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Formulation and development of Famotidine floating tablets for gastric irritation

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Abstract

The purpose of the study was to prolong the gastric residence time of famotidine by designing its floating tablets and to study the influence of different polymers on its release rate. Three formulations of famotidine containing varying concentrations of polymers were designed by optimization. The floating matrix tablets of famotidine were prepared by direct compression method. The prepared tablets were evaluated for physicochemical parameters such as hardness, floating properties (floating lag time, floating time and matrix integrity), and drug content. The physicochemical parameters of formulated tablets were found to be within normal range. The floating lag time of all the formulations was within the prescribed limit (54 Sec). All the formulations showed good matrix integrity and retarded the release of drug for 12 hours. The drug release from F-II was found to follow zero order kinetics. It was also found linear in Higuchi's plot, which confirms that diffusion is one of the mechanisms of drug release.

Key words: Famotidine, floating, floating lag time, floating time.

INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968. [1- 2] It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high-density systems and low density systems that increase the gastric residence time.[3-5] Gastric retention is useful for drugs which (i) act locally; (ii) have a narrow absorption window in the small intestinal region; (iii) unstable in the intestinal environment; (iv) low solubility at high pH environment.[6] Various dosage forms developed for gastric retention include, floating

tablets,[7] floating beads,[8] pellets,[9] floating granules,[10] floating microspheres.[11] In this investigation, an attempt was made to design floating tablets of famotidine using different release retarding polymers along with a gas-generating agent.

Famotidine is a H₂-receptor antagonist. Famotidine is used orally for the treatment of active duodenal or gastric ulcer, gastroesophageal reflux disease, endoscopically diagnosed erosive esophageal reflux disease, endoscopically diagnosed erosive esophagitis, and as maintenance therapy for duodenal ulcer. Oral Famotidine also is used for the management of pathological GI hypersecretory conditions. IV Famotidine is used in hospitalized individuals with pathological GI hypersecretory conditions or intractable ulcers, or when oral therapy is not feasible. The plasma half-life following a single oral dose is 2.5-4hrs. The success of therapy depends on selection of appropriate delivery system as much as it depends on the drug itself. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Thus, Famotidine is chosen as a suitable candidate for sustained release drug delivery system. In this study, an attempt was made to design and formulate the floating matrix tablets of famotidine so as to increase its gastric retention thereby ensuring slower and complete release of famotidine. Also, semi synthetic polymers, hydroxypropylmethyl cellulose (HPMC) K100M on the release rate of drug. Sodium bicarbonate was used as a gas generating agent and citric acid used as a initiating agent.

MATERIALS AND METHODS

Drug: Famotidine is an Active Ingredient (Micro labs, Hosur) and Excipients used in this formulation are hydroxyl propyl methylcellulose K100M used as a Polymer (SD fine chemicals, Boisar), Sodium bi carbonate used as a Buoyancy Imparting agent (SD fine chemicals, Boisar), Citric acid used as a Stabilizing agent (SD fine chemicals, Boisar), Lactose as a Diluent(SD fine chemicals, Boisar), Magnesium state as a Lubricant(SD fine chemicals, Boisar), Purified talc as a Lubricant(SD fine chemicals, Boisar), IP Alcohol as a Granulating(SD fine chemicals, Boisar) Hydrochloric acid and Double Distilled water. And the Instruments used visible spectrophotometer (UV1201) Digital balance and dhona 160D Electronic balance Tablet punching machine. Digital dissolution apparatus USP XXIII paddle. Monsanto tablet hardness tester. Screw gauge (Thickness tester). Roche friabilator.

Methods

Wet granulation technique.

Floating granules were prepared by using wet granulation technique. The hydroxypropyl methylcellulose, lactose, sodium bi carbonate, citric acid and the active ingredients were mixed homogeneously. Alcoholic solution of HPMC (1% W/V) was used as a granulating agent. The granules were dried in a conventional hot air oven. The dried granules were sieved through 40/60 meshes. Magnesium stearate was added as a lubricant and the granules were compressed in to tablets using Single punch tablet machine.

Determination of bulk density and tap density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and Weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$\rho_b = M/V_b$$

The measuring cylinder containing a known mass of powder or granules was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the following formula.

$$\rho_t = M/V_t$$

Compressibility index

The measuring cylinder way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as

$$I = (\rho_t - \rho_o/\rho_t) \times 100$$

ρ_t = tapped density
 ρ_o = initial bulk density

The value below 15% indicates a powder which usually give rise to good flow characteristics whereas above 25% indicate poor flow ability.

Haunsner ratio is an indirect index of ease of powder flow. It is calculated by the formula which follows:

$$\text{Haunsner ratio} = \rho_t / \rho_d$$

Where, ρ_t = tapped density, ρ_o = bulk density.

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose (θ). It was determined using funnel method. The powder or granules were poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated (θ).

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

Hardness test

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsanto hardness tester measured the hardness studies and results were expressed in kg/cm^2 .

Thickness and diameter

The thickness and diameter of the tablet was carried out using vernier caliper. Five tablets were used for the above test from each batch and results were expressed in millimeter.

Weight variation test

Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. specification. As per I.P. not more than 5% and none deviate more than twice that percentage.

Friability test

It was done in biological museum friability test apparatus where the tablets were subjected to combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre-weighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that loss less than 0.5 to 1.0% of their weight are generally considered acceptable.

$$\text{Friability} = \left(1 - \frac{W_2}{W_1}\right) \times 100$$

Drug content uniformity

Ten tablets were weighed and taken in a mortar and crushed to powder form. A quantity of powder weighing equivalent to 100 mg of famotidine was taken in a 100 ml volumetric flask and 0.1N HCL was added. It was then heated at 60 °C for 30 minute. The solution was filtered using membrane filter (0.45µm) and then its absorbance was measured at 266nm. The amount of drug calculated using standard graph.

***In-Vitro* Buoyancy Studies**

The time of tablet took to emerge on the water surface (floating lag time) and the time of tablet constantly float on the water surface (duration of floating) were evaluated in a dissolution vessel (dissolutions apparatus) were with 900 ml of 0.1N HCL (Ph1.2) previously set at 37 ± 0.5°C with paddle rotation at 100 rpm. The results for floating time are presented in table No.6 from the study of floating properties it was observed that the floating lag time ranges from 42 to 63s and tablets of each batch remained buoyant up to 12 hours, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced.

***In-Vitro* Dissolution Studies**

In vitro drug release studies of famotidine were studied using dissolution apparatus USP type II paddle method with a stirring speed of 100 rpm at 37°C±0.5°C in 900 ml of (pH 1.2) simulated gastric fluids for 12 hours. The samples were taken at pre-selected gastric fluids for 12 hours. The samples were taken at per-selected time intervals with replacement of equal volume of dissolution media. The collected samples were diluted and the absorbance was measured spectrophotometrically at 266nm. The percentage of famotidine released at various time intervals were calculated from the standard graph. *In-vitro* dissolution studies were carried out at in

simulated gastric fluid (pH 1.2 buffers) for 12 hours. In order to find out the of order of release and the mechanism, which was predominately influences the drug release from the tablet, the *in vitro* dissolution data was subjected to 3 different mode of graphical treatment.

Release kinetic studies

The formulation F-II formulated with HPMCK100M (100mg) shows release of 99.32%. The *in vitro* release plot has shown that the drug release followed zero order kinetics, which has evinced from the regression value of the above, maintained plot. The Higuchi's plot has shown regression value of 0.9099, which indicated diffusion mechanism influencing the drug release. In order to confirm this fact, Peppas's plot was drawn which has shown slop value of 0.9970, which confirms that the diffusion mechanism involved in the drug release was of non-fickian diffusion type. The formulation F-II is the optimized formulation. The tablet which is composed of a polymeric matrix on contact with water builds a gel layer around the tablet core, which governs the drug release.

Table 1: Formulation of famotidine floating tablet-

S.No	Ingredients	Category	Batch Code		
			F-I	F-II	F-III
1	Famotidine	Active Ingredient	40 mg	40 mg	40 mg
2	HPMC K100M	Polymer	75mg	100mg	125mg
3	Sodium bicarbonate	Buoyancy Imparting agent	50mg	50mg	50mg
4	Citric Acid	Stabilizing agent	10mg	10mg	10mg
5	Lactose	Diluent	119mg	94mg	69mg
6	Magnesium stearate	Lubricant	1%	1%	1%
7	Purified talc	Lubricant	1%	1%	1%
8	Alcoholic Solution of HPMC (1% W/V)	Granulating agent	QS	QS	QS

RESULTS AND DISCUSSION

The oral bioavailability of Famotidine has been reported to be about 40% because of its rapid hepatic first pass metabolism. If the drug dosage form can retain the stomach as long as possible, to allow for maximum absorption, then the bioavailability could be improved. Gastric floating drug delivery is one approach where the gastro intestinal residence time is prolonged because of the floating behavior.

HPMC K100M was used as swellable polymers and chosen because it is widely used as a low-density hydrocolloid system upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH. Citric acid has stabilizing effect and sodium bicarbonate is used as a buoyancy-imparting agent.

In the present study the formulations were prepared by using different proportions of polymer. The prepared formulations were evaluated for different physicochemical characteristics such as thickness and diameter, drug content, weight variation, hardness and friability. The release characteristic of the formulation was studied in in-vitro conditions.

Hardness

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness. Hardness of the tablet was found to increase with increasing polymer concentration. The floating tablets prepared by using HPMC K100M (75mg) was found to be less harder than other tablets prepared using HPMC K100M 100mg and 125mg. (Table 2)

Thickness and Diameter

The thickness and diameter of the tablets were found to be in the range of 4.97mm to 4.99 mm and 7.90mm to 7.93mm respectively. (Table 2)

Friability

The friability loss of the tablet was found to be 0.43 to 0.65% examined by using Roche friabilator. All batches of tablets passed the test and are within the limits. It indicated that the tablets were mechanically stable. (Table 2)

Weight variation test

All the batches of tablets were found to pass the weight variation test. The percentage deviation of the individual tablet weights from the average tablet weight was found to be within the I.P. limits $\pm 7.5\%$ (Table 2)

Drug content uniformity

The drug content uniformity was examined as per I.P. specification. All the batch of tablets was found to comply with uniformity of content test. None of the individual drug content values were outside the average content values. (Table 2)

***In-vitro* buoyancy studies**

Floating lag time was observed that the range of 42 to 63 seconds for all the formulations. Formulations containing 100mg of HPMC K100M have lower floating lag time 42 seconds while formulations containing 125mg of HPMC K100M have higher floating lag time of 63 seconds. (Table 4)

Result indicate that the higher floating lag time may due to tablet porosity, low density, swelling ability and inter particle force of HPMC K100M. Duration of floating for prepared tablet of each batch remained buoyant up to 12 hours, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced.

Table 2: Evaluation Data of Formulated Floating Tablets

SI. No.	Parameters	F-I	F-II	F-III
1	Average hardness (Kg/cm ²)	4.10 ± 0.02	4.22 ± 0.01	4.41 ± 0.02
2	Average thickness (mm)	4.98 ± 0.03	4.97 ± 0.02	4.99 ± 0.03
3	Average diameter (mm)	7.90 ± 0.06	7.90 ± 0.09	7.93 ± 0.05
4	Average Friability (mm)	0.57 ± 0.02	0.43 ± 0.01	0.65 ± 0.03
5	Average Weight Variation (mg)	298.4 ± 0.02	299.3 ± 0.13	298.1 ± 0.01
6	Average content Uniformity (%)	99.53 ± 0.02	98.87 ± 0.04	99.12 ± 0.13

***In-Vitro* Dissolution Study**

Dissolution apparatus USP XXI type II paddle method was used for carried out in-vitro drug release study on the prepared batches of floating tablets with a stirring speed of 100 rpm at 37° C ±0.5° C in 900ml of (pH1.2) simulated gastric fluids for 12hours.

Table 3: Release kinetic of Famotidine

Batch Code	Regression for zero order plot	Regression for first order plot	Regression for Higuchi's plot	Slope for peppa's plot
F-I	0.9966	0.938	0.9159	0.8794
F-II	0.9970	0.824	0.9103	0.8524
F-III	0.9995	0.850	0.9176	0.8635

The formulation F-II formulated with HPMCK100M (100mg) shows release of 99.32%. The in vitro release plot has shown that the drug release followed zero order kinetics, which has evinced from the regression value of the above, maintained plot. The Higuchi's plot has shown regression value of 0.9103, which indicated diffusion mechanism influencing the drug release. In order to confirm this fact, Peppa's plot was drawn which has shown slope value of 0.8524, which confirms that the diffusion mechanism involved in the drug release was of non-fickian diffusion type. The formulation F-II is the optimized formulation. The tablet which is composed of a

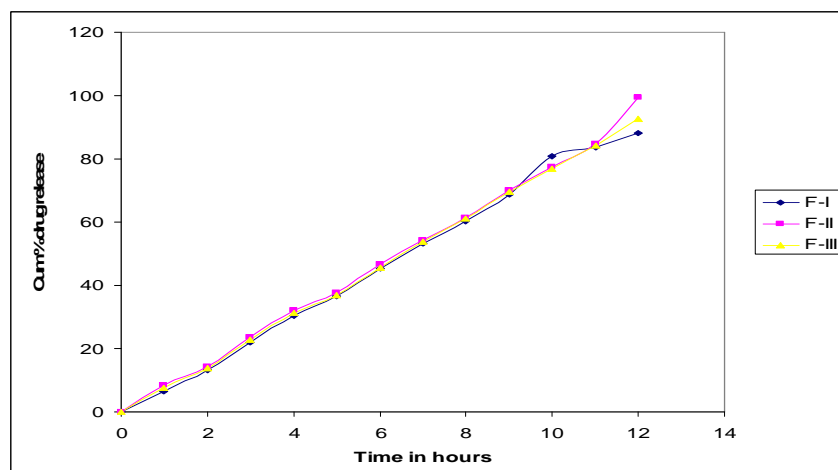
polymeric matrix on contact with water builds a gel layer around the tablet core, which governs the drug release.

Table 4: *In-Vitro* Buoyancy Studies of Floating Tablet

SI. No	Batch Code	Buoyancy lag time (Sec)	Duration of Buoyancy (hrs)
1.	F-I	54	>12
2	F-II	42	>12
3	F-III	63	>12

Table 5: *In-Vitro* Drug Release Data for Formulation-II

Time in hrs	Zero Order Plot	First Order Plot	Higuchi's plot		Peppas's plot	
	Cumulative %Drug release	Log Cumulative % Drug retained	Square root of time	Cumulative %Drug release	Log time	Log% drug release
1	8.33	1.96	1.00	8.33	0	0.92
2	14.41	1.93	1.41	14.41	0.300	1.15
3	23.64	1.88	1.73	23.64	0.477	1.37
4	31.98	1.83	2.00	31.98	0.60	1.50
5	37.61	1.79	2.23	37.61	0.69	1.57
6	46.62	1.72	2.44	46.62	0.77	1.66
7	54.28	1.66	2.64	54.28	0.84	1.73
8	61.49	1.58	2.82	61.49	0.90	1.78
9	70.05	1.47	3.00	70.05	0.95	1.84
10	77.48	1.35	3.16	77.48	1.00	1.88
11	84.91	1.17	3.31	84.91	1.04	1.92
12	99.32	-0.16	3.46	99.32	1.07	1.99



CONCLUSION

The approach of present study was to develop floating tablets of Famotidine and henceforth evaluate the release profiles of these formulations. Formulation F-II containing 100mg of HPMCK100M was found to release a maximum of 99.32% at the 12th hour. The drug release from F-II was found to follow zero order kinetics. It was also found linear in Higuchi's plot, which confirms that diffusion is one of the mechanisms of drug release.

Comparison of all formulation of Famotidine revealed the fact that developed formulation F-II showed comparable release characteristics, thus it may have fair clinical efficiency. Hence, the formulation F-II holds promise for further in vivo studies, which can be extrapolated for the development of floating drug delivery system.

As an extension of this work bioavailability, pharmacokinetic, IR spectral studies, stability studies and in vivo studies can be done in future to develop as suitable candidate for a novel drug delivery system.

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