FORMULATION DEVELOPMENT AND EVALUATION OF FAMOTIDINE FLOATING TABLET

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ABSTRACT

The purpose of this investigation was to prepare a floating drug delivery system of famotidine. Famotidine having poor absorption in acidic environment (upper GIT). When given orally, it shows the bioavailability near to 50%. To overcome these drawbacks, the present study was undertaken to investigate the floating dosage form of famotidine. Floating tablets were prepared using Direct Compression. Six formulations were prepared containing gel-forming agent (HPMC K4M) and retardant (Na-CMC) in different ratio and it was found that gas generating agent ($NaHCO_3$) reacts with HCl and liberates CO_2 which creates pores in tablet and elevates swelling and maintains buoyancy. The prepared tablets were evaluated for content uniformity, hardness, friability, buoyancy, swelling index and *in-vitro* dissolution studies. Further selected formulation was subjected for short term stability studies for one and two month at temperature of 25°c and 40°c respectively.

Keywords: Floating drug delivery system, Famotidine, floating tablet, Direct Compression, *in-vitro* dissolution studies.

INTRODUCTION

Famotidine is histamine H_2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellision syndrome and gastroesophageal reflux disease. In the management of benign gastric and duodenal ulceration the dose is 40 mg daily by mouth at bed time, for 4 to 8 weeks. In gastroesophageal reflux disease the recommended dose is 20 mg by mouth twice a daily for 6 to 12 weeks, where gastroesophageal reflux disease is associated with esophageal ulceration; the recommended dose is 40 mg twice daily for similar period.

For symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 10 mg up to twice daily is suggested. In the Zollinger-Ellision syndrome the initial dose by mouth is 20 mg every 6 hours, increased as necessary, dose upto 80 mg daily have been employed[1]. The low bioavailability (40 – 45%) and short biological half life (2.5 - 4.0 hours) of famotidine following oral administration favors development of a sustained release formulation.

The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of 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 h2 receptor antagonist like famotidine or ranitidine used in combinations 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 reduced 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]

In the present investigation floating tablets of famotidine were prepared by direct compression using HPMC K4M and Na-CMC as gel forming and also release retardant agent. The aim of the work was to evaluate the effect of gel-forming polymer HPMC on floating properties and release characteristics of famotidine floating tablets.

MATERIALS AND METHODS

Materials

Famotidine was received as a gift sample from Tonira pharma Ltd, Ankleshwar, India. HPMC K4M and MCC pH 102 were received as a gift sample from Signet Ltd, Mumbai, India. Na-CMC was received as a gift sample from Aqualon Ltd. Di basic calcium phosphate; Sodium bicarbonate and Hydrochloric acid were purchased from Merck Ltd. Magnesium stearate was procured from Mukesh pharma distribution. Talc was purchased from Nikita pharma.

Methods

Preparation of famotidine floating tablets

The composition of different formulations of famotidine floating tablets is shown in Table no **1.** Famotidine, HPMC K4M, Na-CMC were passed through sieve no. 80 separately. Sodium bicarbonate was passed through sieve no. 44. All the ingredients were mixed in proportion shown in Table no. **1**. The powder blends were lubricated with Magnesium stearate (2% w/w) and Talc (1% w/w), and these lubricated blends were compressed into tablets using 9.5 mm flat faced round tooling on a single punch tablet machine (Rimek mini press II). The compression

force was adjusted to obtain tablets with hardness in range of 4.5 to 5 kg/cm^2. Six formulations were prepared and coded them from FT_1 to FT_6.

Evaluation of famotidine floating tablets

The flow properties of blends (before compression) were characterized in terms of Angle of repose[4], Bulk density and tapped density[5], Carr's index[6] and Hausner's ratio[6].

Physical evaluation of famotidine floating tablets

Two tablets from each formulation were randomly selected and organoleptic properties such as color, odour, taste and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for weight variation[7] using 20 tablets, hardness[7] (Monsanto tester), and friability[7] using 10 tablets (Roche type friabilator)[7].

***In vitro* buoyancy studies**

In vitro buoyancy studies were performed for all the six formulations as per the method described by Rosa *et al*. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for a tablet to rise on surface and float was considered as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time (TFT).

Drug content estimation

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 10 mg was added in 0.1N HCl followed by stirring. 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 0.1N HCl as blank[7].

In vitro buoyancy studies

Buoyancy is determined to find out the ability of the tablet to float on the dissolution medium for the period of 8 to 10 hours during which it remain intact without undergoing disintegration. The floating lag time (time period between placing tablet in the medium and buoyancy beginning) and total floating time was determined by visual observation[8].

***In vitro* dissolution studies**

The release rates of famotidine from floating tablets were determined using *United State Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml 0f 0.1N HCl at 37° ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions were measured at 265 nm using a UV/Visible spectrophotometer. The Cumulative percentage drug release was plotted against time to determine the release profile.

***In vitro* drug release kinetic studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to Zero order[9] and Higuchi square root[9]. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXEL statistical function.

Short term stability studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The promising formulation was tested for Short term testing for a period of 1st month at 25°C ± 2°C/ 60% RH ± 5% and Accelerated testing for a period of 2nd month at 40°C ± 2°C/ 75% RH ± 5%[10], for their drug content and other parameters[10].

Table 1: Composition (mg/tablet) of different floating tablet formulations of famotidine

Ingredients*	FT_1	FT_2	FT_3	FT_4	FT_5	FT_6
Famotidine	40	40	40	40	40	40
HPMC K4M	90	80	70	72	72	72
Na CMC	-	-	-	6	9	12
MCC	47	57	67	59	56	53
DCP	36	36	36	36	36	36
Sodium bicarbonate	78	78	78	78	78	78
Magnesium stearate	6	6	6	6	6	6
Talc	3	3	3	3	3	3
Total weight	300	300	300	300	300	300

Table 2: Results of Precompression flow properties of famotidine blends

Blends	Angle of Repose (θ)	Carr's Index (%)	Hausner's ratio	Flow property
FT_1	20.03°±0.625	13.96±0.361	1.15±0.002	Excellent
FT_2	20.78°±0.686	14.19±0.383	1.17±0.005	Excellent
FT_3	20.29°±0.639	14.07±0.372	1.16±0.003	Excellent
FT_4	20.70°±0.695	14.16±0.380	1.16±0.003	Excellent
FT_5	19.74°±0.581	13.24±0.349	1.15±0.002	Excellent
FT_6	19.24°±0.533	13.05±0.336	1.15±0.002	Excellent

Table 3: Results of Post compression properties of famotidine floating tablets

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug Content (%)
FT_1	3.72±0.019	5.13±0.234	0.63±0.081	302.89±2.821	98.42±0.234
FT_2	3.52±0.037	5.00±0.367	0.71±0.062	302.32±2.892	99.24±0.267
FT_3	3.42±0.043	4.98±0.291	0.59±0.078	299.91±0.998	99.45±0.231
FT_4	3.52±0.048	4.99±0.492	0.63±0.085	301.86±1.784	98.02±0.194
FT_5	3.62±0.026	5.10±0.231	0.69±0.093	299.85±1.028	97.86±0.289
FT_6	3.52±0.038	5.06±0.362	0.72±0.084	303.22±2.995	97.91±0.281

Table 4: Results of In vitro buoyancy study of famotidine floating tablets

Formulation code	Buoyancy lag time (sec)	Total floating time (hrs)
FT1	20 ±1.356 s	>12 hrs
FT2	06 ±2.475 s	>10 hrs
FT3	16 ±1.587 s	>10 hrs
FT4	09 ±1.945 s	>11 hrs
FT5	16 ±2.943 s	>13 hrs
FT6	34 ±3.621 s	>14 hrs

Table 6: Stability study of formulation FT_3

Parameters	1st month 25°C ± 2°C/ 60% RH ± 5%	2nd month 40°C ± 2°C/ 75% RH ± 5%
Physical appearance	Off white, flat faced	Off white, flat faced
Weight variation (mg)	299.83±0.764	299.48±0.921
Hardness (kg/cm^2)	4.98±0.367	4.98±0.568
Friability	0.59±0.082	0.59±0.089
Drug content (%)	98.98±0.462	98.87±0.481
Floating lag time (sec)	16±2.873	17±2.562
Total floating time (hrs)	>10	>10
In-vitro release (%)	75.20±0.468	74.85±0.321
Buoyancy on disturbing	float	float

RESULTS AND DISSCUSION

Floating tablets of Famotidine were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug. The tablets were made using gel forming polymers HPMC K4M and Na-CMC along with effervescent agent Sodium bicarbonate to optimize the drug content, *in vitro* buoyancy, swelling index, *in vitro* drug dissolution studies. All the formulations were prepared by direct preparation. Talc and Magnesium stearate was employed for their glidant and lubricating properties.

The prepared tablets of all the formulations were evaluated for precompression parameters like angle of repose, bulk density, tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation, buoyancy lag time, total floating time, *in vitro* drug release. The main aim was to control the release of drug up to 8 hrs.

Precompression parameters of Famotidine blends

The formulations showed good flow property and Carr's index (Table no **2**). Angle of repose ranged from 19° 24' ± 0.533 to 20°78' ± 0.686, Carr's index ranged from 13.05 ± 0.336 to 14.19 ± 0.383 and the Hausner ratio ranged from 1.15 ± 0.002 to 1.17 ± 0.005.

Post compression parameters of Famotidine tablets

The shape of tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The thickness and diameter of tablets was measured by vernier calipers and was ranged between 3.42 ± 0.043 mm to 3.72 ± 0.019 mm and 9.5 to 9.6 mm respectively. The hardness of the tablets was measured by Monsanto tester (ThermoLab, Mumbai, India) and was in between 4.99 to 5.13 kg/cm^2. The friability was measured by friabilator (Roche friabilator) and was found to be 0.59 ± 0.078 to 0.72 ± 0.084%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 97.86 ± 0.289 to 99.45 ± 0.231% which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within Pharmacopoeial limits. The results are shown in Table no **3**.

In vitro buoyancy studies

All the tablets were prepared by direct compression. Sodium bicarbonate was added as gas generating agent. On contact with dissolution medium (0.1N HCl), carbon dioxide gas was generated. It was observed that the gas generated is trapped and protected within gel, formed by hydration of polymer (HPMC), thus decreasing the density of the tablet below 1 and tablet becomes buoyant.

All the batches of tablets were found to exhibit short floating lag time due to presence of sodium bicarbonate. The tablets with low viscosity grade HPMC K4M exhibited short floating lag time as compared with formulations containing both HPM K4M and Na-CMC. Reduction in HPMC level in formulations prolonged the floating lag time. With reference to buoyancy studies results it can be concluded that the batches containing HPMC K4M polymers showed good floating lag time (FLT) and Total floating time (TFT). (Table no **4**).

In vitro dissolution studies

In vitro dissolution studies of all the formulations of floating tablets of famotidine were carried out in 0.1n HCl. The study was performed for 8 hours and cumulative drug release was calculated for every one hour time interval. In vitro dissolution studies of all the formulations are shown in Fig no **1** and **2**. HPMC K4M and Na-CMC were used to formulate the floating tablets. It was observed that the type of polymer influences the drug release pattern.

Figure 1: Comparison of in vitro dissolution profiles of FT_1 to FT_3

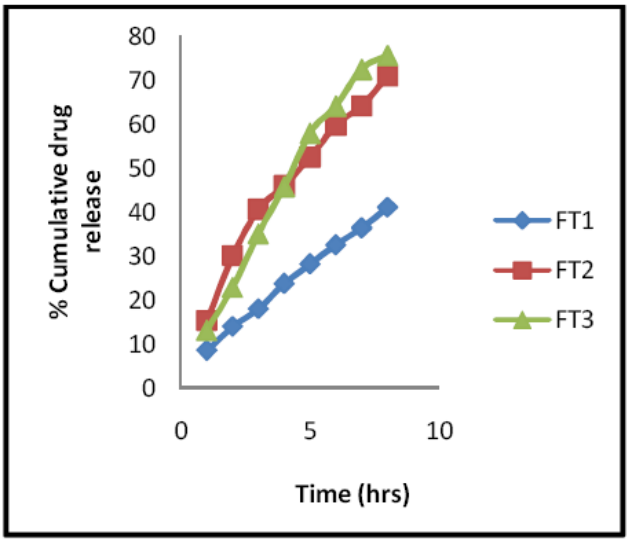


Figure 2: Comparison of in vitro dissolution profiles of FT_4 to FT_6

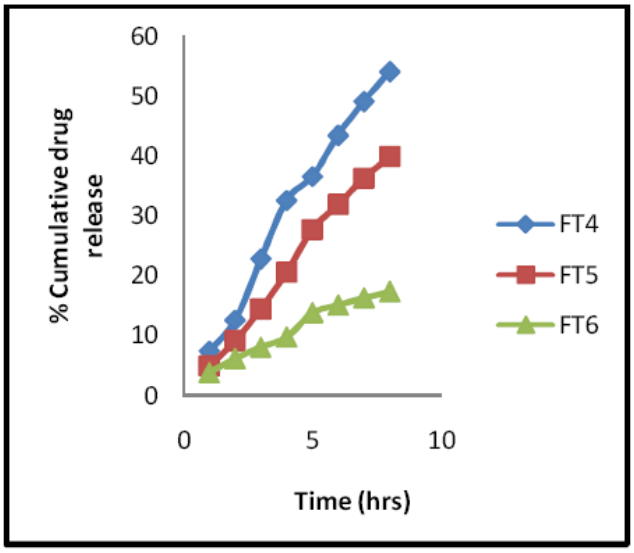


Figure 3: Zero order release kinetics of FT_3

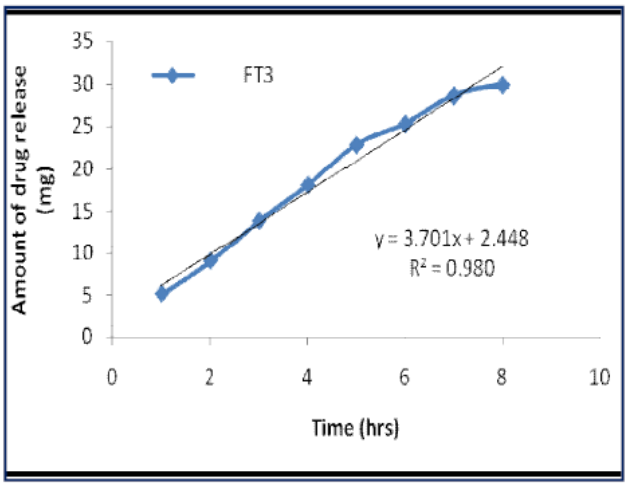
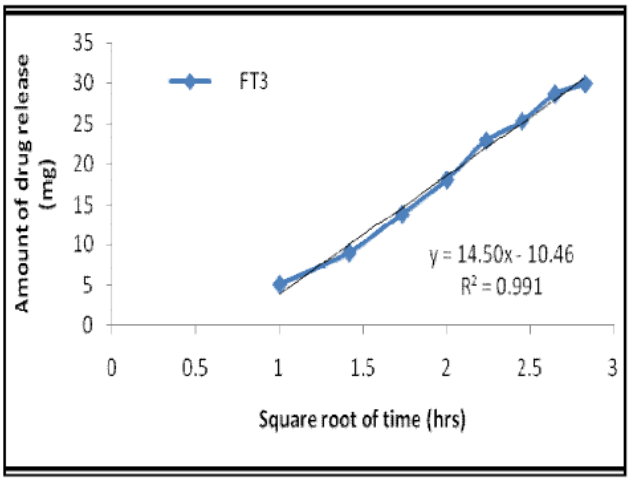


Figure 4: Higuchi matrix release kinetics of FT_3



All the formulation containing equal amount of sodium bicarbonate. A significantly higher amount of drug release was observed from the batches based on HPMC K4M. Drug release from HPMC K4M and Na-CMC combination was lesser due to its high viscosity and less permeability of water. After 1 hr the drug dissolved from HPMC alone was more than that of HPMC and Na-CMC combination. This showed that HPMC hydrated more rapidly than that of HPMC and Na-CMC combination. Also, the drug release rate of the formulations FT_1-FT_3 was more than that of formulations FT_4-FT_6.

Analysis of release mechanism

The drug release data of famotidine were fitted to models representing Zero order and Higuchi's kinetics to know the release mechanisms. The data were processed for regression analysis using MS-EXCEL statistical function. The results are shown in Table no **5** and graphs in Fig no **3** and 4. diffusion is related to the transport of drug from the dosage form in the *in vitro* fluid depending on the concentration. In the present study, in vitro release profiles could be best expressed by Higuchi's equation as formulation showed good linearity (R^2: 0.991) indicates that the diffusion is dominant mechanism of drug release with these formulations.

Table 5: Kinetic release data of different model for formulation FT_3

Model	Slope	R^2
Zero order	3.701	0.980
Higuchi	14.50	0.991

Short term stability studies

The formulation (FT_3) was selected for stability studies on the basis of *in vitro* buoyancy and *in vitro* drug dissolution studies. The tablets were investigated at 25°C ± 2°C/ 60% RH ± 5% for 1st month and at 40°C ± 2°C/ 75% RH ± 5% for 2nd month. From the data, the formulation found to be stable under the conditioned mentioned before since there was no significant change in the percentage amount of drug content (Table no **6**). Thus, it was found that the floating tablet of famotidine remains stable under these storage conditions for at least 2 months.

CONCLUSION

This study discusses the preparation of floating tablets of famotidine. The addition of gel forming polymers HPMC K4M, Na-CMC and gas generating agent Sodium bicarbonate was essential to achieve *in vitro* buoyancy. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. The dissolution studies of six formulations showed that the formulation having lesser amount of polymer exhibits better drug release. Formulations containing HPMC in concentration of 80 mg and 70 mg showed more release in comparison to formulation containing HPMC and Na-CMC in combination. As the concentration of HPMC decreased from 90 mg to 70 mg, the release rate of drug increased. The formulation having lesser floating lag time (16 s). Good stability was observed for 2 months during stability studies.

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