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International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Formulation and Evaluation of Gastro-retentive Drug Delivery System of Novel Famotidine Phospholipid Complex

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ARTICLE INFO

Article history:

Received: 08 October, 2022

Revised: 24 April, 2023

Accepted: 05 May, 2023

Published: 30 May, 2023

Keywords:

Gastro-retentive drug delivery, Famotidine phospholipid complex, Floating tablet, *In-vitro* buoyancy study, *In-vitro* dissolution, Kinetic modeling.

DOI:

10.25004/IJPSDR.2023.150304

ABSTRACT

Famotidine is an H_2 receptor antagonist belonging to the BCS Class II, characterized by low solubility and limited oral bioavailability. The current study encompasses the formulation of novel famotidine phospholipid complex (FHC) with the aid of design of experiments (Central Composite Design) using solvent evaporation technique to overcome the disadvantages of Famotidine. To further enhance the physicochemical properties of FHC, it was incorporated into gastro-retentive floating tablets (GRDDS) using direct compression technique with sodium bicarbonate as a gas generating agent and its properties were compared to famotidine floating tablets. The pre-compression parameters, namely bulk density, tapped density, Hausner's ratio, Carr's compressibility index and angle of repose were evaluated. The flow properties of FHC granules were found to be better than the plain famotidine granules. The post-compression parameters, namely thickness, hardness, friability, weight variation, drug content and swelling index showed better results for FHC as compared to famotidine floating tablets. *In-vitro* buoyancy study indicated that the floating lag time for FHC tablets (110 ± 0.021 seconds) was higher than famotidine tablets (36 ± 0.033 seconds) owing to the higher molecular weight of phosphatidylcholine. But the total floating time for FHC tablets was found to be more than 18 hours and for famotidine tablets it was ~12 hours, indicating the improved residence time and buoyancy. The *in-vitro* dissolution study depicted that the cumulative release for FHC tablets (99.84 ± 0.058%) was enhanced 1.07 fold than Famotidine tablets (92.73 ± 0.028%) and 1.6 fold than marketed tablet, Famocid (62.24 ± 0.023%). When kinetic modeling was performed, famotidine tablet followed zero order kinetics, whereas FHC tablet followed Higuchi model indicating a modified and sustained release pattern. The statistical analysis for %cumulative release performed using ANOVA and Dunnett's test showed the *p-value* to be below 0.05 (0.0043) indicating that the analysis model was significant. An accelerated stability study was performed for a period of 6 months at 25 ± 2°C; 60 ± 5% RH. FHC tablets showed a better stability profile than famotidine tablets. In conclusion, FHC gastro-retentive floating tablets showed improved flow properties, post compression properties, better drug content, improved *in-vitro* buoyancy and enhanced cumulative release and stability profile.

INTRODUCTION

Famotidine belongs to the biopharmaceutical class II drug category and is a competitive H_2 receptor antagonist. It acts by inhibiting gastrointestinal acid production by competing with histamine for binding with the receptors located at the basolateral membrane of the parietal cells. Peptic ulcers are caused when there is breakage of the gastrointestinal mucosa due to the secreted acid and pepsin.[1] Famotidine inhibits this aggression shown by the acid in the gastrointestinal tract to prevent a variety of ulcers. But famotidine has the disadvantage of low solubility, poor oral bioavailability (40–45%), and a short half-life of 2.5 to 4 hours in the blood plasma.[2,3] When Famotidine is administered by oral route, it is absorbed incompletely and shows a minimal first pass metabolism.[4,5] It is also insoluble and unstable at alkaline pH values. Famotidine was converted into a lipid-based novel drug delivery system called phospholipid complex and

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

optimized using Central composite design[6,7] to overcome these disadvantages. A phospholipid complex is a lipid-compatible structure formed between the polar moieties of the drug and the phospholipid. As famotidine possessed four polar amino groups, it was structurally able to bind with the polar part of PHOSPHOLIPON 90H to successfully form the phospholipid complex.[8] To further enhance the properties and stability of famotidine, its phospholipid complex was incorporated into a gastro-retentive drug delivery system (GRDDS) in the dosage form of floating tablet.[9]

A GRDDS comprises dosage forms that can remain in the gastric area for a longer period of time and enhance the residence time of drugs. This results in the improvement of the solubility and bioavailability of the drugs with low solubility in higher pH regions by prolonging their gastric retention.[10,11] The gastric retention of dosage forms can be controlled by different approaches such as sedimentation, muco-adhesion techniques, floating systems, modified shape or by incorporating pharmacological agents that are responsible for delaying gastric emptying.[13,14] GRDDS in the form of floating tablets have proven as a potential dosage form for controlled release of drugs. A floating tablet is a dynamically controlled system that possesses adequate buoyancy to remain above the gastric contents without affecting gastric emptying for a long time.[15,16] Famotidine has been reported to have a limited oral bioavailability and short half-life, so it favoured the development of a sustained release dosage form as a floating tablet.

The aim of the present research study was to overcome the limitations of famotidine by first converting it into a phospholipid complex with phosphatidylcholine (PHOSPHOLIPON 90H) and then incorporating it into a gastro-retentive floating tablet to enhance the compression parameters cumulative release and stability. The floating tablet of plain famotidine was also prepared for comparative study.

The objectives of the present study were formulation and optimization of famotidine phospholipid complex by central composite design using solvent evaporation technique; subsequent incorporation of the complex into floating tablets (GRDDS), comparison of pre-compression and post-compression properties of floating tablets of famotidine phospholipid complex with plain famotidine floating tablets, comparative *in-vitro* dissolution along with kinetic modeling and stability study.

MATERIALS AND METHODS

Materials

Famotidine was obtained as a gratis sample from Dr. Reddy's Laboratories, Hyderabad and ZIM Laboratories, Nagpur (India). PHOSPHOLIPON 90H (Phosphatidylcholine) was obtained as a gratis sample from LIPOID, Germany. All other chemicals and reagents which were utilized were of the analytical grade.

Methods

Formulation of Famotidine Phospholipid Complex (FHC) using Solvent Evaporation

Famotidine (33.75 mg) and PHOSPHOLIPON 90H (79.01 mg) were accurately weighed in a stoichiometric ratio (1:1/1:2/1:3) by taking one-tenth of the molecular weights as per the batches generated by design of experiments. They were dissolved in a solvent system comprising 20 mL of dichloromethane and 10 mL of ethanol. This solution was subjected to reflux under a cold-water condenser on a magnetic stirrer for a specified amount of reaction time (1, 2, 3 hours) at a specific process temperature (40, 50, 60°C). After this the solution was heated to evaporate the solvent system until approximately 2 to 3 mL of it remained. Then the antisolvent n-hexane was added to the solution to precipitate the phospholipid complex and scrapped out. The complex obtained was dried at room temperature to remove all the solvent and stored in air tight containers in a desiccator.[17,18]

Optimization using Design of Experiments (Central Composite Design)

Optimization of FHC was done using central composite design and its statistical analysis and validation was performed by Design Expert® (Version 11.1.2.0, Stat-Ease Inc., Minneapolis, MN) on the basis of one way analysis of variance and polynomial equation to find the optimized set of process parameters. A 3-factor, 3-level design was applied to determine the interaction between the dependent and independent variables and to obtain the quadratic terms to construct a polynomial equation. Independent variables selected were PHOSPHOLIPON 90H-Famotidine ratio (X_1), reaction time (X_2) and process temperature (X_3) for dependant variable of complexation rate (Y_1). Central composite design showed 20 total batches out of which 6 were identical and hence the best batch amongst them was selected with highest complexation rate and the final model comprised of 15 batches. The model was evaluated in terms of significant coefficients i.e. F value and *p-value* ($p<0.05$ being statistically significant). The relationship between independent and dependant variables was studied using 3D surface response curve and contour plot. The relationship between the experimental values of the responses and the error was depicted by normal plot of residuals.[19,20]

- *Evaluation of complexation rate*

FHC was weighed equivalent to 10 mg of famotidine and dispersed in 5 mL of chloroform. It was allowed to mix on a magnetic stirrer for 30 minutes. PHOSPHOLIPON 90H and FHC were soluble in chloroform but free famotidine remained practically insoluble in it. This non-complexed

famotidine was separated by filtering the solution using a Whatman filter paper (110 mm) and extracted using methanol as a solvent. The volume of the solution was made up to 10 mL and analysed using a UV spectrophotometer at wavelength of 209 nm. The free drug was calculated using standard calibration curve equation of famotidine. This was performed for all the 15 batches of the complex. The complexation rate was calculated using the following formula.[20]

$$\text{Complexation rate (\%)} = (m_2 / m_1) \times 100 = [(m_1 - m_3)/m_1] \times 100$$

Where m_1 is the total weight of Famotidine added, m_2 is the content of Famotidine present as a complex and m_3 is the non-complexed Famotidine.

Formulation of GRDDS of FHC

- *Direct Compression Technique*

As phosphatidylcholine possessed the disadvantages of limited flowability, potential stickiness and low apparent density, a direct compression method was the most suitable for incorporating the phospholipid complex into tablets.[21] Sodium bicarbonate was used as the gas generating agent.

In a mortar, accurately weighed Famotidine (10.6 mg)/ FHC (80 mg) was taken. To it HPMC K4M, citric acid, sodium bicarbonate, Carbopol 934P and lactose were added according to the formula given in Table 1. All the ingredients were mixed using a pestle. The mixture was passed through sieve #60. Then talc and magnesium stearate were added and the granules were mixed in geometric progression and evaluated for its flow properties. The granules were then directly punched into tablets using a ten stationed pilot press tablet machine (CPM, Pvt. Ltd.) and the post compression parameters were evaluated.[15,22-23]

Evaluation of Pre-compression Parameters of FHC and Famotidine Granules

- *Bulk Density*

An accurately weighed 20 g granules of FHC and Famotidine were lightly shaken to break any agglomerates formed and were introduced in to a 100 mL measuring cylinder. The volume occupied by the respective granules was measured as the bulk volume.[24] The bulk density of was determined using the following formula-

Bulk density = Total weight of granules/Bulk volume

- *Tapped Density*

An accurately weighed 20 g granules of FHC and Famotidine were lightly shaken to break any agglomerates formed and were introduced in to a 100 mL measuring cylinder. The measuring cylinder was tapped (100 times) on a uniform surface until no further change in volume was noted and was measured as the tapped volume.[24] The tapped density was determined using the following formula-

Tapped density = Total weight of granules/Tapped volume

Table 1: Formula for FHC and famotidine floating tablets

Name of the ingredient	*Quantity (mg)*
Famotidine/ equivalent fhc	10.6/80
Hpmc K4M	100
Citric acid	32
Sodium bicarbonate	200
Carbopol 934 p	40
Lactose	177.4/108
Magnesium stearate	20
Talc	20
Total weight of one tablet	600

- *Angle of Repose*

The angle of repose of FHC and famotidine granules was determined by the funnel method. Accurately weighed 10 g of granules were gradually introduced into the funnel. The height of the funnel was kept constant at 1.5 cm from the surface of the platform and adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow from the funnel on the surface.[24] The diameter and height of the heap formed were measured (Fig. 1). The angle of repose was calculated using the following formula-

$$\text{Tan } \theta = h/r$$

where, θ is the angle of repose, h is the height of the heap and r is the radius of the heap of granules

- *Hausner's Ratio*

It is measured as the frictional resistance of the drug. It was determined by the following formula.[25]

Hausner's ratio = Tapped Density / Bulk Density

- *Carr's Index*

The Carr's index was the indication of the compressibility of the granules and was calculated from bulk density and

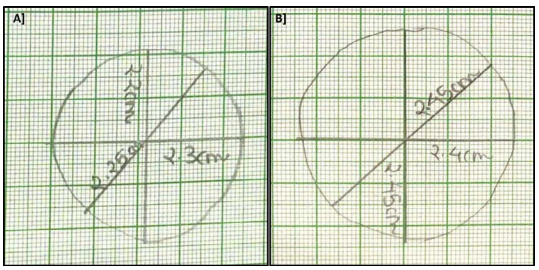

Fig. 1: Measurement of radius for the heap of A] Famotidine granules and B] FHC granules

tapped density of the granules by using the following formula [25].

Carr's index (%) = [(Tapped density–Bulk density) / Tapped density] X 100

Evaluation of Post-compression parameters of FHC and Famotidine floating tablets

- *Shape of tablet*

Directly compressed tablets were examined under the magnified lens to study and evaluate the shape of the tablets.

- *Thickness*

Ten tablets from the punched tablets were randomly selected and individual tablet thickness was measured by using a Vernier caliper.

- *Hardness*

Tablet hardness was measured using Pfizer hardness tester. From respective FHC and Famotidine floating tablets, six tablets were measured for the hardness and average of six values was noted along with standard deviation.[26]

- *Friability testing*

From respective FHC and Famotidine floating tablets, ten tablets were accurately weighed and placed in the friability test apparatus (Roche Friabilator). The apparatus was operated at 25 rpm for 4 minutes and tablets were observed while undergoing rotations. The tablets were then taken out after 100 rotations, dusted and reweighed.[26] The friability was calculated as the percentage weight loss using the following formula.

$$\%\text{Friability} = [(W_1 - W_2) / W_1] \times 100$$

Where W_1 = Initial weight of the Tablets, W_2 = Final weight of the Tablets after testing

- *Weight variation*

To study the weight variation of tablets, individual weights of 20 tablets from each formulation were noted using electronic balance (Shimadzu). The average weight of the 20 tablets was calculated and percent weight variation was detected.[27] The values were compared with the standard values (Table 2) as given in the Pharmacopoeia.

Table 2: Standard weight variation values as per I.P and U.S.P

Sr. no.	*Average weight of Tablet as per I.P (mg)*	*Average weight of Tablet as per U.S.P (mg)*	*Maximum percent difference allowed (%)*
1	84 mg or less	130 mg or less	10
2	84–250 mg	130–324 mg	7.5
3	>250 mg	>324 mg	5

- *Drug content*

Ten tablets were randomly weighed, crushed and finely powdered in a mortar using a pestle. 100 mg of the powdered sample was taken in a beaker containing 100 mL of 1.2 pH buffer. The contents of the beaker were sonicated for 30 minutes to extract and dissolve out the drug from excipient particles. The solution was centrifuged at 3000 rpm for 10 minutes and the supernatant was analysed after suitable dilution at 265 nm using UV spectrophotometer. The mean percent drug content was calculated as an average of three determinations.[27]

- *In vitro buoyancy study*

The *in vitro* buoyancy study for FHC and Famotidine floating tablets included.

- *Floating lag time (FLT):* Tablet (n=3) was placed in a dissolution flask with 100 mL of 1.2 pH buffer solution maintained at 37 ± 1°C. Then the time in minutes taken by tablet to rise from the bottom to top of the flask was measured as the floating lag time. This was performed in triplicate for both the tablet formulations.[28,29]
- *Total Floating Time (TFT):* Tablet (n=3) was placed in a dissolution flask containing 100 mL of 1.2 pH buffer solution maintained at 37 ± 1°C. The total duration of time required by the tablet to constantly float over the surface of the medium was determined as the total floating time. This was also performed in triplicate for both the tablet formulations.[30]

- *Swelling index of the tablets*

The swelling index of tablets was measured in 1.2 pH buffer solution. The initial weight of FHC and Famotidine tablets (n=3) was taken. Then they were immersed in 900 mL of 1.2 pH buffer solution and after 24 hours they were weighed again.[31] The swelling index was calculated as follows.

$$\text{Swelling Index} = [(W_f - W_0) / W_0] \text{ X } 100$$

where, W_f is the final weight of tablet and W_0 is the initial weight of tablet

In-vitro Dissolution Study

- *Preparation of 1.2 pH buffer solution*

For this, 250.0 mL of 0.2M potassium chloride was placed in a 1000 mL volumetric flask and 425.0 mL of 0.2M hydrochloric acid was added to it. The remaining volume was made up using distilled water. The pH of the solution was checked using a pH meter (μ pH system 362, Systronics) and adjusted using 1M HCl/NaOH.[32]

- *Calibration of Famotidine in 1.2 pH buffer solution*

A standard stock solution was prepared by dissolving accurately weighed 25 mg of pure Famotidine in 25 mL of 1.2 pH buffer solution to obtain a solution of 1000 ppm.

From the stock solution, 10 ppm solution was prepared using a micropipette and scanned using UV spectrophotometer in the range of 200 to 400 nm to obtain a spectrum and λ_{max} value.[33]

- *Preparation of working solutions*

From the standard stock solution (1000 ppm), solutions of different concentrations (2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30 ppm) were prepared and scanned at the λ_{max} to obtain the calibration curve and regression equation by plotting concentration vs absorbance for each solvent.[33]

- *Procedure*

The *in-vitro* dissolution was performed for FHC floating tablets, famotidine floating tablets and marketed tablets (Famocid) using USP Type II (Paddle type) dissolution apparatus (LABINDIA, DS 8000). The medium used was 900 mL of 1.2 pH buffer at 37 ± 0.5°C at a speed of 100 rpm. Samples (n=6) of 10 mL were withdrawn from each dissolution vessel and 10 mL of fresh buffer maintained at 37 ± 0.5°C was added to each vessel to maintain the sink condition. The samples withdrawn were diluted ten times as required, filtered using Whatman filter paper and analysed at 265 nm using UV spectrophotometer. The % cumulative release was determined for FHC, famotidine floating tablets and marketed tablet (Famocid). The % cumulative release after 24 hours was compared and statistically analysed using ANOVA and Dunnett's test using GRAPHPAD PRISM 9 software.[34]

- *Drug release Kinetics study*

The kinetics of the drug release were studied by incorporating the dissolution data into different kinetic models like zero order, first order, Higuchi model and Korsmeyer Peppas model. The regression equations were compared and the model was selected on the basis of the highest correlation coefficient.[35]

Stability Study

An accelerated stability study was performed for FHC and famotidine floating tablets, for a period of 6 months at 25 ± 2°C and 60 ± 5% RH. The samples were packed thoroughly and stored in an environmental test chamber and tested at an interval of 30 days. The floating tablets were evaluated on the basis of % cumulative release after 24 hours and floating lag time to evaluate and compare the stability.[36,37]

RESULTS AND DISCUSSION

Formulation of Famotidine Phospholipid Complex (FHC) and Optimization using Central Composite Design

Famotidine phospholipid complex was successfully formulated using solvent evaporation method as shown in Fig. 2 and showed the particle size in nanometre range

Fig. 2: Formulated Famotidine Phospholipid Complex

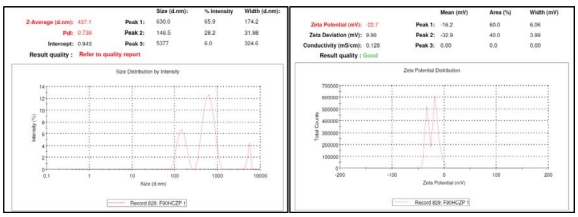

Fig. 3: Size distribution and zeta potential for FHC

(437.1 ± 0.24 nm) with a zeta potential of -22.7 ± 0.84 mV indicating good stability (Fig. 3).

For FHC, the optimized batch was selected amongst the 15 runs using central composite design on the basis of the response, complexation rate (%) as shown in Table 3. The batch 12 was found to be optimized with the composition of Famotidine: PHOSPHOLIPON 90H as 1:3 with reaction time of 60 minutes and process temperature of 60°C as analysed by Design Expert® Software (Version 11.1.2.0, Stat-Ease Inc., Minneapolis, MN). The complexation rate for all the batches was summarized in Table 3 and the optimized batch 12 had the maximum complexation rate of 98.59 ± 0.038% indicating high potential of phosphatidylcholine to bind with famotidine.

In this case, the model for complexation rate was found to be linear and analysed using ANOVA technique. For complexation rate, the model F-value of 4.82 implied that the model was significant and the *p-value* was found to be 0.020. The *p-value* below 0.050 indicated that the model was significant. The equation obtained for Y_1 from the modified quadratic model with X_1 and X_2X_3 as the significant model terms was as follows.

$$Y_1 = 93.17 + 2.10\,X_1 + 1.06\,X_2 - 0.6637\,X_3 + 2.74\,X_2X_3$$

The optimized batch 12 was selected on the basis of highest desirability value of 0.953. The positive sign in the equation indicated that as the values of the independent variables were increased, the response also increased implying a direct relationship. The negative sign indicated that as the values of the independent variables were increased, the responses decreased implying an inverse relationship as depicted by contour plot and 3D surface response plot shown in Fig. 4.

The normal plot of residuals depicted the normal distribution of the regression model for complexation rate of FHC and the set of error terms as shown in Fig. 5. The error terms were depicted as the studentized residuals

Table 3: Optimization of FHC using Central composite design

Run	*Phospholipon 90h: famotidine (x_1)*	*Reaction time (x_2) in hours*	*Reaction temperature (x_3) in ºc*	*Complexation rate (y_1) in %*
1	2	2	50	92.64 ± 0.031
2	3.68179	2	50	96.91 ± 0.043
3	2	0.318207	50	86.58 ± 0.061
4	2	3.68179	50	96.93 ± 0.065
5	1	1	40	94.8 ± 0.026
6	0.318207	2	50	91.53 ± 0.060
7	2	2	33.1821	97.49 ± 0.037
8	1	1	60	87.53 ± 0.023
9	3	1	60	92.05 ± 0.062
10	1	3	60	90.51 ± 0.108
11	3	1	40	97.62 ± 0.024
12	3	3	60	98.59 ± 0.038
13	2	2	66.8179	94.33 ± 0.048
14	3	3	40	92.12 ± 0.085
15	1	3	40	87.89 ± 0.064

Data is represented as mean value ± SD (n=3)

which were caused by the experimental error. As the resulting plot was approximately linear, it was concluded that the error terms were normally distributed.

The predicted and observed values for the optimized batch 12 was compared in Table 4. No significant difference was found between these values indicating the precision of the model.

Formulation of Gastro-retentive Floating Tablets of FHC

The gastro-retentive floating tablets of FHC and famotidine were successfully prepared by using direct compression technique (Figs 6 and 7) to avoid the disadvantages of phosphatidylcholine and to obtain free flowing granules.

Evaluation of Pre-compression Parameters of FHC and Famotidine Granules

The comparative pre-compression parameters of FHC and Famotidine granules were depicted in Table 5 and the flow properties were predicted on the basis of the standard values given in Table 6.

From the comparative results of pre-compression parameters it was found that the values of angle of repose indicated good flowability for both FHC and famotidine granules. The lower values of Hausner's ratio and Carr's compressibility index depicted excellent flow for FHC granules whereas good flow for famotidine granules. The minimum difference between the bulk and tapped density indicated the free flowing nature of the granules. It was concluded that the flow properties of FHC granules was better than the plain famotidine granules which indicated the enhancement of flow properties in the form of complex.

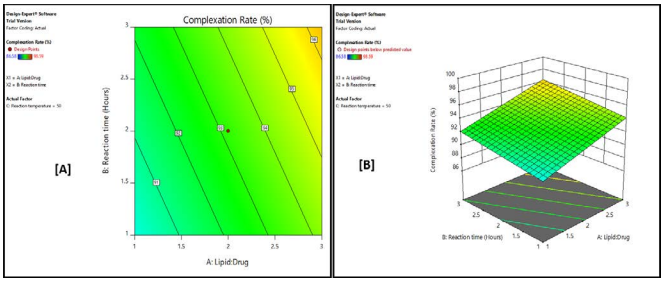

Fig. 4: [A] Contour plot and [B] 3D surface response plot of FHC for complexation rate

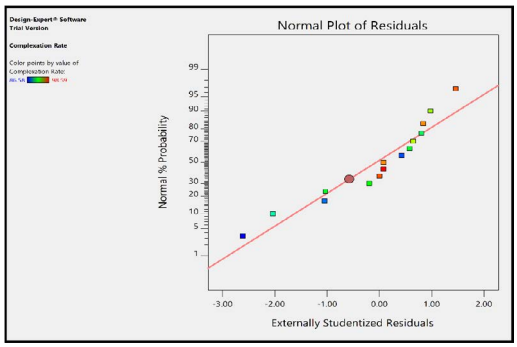

Fig. 5: Normal plot of residuals of FHC for complexation rate

Table 4: Observed and predicted values of optimized batch for FHC

Response	*Predicted values*	*Observed values (Optimized batch 12)*
Complexation rate	98.41 ± 0.067 %	98.59 ± 0.038 %

Data is represented as mean value ± SD (n = 3)

Fig. 6: Formulated FHC floating tablet

Fig. 7: FHC floating tablet showing *in vitro* buoyancy

Table 5: Comparative pre-compression parameters of FHC and famotidine

Pre-compression parameter	*Fhc granules*	*Famotidine granules*
bulk density (g/ml)	0.728 ± 0.016	0.407 ± 0.071
Tapped density (g/ml)	0.790 ± 0.301	0.455 ± 0.018
Angle of repose (degree)	31.67 ± 0.014	33.70 ± 0.113
Hausner's ratio	1.09 ± 0.043	1.12 ± 0.009
Carr's compressibility index	7.85 ± 0.053	10.54 ± 0.016

Data is represented as mean value ± SD (n = 3)

Table 6: Standard values for pre-compression parameters of tablets

Pre-compression parameter with standard value			Indication of flow property
Angle of repose	Hausner's ratio	Carr's index	
25–30	1.00–1.11	< 10	Excellent
31–35	1.12–1.18	11–15	Good
36–40	1.19–1.25	16–20	Fair
41–45	1.26–1.34	21–25	Passable
46–55	1.35–1.45	26–31	Poor
56–65	1.46–1.59	32–37	Very poor
>66	>1.60	>38	Extremely poor

Table 7: Comparative post-compression parameters of FHC and famotidine floating tablets

Post compression parameter	*Famotidine floating tablet*	*Fhc floating tablet*
Shape of tablet	Round and flat	Round and flat
Thickness (cm)	0.25 ± 0.066	0.38 ± 0.121
Hardness (kgs)	4.3 ± 0.025	6.8 ± 0.015
Friability (%)	0.88 ± 0.022	0.82 ± 0.114
Weight variation (mg)	39.63 ± 0.13 (5% of average weight as per ip and usp)	35.099 ± 0.026 (5% of average weight as per ip and usp)
Drug content (%)	96.8 ± 0.119	98.44 ± 0.089
Floating lag time (seconds)	36 ± 0.033	110 ± 0.021
Total floating time (seconds)	~12 hours	>18 hours
Swelling index (si %)	W_0 = 603 mg, w_f = 761 mg Si = 26.33 ± 0.018	W_0 = 601 mg, w_f = 772 mg Si = 28.5 ± 0.05

Data is represented as mean value ± SD

Evaluation of Post-compression Parameters of FHC and Famotidine Floating Tablets

The comparative post-compression parameters of FHC and Famotidine floating tablets were depicted in Table 7. The shape of both the tablet formulations was round and flat owing to the die cavity. The thickness measured using a Vernier caliper indicated that FHC tablets had a higher thickness value than the famotidine tablets due to the phospholipid present in the formulation. Hardness values indicated good mechanical strength and FHC tablets were found to show increased hardness values as compared to famotidine tablets. The friability below 1% indicated good mechanical resistance. FHC tablets showed enhanced mechanical resistance as compared to famotidine tablets. The weights of the FHC floating tablets varied form 564.9 to 635.1 mg and that of Famotidine floating tablets varied from 560.37 to 639.63 mg. The weight variation for both the tablet formulations was within ± 5% as per the Indian and United States Pharmacopoeia standard. The low standard deviation values indicated uniformity of weight. The weight variation FHC tablets showed was less than famotidine tablets, implying closeness to the standard weight. The drug content of FHC tablets was enhanced as compared to Famotidine tablets.

The *in-vitro* buoyancy study indicated that the floating lag time of FHC tablets was more than that of famotidine tablets due to the high molecular weight of phosphatidylcholine. But the total floating time for FHC tablet was more than 18 hours whereas that for famotidine tablet was approximately 12 hours indicating enhanced buoyancy and residence time in the form of complex.

The swelling shown by FHC tablets was uniform axially and radially as compared to famotidine tablets. The higher swelling index for FHC tablets indicated enhanced buoyancy and residence time, indicating a controlled release of drug as compared to famotidine tablets. In conclusion, FHC floating tablets showed better post-compression characteristics as compared to Famotidine tablets.

In-vitro Dissolution Study

Calibration of Famotidine in 1.2 pH buffer solution

The highest peak from the absorbance vs wavelength curve gave the absorption maxima for famotidine (265 nm). The calibration curve (Table 8) was plotted and the regression equation obtained was y = 0.0315x + 0.0154, with a correlation coefficient of 0.999 indicating that it followed Lambert Beer's law. The calibration curve and absorption maxima is depicted in Fig. 8.

Release Kinetic Study

The comparative release from FHC, famotidine and marketed tablet for 24 hours is shown in Table 9. In case of gastro-retentive floating tablets, the release from FHC tablet was greater (1.03 fold) than plain Famotidine tablet after 24 hours. When the release of these tablets was compared (Fig. 9) with that of the marketed tablet (Famocid), it was found that the release from FHC tablet (1.60 fold) showed enhanced and sustained release after 24 hours whereas the marketed tablet showed maximum of only 62.24% cumulative release and after that its release was decreased as no more drug was released from it. The % cumulative release was in the order.

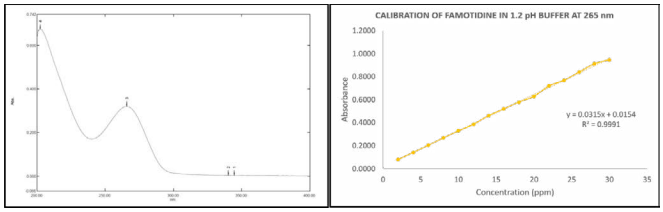

Fig. 8: Absorption maxima and calibration curve of famotidine in 1.2 pH buffer

Table 8: Calibration values of famotidine in 1.2 pH buffer

Concentration (ppm)	*Absorbance*
2	0.081 ± 0.066
4	0.142 ± 0.033
6	0.204 ± 0.003
8	0.269 ± 0.005
10	0.329 ± 0.002
12	0.385 ± 0.001
14	0.462 ± 0.009
16	0.519 ± 0.007
18	0.579 ± 0.002
20	0.627 ± 0.002
22	0.721 ± 0.001
24	0.768 ± 0.005
26	0.839 ± 0.006
28	0.911 ± 0.003
30	0.945 ± 0.001

Data is represented as mean value ± SD (n = 3)

Table 9: Comparative %cumulative release of FHC floating tablets, famotidine floating tablets and marketed tablet

Time	*%Cumulative release*		
minutes	*Famotidine floating tablet*	*Fhc floating tablet*	*Marketed tablet (Famocid)*
60	21.62 ± 0.006	27.73 ± 0.001	22.35 ± 0.017
120	30.51 ± 0.006	42.90 ± 0.030	25.05 ± 0.058
180	39.73 ± 0.001	50.80 ± 0.220	55.41 ± 0.012
240	41.57 ± 007	58.02 ± 0.112	58.06 ± 0.058
300	55.11 ± 0.017	68.56 ± 0.004	59.56 ± 0.012
360	69.73 ± 0.006	71.58 ± 0.004	60.77 ± 0.006
420	71.65 ± 0.001	72.92 ± 0.216	63.46 ± 0.012
480	72.89 ± 0.023	76.55 ± 0.001	64.70 ± 0.052
540	80.44 ± 0.007	86.88 ± 0.043	66.54 ± 0.007
600	88.76 ± 0.035	90.07 ± 0.106	68.09 ± 0.115
660	92.73 ± 0.028	95.01 ± 0.061	69.66 ± 0.058
720	95.33 ± 0.087	98.08 ± 0.091	70.95 ± 0.029
1440	97.24 ± 0.098	99.84 ± 0.058	62.24 ± 0.023

Data is represented as mean value ± SD (n = 3)

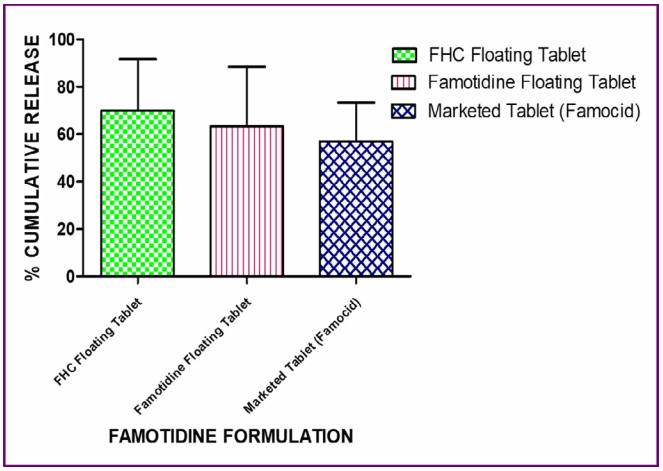

Fig. 9: Comparative %cumulative release for famotidine formulations

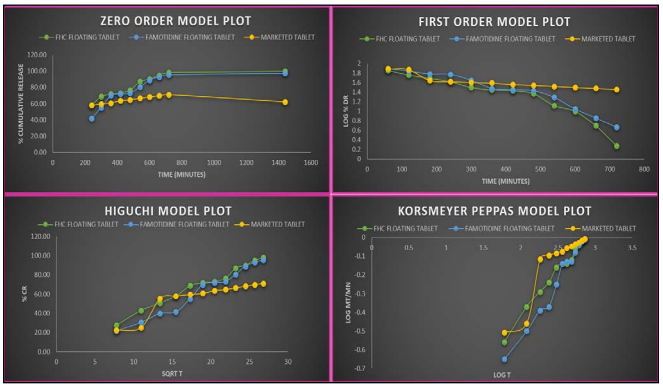

Fig. 10: Comparative kinetic model plots

FHC Floating tablets > Famotidine Floating tablets > Marketed tablet (Famocid)

The statistical analysis for %cumulative release for all tablet formulations was performed using ANOVA and Dunnett's test with the aid of Graphpad Prism 9 software and the *p-value* was found to be 0.0043 which was below 0.05 indicating that the analysis model was significant. From the results it was evident that FHC floating tablets showed improved %cumulative release and showed a sustained release pattern as compared to famotidine tablets and marketed tablet preparation.

When the kinetic modelling was performed, it was found that famotidine tablet followed zero-order release kinetics whereas FHC tablet followed Higuchi model on the basis of the highest correlation coefficient indicating a modified release pattern from a matrix system. The marketed tablet (Famocid) showed first-order release kinetics. Therefore, it was evident from the kinetic modelling study that in comparison to famotidine floating tablets and marketed tablet, FHC floating tablets showed sustained release kinetics. The comparative kinetic models and correlation coefficients are depicted in Fig. 10 and Table 10, respectively.

Table 10: Comparative R^2 values of kinetic models for FHC, famotidine and marketed tablets

Formulation	*Correlation coefficient (R^2)*			
	Zero order	*First order*	*Higuchi plot*	*Korsmeyer peppas plot*
Famotidine floating tablet	0.9907	0.9333	0.98	0.9806
FHC floating tablet	0.9589	0.8809	0.9894	0.9887
Marketed tablet (Famocid)	0.7063	0.8339	0.8119	0.8104

Table 11: Stability study of FHC and famotidine floating tablets for 6 months

Storage conditions	*Time interval*	*Famotidine floating tablet*		*FHC floating tablet*	
25 ± 2°C/ 60 ± 5% RH		Floating lag time (seconds)	%CR after 24 hours	Floating lag time (seconds)	%C R after 24 hours
	0	36 ± 0.033	97.24 ± 0.098	110 ± 0.021	99.84 ± 0.058
	1	32 ± 0.035	96.66 ± 0.103	96 ± 0.032	100.76 ± 0.062
	2	39 ± 0.043	96.36 ± 0.112	108 ± 0.065	99.82 ± 0.087
	3	43 ± 0.046	97.17 ± 0.086	99 ± 0.009	100.63 ± 0.066
	4	41 ± 0.052	97.11 ± 0.066	102 ± 0.058	99.85 ± 0.049
	5	36 ± 0.039	96.90 ± 0.079	98 ± 0.067	98.96 ± 0.006
	6	37 ± 0.038	96.54 ± 0.121	112 ± 0.033	99.31 ± 0.004

Data is represented as mean value ± SD (n = 3)

Stability Study

The accelerated stability study of FHC floating tablets and Famotidine floating tablets was performed at 25 ± 2°C, 60 ± 5% relative humidity (RH) in an environmental test chamber. The results indicated that the optimized batches did not show any physical changes during the study period of 6 months. The chemical stability of the samples was evaluated by studying the major properties of the floating tablets, namely, floating lag time and %cumulative release after 24 hours as shown in Table 11. No significant chemical difference was observed over the period of 6 months. FHC floating tablets showed better results than famotidine floating tablets indicating enhanced stability due to the formation of complex.

ACKNOWLEDGEMENT

The authors would like to thank the Department of Pharmaceutical Sciences, R.T.M. Nagpur University, Nagpur (M.S), India for providing the facility to carry out the experimental work. The authors are grateful to Dr. Reddy's Laboratories, Hyderabad; ZIM Laboratories, Nagpur (India) and LIPOID, Germany for providing the drug and phospholipid.

CONFLICT OF INTEREST

The authors P. A. Ittadwar and P. K. Puranik declare no conflict of interest.

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HOW TO CITE THIS ARTICLE: Ittadwar PA, Puranik PK. Formulation and Evaluation of Gastro-retentive Drug Delivery System of Novel Famotidine Phospholipid Complex. Int. J. Pharm. Sci. Drug Res. 2023;15(3):250-259. **DOI:** 10.25004/IJPSDR.2023.150304