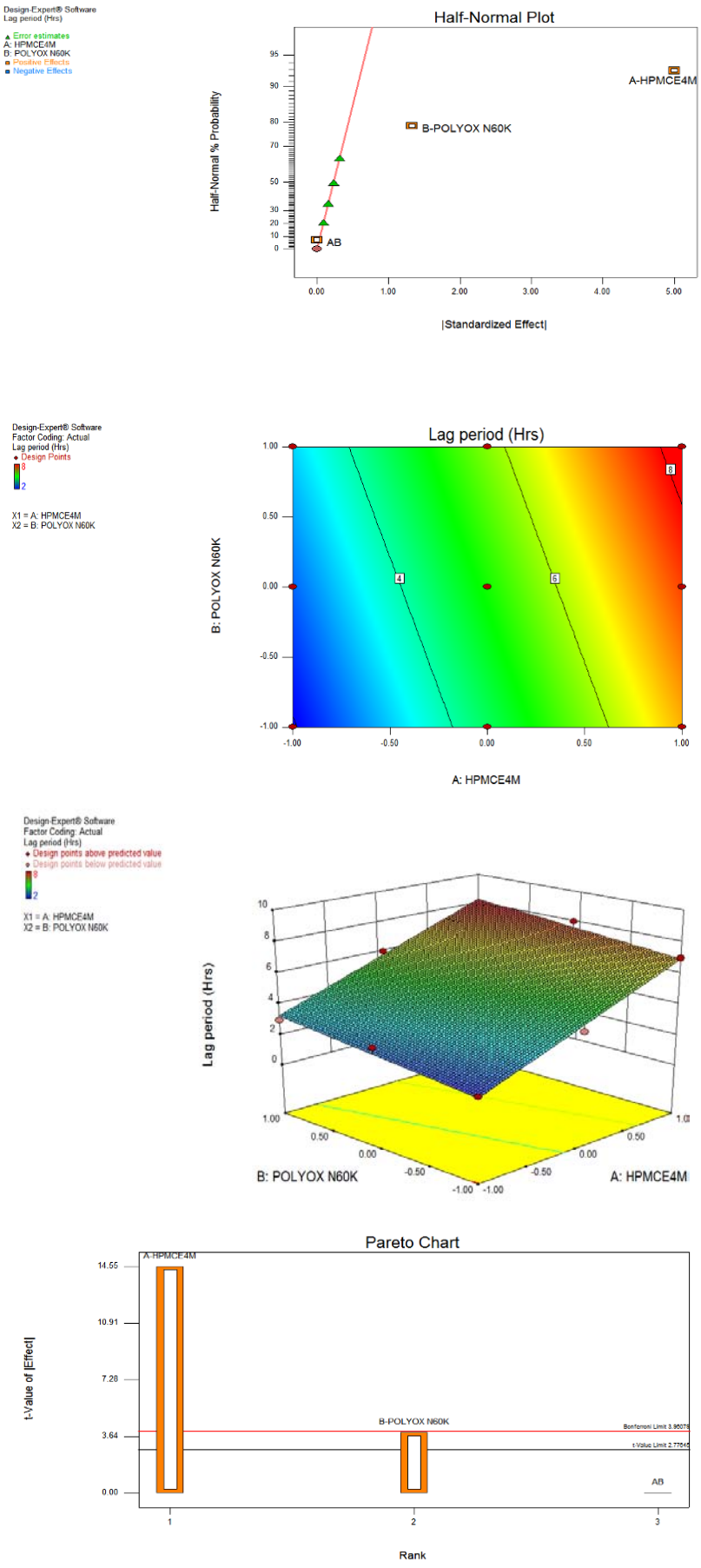


Fig. 4: (a) Half-normal plot showing the influence on lag period, (b) Pareto chart, (c) Response surface plot, and (d) contour plot

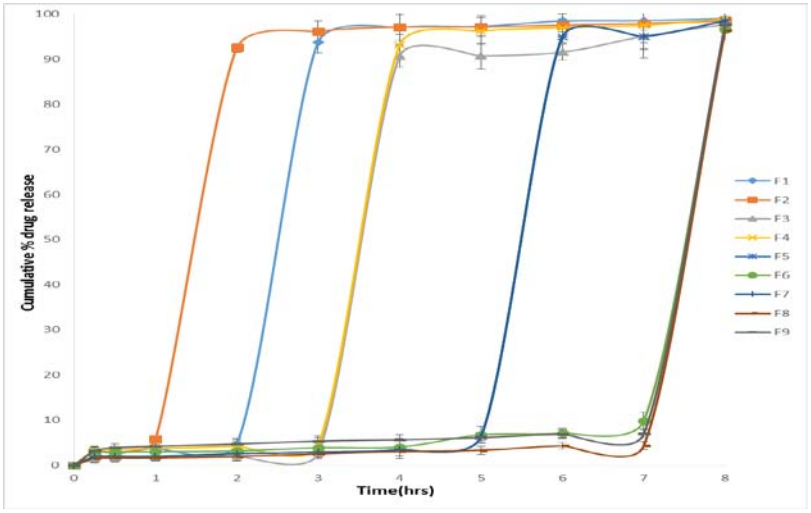
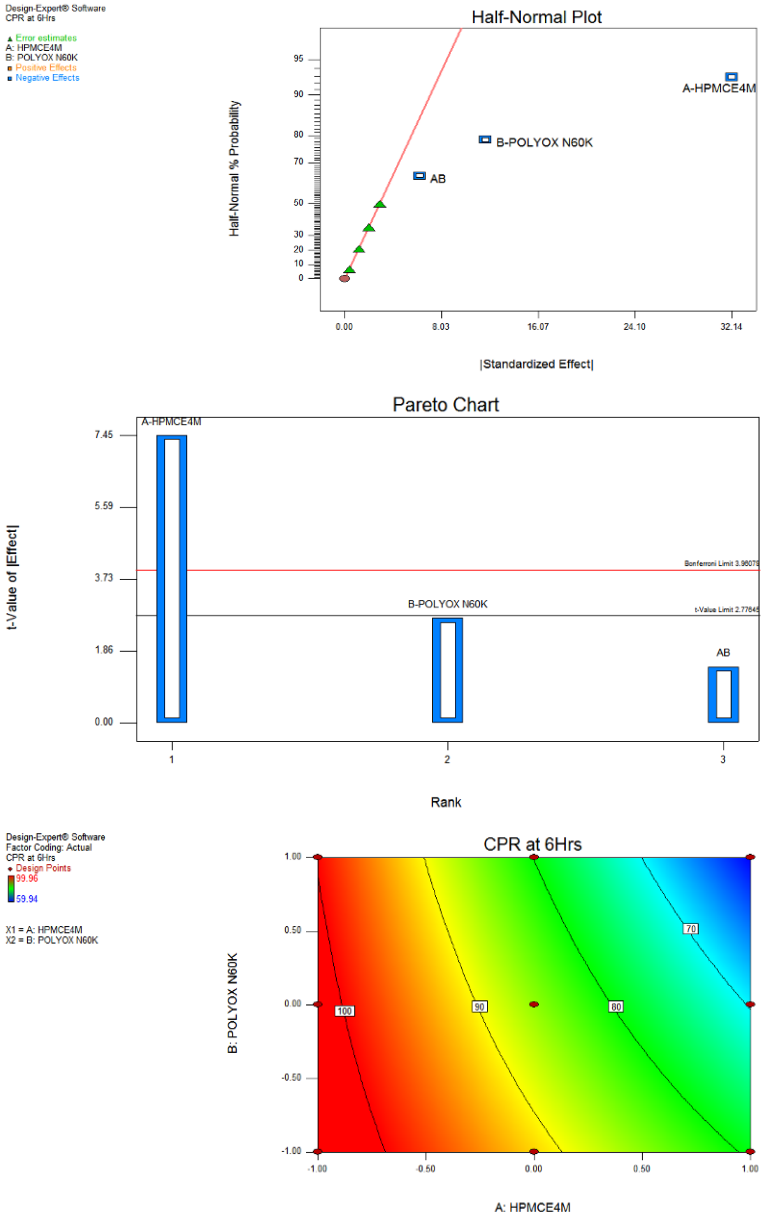


Fig. 5: ***In vitro*** **drug release profiles of floating pulsatile release tablets of batches F1–F9. All values are represented as mean±SD (n=6)**



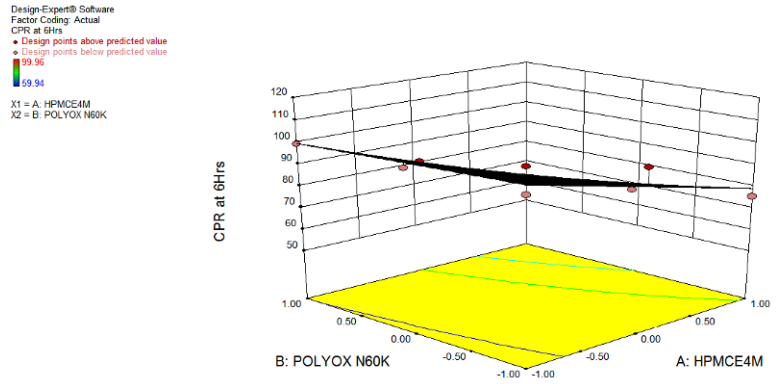
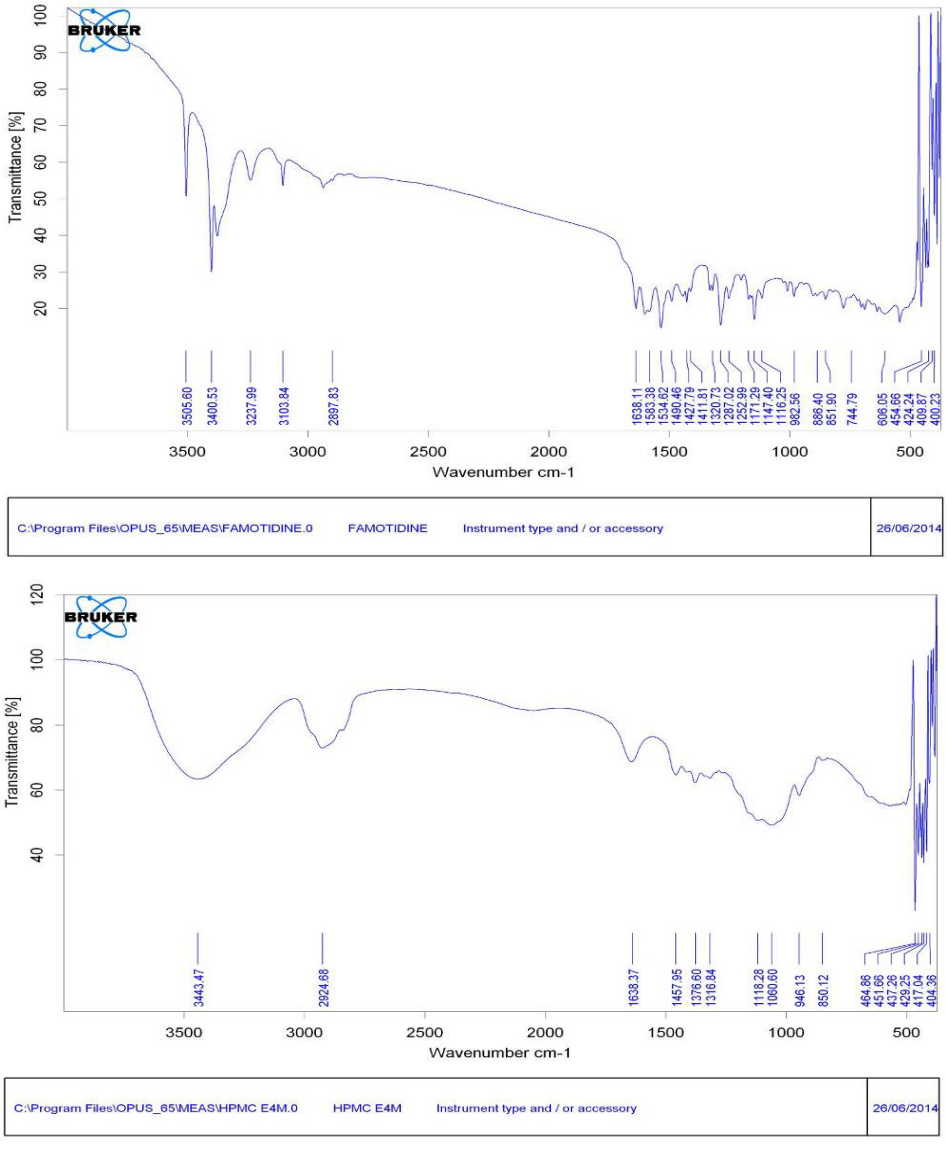


Fig. 6: (a) Half-normal Plot showing the influence on cumulative % drug released at 6 h, (b) Pareto chart, (c) Response surface plot, and (d) contour plot

FTIR study

There was no interaction between the drug and polymers as showed in IR Graphs (fig. 7). IR spectrum of famotidine is characterized by the absorption of N-H group at 3400 cm^{-1}. HPMC E4M has shown a major peak at 3443 and 2924. cm^{-1}. Major peaks of the polymer are retained in spectra showing no chemical interaction between drug and polymer. In formulation due to cross-linking of polymers, few bands disappeared and merged.

Whereas optimised formulation spectra shown 3401 cm^{-1} peaks indicating of pure drug and no change in the structure of the drug.



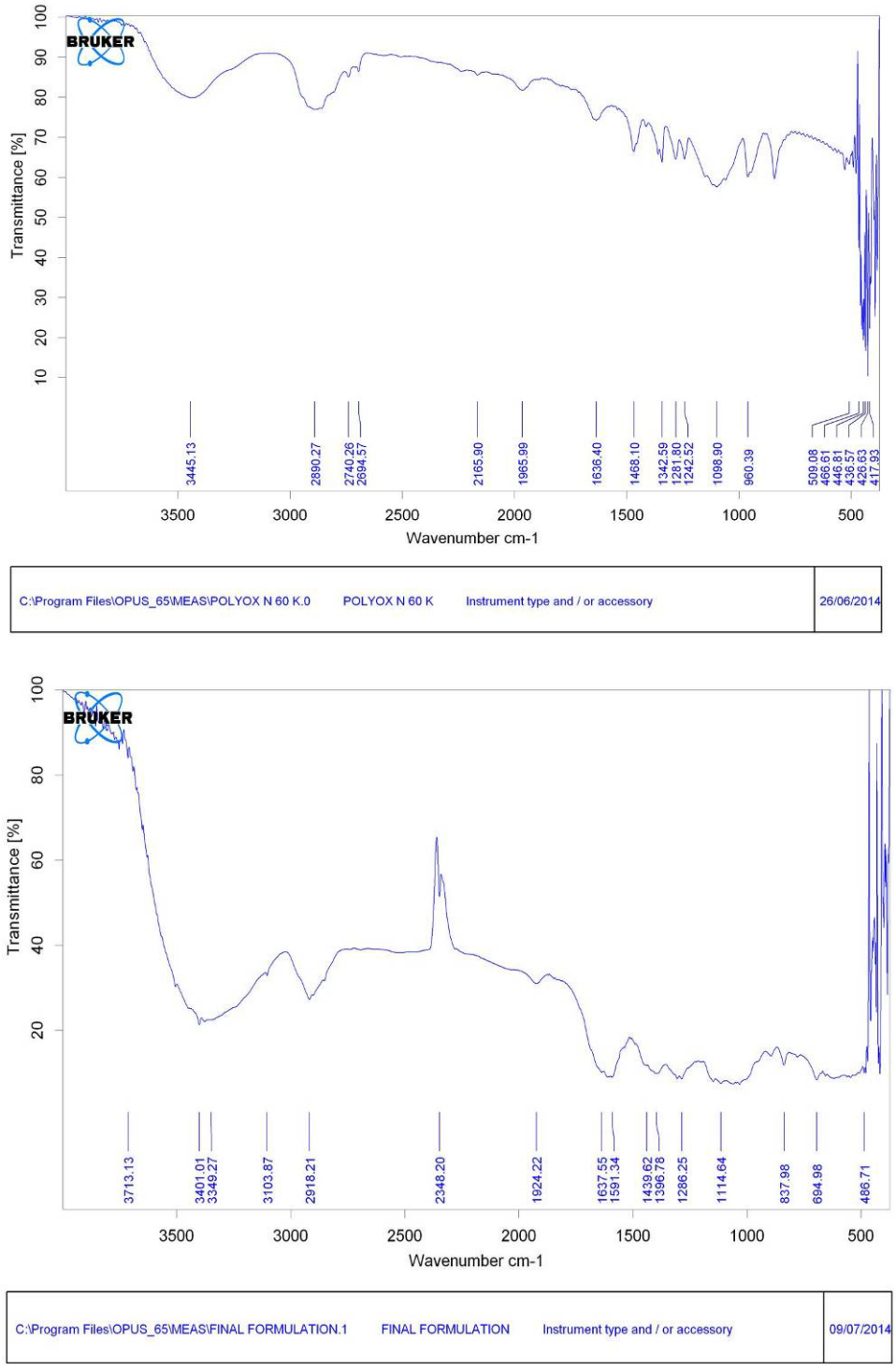


Fig. 7: FTIR graphs of famotidine, HPMC E4M, POLYOX N60K and optimised formulation Stability testing of the best formulation

Optimised Formulation F4 was selected for the stability studies out of the total formulation batches. For condition 25 °C (±2 °C) and 60% RH (±5%) and 40 °C (±2 °C) and 75% RH (±5%) was observed floating time (7.0–7.4±0.8 h) and assay (>97.35%) from initial to 3 mo. From stability data, it can be concluded that there were no changes in any parameter tested in the formulation.

CONCLUSION

Floating pulsatile drug delivery system of famotidine was successfully developed using full factorial statistical design. The present research work demonstrates that famotidine could be successfully delivered to provide night-time relief of gastric acidity by formulating floating pulsatile drug delivery system. The dosage form needs to be taken after meal; where immediate release dose will provide relief from acid secretion in response to the meal, while programmed pulsatile release floating tablet with delayed "burst" release will reduce midnight acidity. This will provide an ideal therapeutic regimen with enhanced patient compliance.

Concerning statistical analysis, it was shown that appropriate factorial design and optimization technique can be successfully used in the development of time-lagged press coating of formulations based on different levels of polymers to achieve the desired pulsed

release profile after a programmed lag time. Response surface methodology is an important tool for understanding the change of responses and locating the area of interest. The press-coated formulation containing HPMCE4M and Polyox WSR N60K at 0,-1 level was in the optimum zone and has the potential for time-controlled pulsatile delivery of Famotidine. The optimized formulation exhibited release profiles which were close to the predicted responses.

Thus, the designed device can be considered as one of the promising formulation technique for preparing floating pulsatile drug delivery systems and hence in the chronotherapeutic management of nocturnal acid breakthrough by opening a "new therapeutic dimension" to an existing drug molecule.

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CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Duncan WC Jr. Circadian rhythms and the pharmacology of affective illness. Pharmacol Ther 1996;71 Suppl 3:253-312.
2. Lemmer B. Chronopharmacology: time, a key in drug treatment. Ann Biol Clin 1994;52 Suppl 1:1-7.
3. Ravi V, Reddy Y, Nageswara A, Dhachinamoorthi D, Chandra K. An art of dosage form designing. Chronotherapeutics 2010;3:1690–6.
4. Shargel L, Wu-Pong S, Yu A. Applied biopharmaceutics, and pharmacokinetics. 5th edition. McGraw-Hill, New York, NY, USA; 2005.
5. Smolensky MH, Labrecque G. Chronotherapeutics. Pharm News 1997;4:10–6.
6. Smolensky MH, D'Alonzo GE. Medical chronobiology: concepts and applications. Am Rev Respir Dis 1993;147:S2-19.
7. LV Allen, NG Popovich, HC Ansel. Ansel's pharmaceutical dosage forms and drug delivery systems. 9th edition. Lippincott Williams and Wilkins, Philadelphia, Pa, USA; 2010.
8. Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. Adv Drug Delivery Rev 2007;59:828-51.
9. Reinberg AE. Concepts of circadian Chrono pharmacology. Ann N Y Acad Sci 1991;618:102-15.
10. Ohdo S. Chronopharmaceutics: pharmaceutics focused on biological rhythm. Biol Pharm Bull 2010;33 Suppl 2:159-67.
11. Labrecque G, Bélanger PM. Biological rhythms in the absorption, distribution, metabolism and excretion of drugs. Pharmacol Ther 1991;52 Suppl 1:95-107.
12. Dimitrov M, Lambov N. Study of verapamil hydrochloride release from compressed hydrophilic Polyox-Wsr tablets. Int J Pharm 1999;189 Suppl 1:105–11.
13. Lin SY, Kawashima Y. Current status and approaches to developing press-coated chronodelivery drug systems. J Controlled Release 2012;157 Suppl 3:331–53.
14. Dinakar P, Varalakshmi C, Reddy P, Mohanlakshmi S. Formulation and evaluation of Bisoprolol fumarate transdermal patches. J Pharm Res 2010;3:1955–7.
15. Niwa K, Takaya T, Morimoto T, Takada K. Preparation and evaluation of a time-controlled release capsule made of ethylcellulose for colon delivery of drugs. J Drug Targeting 1995;3 Suppl 2:83-9.
16. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int J Pharm 2004;277:141-53.
17. Jagdale SC, Bari NA, Kuchekar BS, Chabukswar AR. Optimization studies on compression coated floating-pulsatile drug delivery of bisoprolol. Biomed Res Int 2013. Doi.org/10.1155/2013/801769.
18. Gazzaniga A, Busetti C, Moro L, Crimella T, Sangalli ME, Giordano F. Evaluation of viscosity HPMC as a retarding coating material in the preparation of a time-based oral colon specific delivery system. Proc Int Symp Controlled Release Bioact Mater 1995;22:242–3.
19. Shailesh P, Laxmanbhai P, Chhaganbhai P. Floating matrix tablets of domperidone: formulation and optimization using simplex lattice design. Iran J Pharm Res 2011;10 Suppl 3:447–55.
20. Saigal N, Baboota S, Ahuja A, Ali J. Site-specific Chronotherapeutic drug delivery systems: a patent review. Recent Pat Drug Delivery Formulation 2009;3 Suppl 1:64-70.
21. Jin SJ, Yoo YH, Kim MS, Kim JS, Park JS, Hwang SJ. Paroxetine hydrochloride controlled release POLYOX matrix tablets: screening of formulation variables using plackett-burman screening design. Arch Pharm Res 2008;31:399–405.
22. Lemmer B. The clinical relevance of Chrono pharmacology in therapeutics. Pharmacol Res 1996;33:107–15.
23. Lin SY, Kawashima Y. Current status and approaches to developing press-coated chronodelivery drug systems. J Controlled Release 2012;157:331-53.
24. Roy P, Shahiwala A. Statistical optimization of ranitidine HCl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. Eur J Pharm Sci 2009;37:363-9.
25. Kshirsagar SJ, Patil SV, Bhalekar MR. Statistical optimization of floating pulsatile drug delivery system for chronotherapy of hypertension. Int J Pharm Investig 2011;1 Suppl 4:207-13.