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Design and Evaluation of Famotidine Floating Tablets

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ABSTRACT

Floating drug delivery system overcomes the physiological problems of gastric retention by decreasing fluctuations in blood drug concentration with consequent reduction in undesirable toxicity and poor efficiency. Famotidine is a potent H_2 receptor antagonist used in the management of benign gastric and duodenal ulceration. Famotidine is incompletely absorbed from the GI tract following oral administration. The low bioavailability (40-45%) and short biological half-life (2.5 - 4 hrs) of famotidine by oral administration favors development of a sustained release formulation. The purpose of the study was to prolong the gastric residence time of famotidine by designing as floating tablets and to study the influence of different polymers on its release rate. Nine formulations of famotidine containing varying concentrations of polymers (HPMC E15, HPMC K4M and sodium alginate) were designed The floating matrix tablets of famotidine were prepared by direct compression method. The powder blend was evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and Hausner's ratio; all these values are within the specified limit which indicates good flow properties. The prepared tablets were evaluated for physicochemical parameters such as weight variation, hardness, friability**,** floating properties (floating lag time, floating time) and drug content. *Invitro* release studies revealed that out of 9 formulations, formulation F8 was found to be optimized which showed sustain the drug release of 97.11% for 10 hours.

Keywords: Bioavailability, Famotidine**,** Floating drug delivery system, Gastric residence time, Sodium alginate, Sustained release.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste and improves solubility of drugs that are less soluble in high pH environment. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents, that delaying gastric emptying (Arunachalam *et al*., 2007). Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs. Famotidine is a potent H_2 receptor antagonist used in the management of benign gastric and duodenal ulceration is selected as a model drug in the present study. Conventional oral formulations of famotidine are administered multiple times a day. Treatment of gastric acid secretion using conventional formulations of

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famotidine is found have many drawbacks and adverse effects that results in accumulation of drug in multi dose therapy and also poor patient compliance. Floating tablets are designed to prolong the gastric residence time after oral administration (Abhishek Kumar Chauhan *et al*., 2010). It is useful for achieving controlled plasma levels as well as improving bioavailability. With this objective famotidine floating tablets were designed. Famotidine has low bioavailability (40%) and short biological half-life (2.5-4 hrs) favours for the development of floating tablets (Umarunnisha A.M. *et al*., 2010). The aim of the research work is to formulate and evaluate famotidine floating tablets in order to enhance bioavailability by prolonging gastric residence time in upper part of the GIT in order to maximize the drug release. Floating drug delivery systems are classified depending up on the two formulations variables Effervescent and Non-effervescent systems (Vedha Hari *et al*., 2010). Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

MATERIALS AND METHODS

Materials

Famotidine (Sms pharmaceuticals Ltd., Hyd.), HPMC K4M, Sodium alginate (HiMedia Pvt. Ltd., Mumbai) HPMC E 15, Lactose, Magnesium stearate, Talc (Oxford Laboratory, Mumbai) Sodium bicarbonate, Citric acid (Sd fine chemicals Ltd., Mumbai),Hydrochloric acid (Avantor Performance Materials Pvt. Ltd., Maharashtra)

Preparation of Famotidine floating tablets

Effervescent floating tablets containing famotidine were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then except magnesium stearate all other ingredients were blended uniformly in glass mortar after sufficient mixing of drug as well as other components, mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation (Pare *et al*., 2008). Composition of different formulations of Famotidine floating tablets were shown in Table.1.

Pre compression studies (CVS Subrahmanyam)

The powder blend was subjected for the following studies

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

Angle of repose

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The effect of angle of repose on flow property of powders was listed in Table.2 and the results were tabulated in Table.5.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

Bulk density and tapped density

A quantity of 10gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula and the results were tabulated in Table.5.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The effect of carr's index on flow property of powders was listed in Table.3. The formula for carr's Index is given below and the results were tabulated in Table.5.

$$\text{Carr's index}\ (\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula and the effect of hausner's ratio on flow property of powders was listed in Table No. 4. The results were tabulated in Table No. 5.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Post compression studies (Lachman *et al*)

Thickness

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were tabulated in Table No. 6.

Hardness

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. An average of three observations is reported. The results were tabulated in Table No. 6.

Friability test

Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were tabulated in Table No. 6.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation

The weight variation test is done by weighing 10 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The results were tabulated in Table No. 6.

$$\%\ \text{Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

Evaluation of Famotidine floating tablets

Drug content

Five tablets were taken and powdered; the powder equivalent to 40 mg of famotidine was dissolved in 100 ml of 0.1 N HCl of p^H 1.2, filtered, diluted suitably to 20 mcg/ml concentration and analyzed at 265 nm using UV-Visible spectrophotometer (Patel Manish *et al*).The results were tabulated in Table No. 7.

***In vitro* buoyancy/ floating study**

In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 200 ml beaker containing 0.1 N HCl of pH 1.2. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT) the duration of the dosage form constantly remained on the surface of the medium was determined as the floating time (FT) (Chandrasekhara Rao Baru *et al*). The results were tabulated in Table No. 7.

***In vitro* dissolution studies**

In vitro drug release rate of Famotidine from floating tablets was determined using United States Pharmacopoeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl for 12 hrs. A sample (5 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 a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N HCl for 12 hrs. Absorbance of these solutions was measured at 265 nm using a UV/ Visible spectrophotometer. Percentage of drug dissolved was calculated by plotting time on X- axis against % cumulative drug release on Y-axis (Sonia dhiman *et al*).The results were tabulated in Table No. 8 and Figure No.1.

RESULTS AND DISCUSSION

The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.400 to 0.526 gm/ml, whereas the tapped density was observed between 0.454 to 0.588 gm/ml. From the values of bulk density and tapped density the values for compressibility index and hausner's ratio were calculated. The values for compressibility index were found between 9.50 to 14.96 %. The values for hausner's ratio were found in between 1.09 to1.17. All these values are within the specified limit which indicates good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall these values indicate good flow properties of powder blend, uniform die fill and better compression ability (Table No.5).

Table.1 Composition of different formulations of Famotidine floating tablets

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine	40	40	40	40	40	40	40	40	40
HPMC E15	100	150	200	-	-	-	-	-	-
HPMC K4M	-	-	-	100	150	200	-	-	-
Sodium alginate	-	-	-	-	-	-	100	150	200
Lactose	160	110	60	160	110	60	160	110	60
Sodium bicarbonate	60	60	60	60	60	60	60	60	60
Citric acid	10	10	10	10	10	10	10	10	10
PVK 30	20	20	20	20	20	20	20	20	20
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight	400	400	400	400	400	400	400	400	400

Table.2 Effect of angle of repose on flow property of powders

Angle of repose	Type of flow of powder
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Table.3 Effect of Carr's index on flow property of powders

Carr's index	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Very very poor

Table.4 Effect of hausner's ratio on flow property of powders

Hausner's ratio	Flow property
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

Table.5 Physical parameters of powder blend

S. No	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})
1	F1	0.434	0.500	13.20	1.15	29.50
2	F2	0.434	0.476	9.67	1.09	29.35
3	F3	0.400	0.454	11.89	1.13	29.33
4	F4	0.454	0.526	12.24	1.15	21.20
5	F5	0.500	0.588	14.96	1.17	28.05
6	F6	0.500	0.588	14.96	1.17	28.72
7	F7	0.476	0.555	14.23	1.16	26.56
8	F8	0.476	0.526	9.50	1.10	27.96
9	F9	0.526	0.588	11.78	1.11	28.72

Table.6 Physical parameters of Famotidine floating tablets

S.No	Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	% Friability	% Weight variation.
1	F1	4.8	5.4	0.075	1.375
2	F2	5.1	5.1	0.050	2.733
3	F3	5.0	5.5	0.025	1.633
4	F4	4.8	4.9	0.100	1.932
5	F5	4.8	5.0	0.150	1.638
6	F6	5.1	5.4	0.126	1.569
7	F7	4.5	4.9	0.1501	1.650
8	F8	4.6	5.4	0.224	1.830
9	F9	4.9	4.7	0.302	1.513

Table.7 Evaluation tests of Famotidine floating tablets

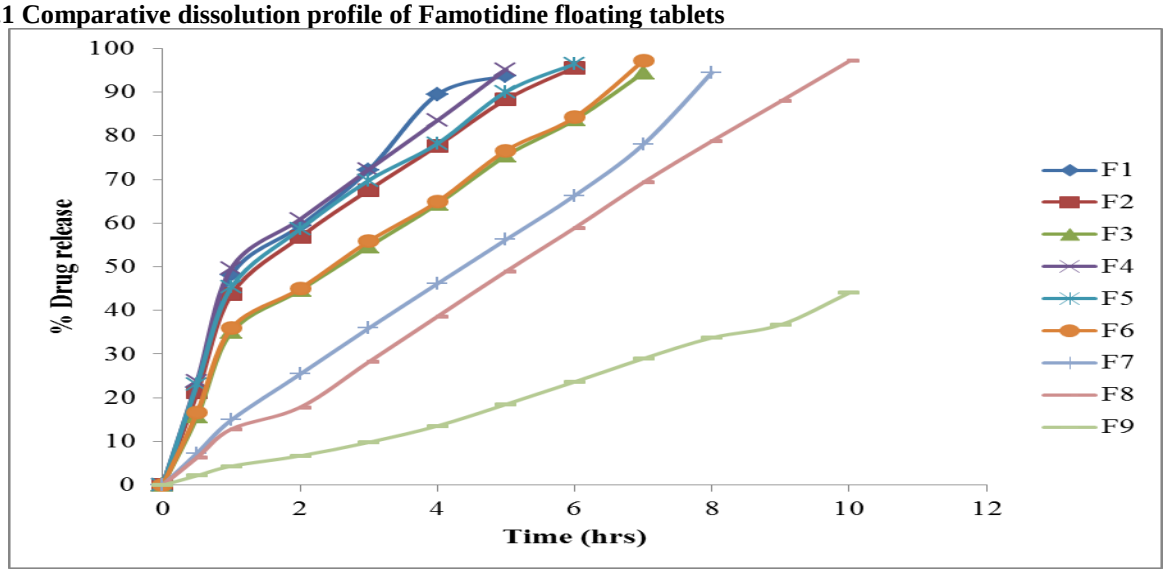
S.No	Formulation code	% Drug content	Floating lag time (min)	Total floating time (hrs)
1	F1	95.27	3.0	1.5
2	F2	98.60	3.5	2
3	F3	96.85	Fail	Fail
4	F4	96.32	4.0	2.5

5	F5	94.40	5.5	3
6	F6	93.80	Fail	Fail
7	F7	95.90	4.5	18
8	F8	99.40	3.5	24
9	F9	98.25	5.0	>24

Table.8 Comparative dissolution data of Famotidine floating tablets

S. No.	Time (hrs)	% Cumulative drug release								
		Formulation containing HPMC E 15			Formulation containing HPMC K4M			Formulation containing sodium alginate		
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0.5	22.27	21.17	15.72	23.76	23.16	16.60	7.32	6.32	2.17
2	1	48.10	43.70	35.02	49.67	45.34	35.92	14.92	12.85	4.35
3	2	59.40	56.82	44.62	60.87	58.60	45.02	25.40	17.80	6.70
4	3	72.17	67.60	54.62	72.27	69.77	55.84	35.92	28.21	9.80
5	4	89.47	77.70	64.35	83.50	78.20	64.92	46.12	38.60	13.55
6	5	93.65	88.30	75.42	95.22	90.07	76.62	56.22	48.95	18.50
7	6		95.62	83.65		96.42	84.24	66.30	58.90	23.65
8	7			94.42			97.20	78.01	69.30	28.97
9	8							94.50	78.80	33.75
10	9								87.90	36.72
11	10								97.11	44.05

Figure.1 Comparative dissolution profile of Famotidine floating tablets



Hardness test for all formulations was carried out and observations obtained were in the range of 4.5 to 5.1 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that crushing strength of all formulations was maintained after direct compression. The thickness of all formulations was found to be uniform as it was obtained in the range of 4.7 to 5.4 mm. Friability test was conducted for all formulations, % friability was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The % weight variation of all formulations was found to be in the range of less than 5%. None of the tablet was found to deviate from the average weight of tablets (variation with deviation less than ± 5, which complies with USP specification) signifies that there is uniformity in flow of powder blend which leads to uniform die fill (Table No.6). Drug content of all formulations was observed between 93.80 to 99.40%. Drug content for all formulations had shown uniformity which indicating that there was uniform flow and uniform distribution of drug. Floating lag time of all formulations was found between 3 to 5 min. Total floating time of all formulations was found between 1.5 to 24 hrs (Table No.7). *In vitro* dissolution revealed that Famotidine floating tablets prepared with sodium alginate showed better sustained drug release than Famotidine floating tablets prepared with HPMC E15 and HPMC K4M (Table No.8).

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