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Research Article

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS OF FAMOTIDINE USING NATURAL POLYMERS

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ABSTRACT
In the present investigation effervescent floating matrix tablets of famotidine are formulated to achieve gastric retention for a period of 8 to 10 hrs. Famotidine is H_2 receptor antagonist widely prescribed in gastric ulcer, Duodenal ulcer, Zollinger Ellison syndrome & Gastro-esophageal reflux disease. Famotidine has low oral bioavailability of 35% & short biological half life of 2 – 3 hrs. This favors development of sustained release dosage form. Besides this, it is primarily absorbed from stomach. Local delivery increase stomach wall receptor site bioavailability and increase efficacy of drug to reduce acid secretion. Hence the principle of Floating drug delivery system was applied to improve systemic as well as local drug delivery. Natural polysaccharides such as xanthan gum and chitosan were used to achieve sustained release of the drug. Thus it can be concluded that floating matrix famotidine tablets so formulated achieved desired gastric retention for 8 to 10 hrs and sustained the drug release. Thus one tablet daily is sufficient to reduce gastric acidity as compared to conventional tablets in hyperacidity conditions.
Keywords: Gastroretentive, Floating, Matrix, Zollinger-Ellison syndrome

INTRODUCTION

Floating drug delivery system is one of the approaches to increase the gastric residence time of the drug. The brief gastric emptying time in humans (2-3 hrs through the major absorption zone-stomach or upper part of the intestine) can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose.[1] Thus, placement of the drug delivery system in a specific region of the gastrointestinal tract offers numerous advantages, especially to the drugs having narrow absorption window in gastrointestinal tract, primary absorption in the stomach, stability problem in intestine, poor solubility at alkaline pH, local activity in stomach and property to degrade in colon.[2] Compounding the drugs with narrow absorption window in a unique pharmaceutical dosage form, which prolongs the gastric residence time would enable an extended absorption phase of these drugs.[3,4]

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastroretentive dosage forms which are the drug delivery systems that are designed to be retained in the stomach for a prolonged time and release their active materials and thereby enable sustained input of the drug to the upper part of the gastrointestinal tract.[5,6] Many approaches are utilized in the development of gastroretentive dosage forms viz., floating systems, swelling, expanding, high density, super porous hydrogels, bioadhesive, modified shape systems, ion exchange resin and by the simultaneous administration of drugs that delay gastric emptying. By utilizing one of these techniques, it is possible to deliver drugs which have narrow absorption window. [7,8]

This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper gastrointestinal tract can greatly improve their oral bioavailability and/or their therapeutic outcome. [9,10]

From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach in the development of gastroretentive dosage forms.[11,12] Floating drug delivery system float on the gastric fluid only when it has density less than that of gastric fluids, i.e. $<1 g/cm^3$. This system provides several advantages as prolonged gastric retention of drugs, improves bioavailability, reduces drug wastage and improves solubility for drugs that are less soluble in alkaline pH environment and provides local drug delivery to the stomach and proximal small intestine.[13,14,15]

MATERIALS & METHODS

The chemicals required for present investigation were obtained from following sources Famotidine was obtained from Glenmark Pharmaceuticals, Nashik. Chitosan and Xanthan gum from Technolabs, Mumbai, Sodium bicarbonate & Magnesium stearate from Loba Chemicals. Direct compression method was used for formulating tablets using multistation rotary punch tablet compression machine.

At the start of the investigation Spectroscopic study (UV, IR) was done to confirm no interaction between drug and polymer. The tablets containing varying concentration of effervescent agent sodium bicarbonate were prepared as shown in table no. 1 to achieve desired floating lag time (FLT) i.e the time required for the tablet to rise to the surface and afloat and total floating time (TFT) i.e the duration for which the tablet remains afloat on surface of solution was determined.[16,17] In the next step famotidine tablets were prepared using each single polymer and various ratios of combination of both polymers and drug as shown in table no. 2 by direct compression method.[18,19,20,21]

The powder blend was initially evaluated for angle of repose, bulk density, Carr's compressibility index. The matrix tablets were prepared by direct compression method using Multi station rotary punch tablet compression machine (A- Jaguar JMD-4-8). After compression, the tablets were evaluated for Appearance, Thickness, Hardness, Friability, Weight variation as shown in table no.3. Floating behavior & Swelling behavior as shown in table no. 4, Drug content, In vitro drug release as shown in table no. 5.[22,23]

RESULTS

Evaluation of floating properties of famotidine containing varying quantity of sodium bicarbonate

The table no. 1 illustrates floating characteristics of tablets with varying quantity of Sodium bicarbonate. The tablets prepared without Sodium bicarbonate (A1) did not show floating. Therefore Sodium bicarbonate was incorporated as a gas generating agent. The Sodium bicarbonate induces CO_2 gas generation in the presence of dissolution medium (0.1N HCl). The gas generated gets trapped into the gel formed by hydration of polymer thus, decreasing density of tablet below 1 gm/ml and the tablet becomes buoyant. From the overall study effect of Sodium bicarbonate on floating lag time and floating time, it was found that as the amount of Sodium bicarbonate increased the floating lag time decreased & floating time increased. At least 16% of Sodium bicarbonate was essential to achieve satisfactory in-vitro buoyancy (floating lag time 2-3 mins. and floating time >12 hrs). Further increase in the amount of Sodium bicarbonate causes a large amount of effervescence and pore formation. This leads to rapid hydration of hydrophilic matrix and thereby rapid erosion. Hence, 16% of Sodium bicarbonate per tablet was kept constant in further formulations.

Evaluation of powder blend of famotidine tablet containing different drug to polymer ratios

The powder blends were evaluated for angle of repose, Bulk Density, Tapped Bulk Density and Carr's index. These properties indicate the flow characteristics of the powder blend. The values of Bulk Density, Tapped Bulk Density were found to be in the range from 0.593 to 0.624 gm/ml and from 0.667 to 0.692 gm/ml respectively. The Carr's Compressibility indices were in the range of 08.99 % to 14.30 % and angle of repose were 27.12 to 31.32, this indicated good flow property for formulations.

Evaluation of famotidine tablet containing different drug to polymer ratios

Appearance The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

Weight Variation The weight of the tablets of different formulations varied with change in drug to polymer ratio. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation.

Thickness The thickness of tablets was measured using vernier calliper. The thickness of tablets was between 1.41 mm to 1.95 mm.

Hardness The Hardness of tablets was determined using Monsanto hardness tester. It was found in the range of 4.1- 4.7 kg/cm^2. Hardness values were satisfactory and indicated good mechanical strength of tablets.

Friability All the tablets showed loss of less than 1 % in weight which is considered acceptable.

Drug Content Drug content of all the tablets was found between 99 % to 101 % which is in limits of pharmacopeial specifications.

Evaluation of floating & swelling behavior of tablets containing different drug to polymer ratios

Floating Lag Time The floating lag time for all the formulations was tested in dissolution vessel containing 900 ml of 0.1N HCl solution. All the tablets showed floating lag time between 1-2 minutes.

Total Floating Time The floating time for all the formulations tested in dissolution vessel containing 900 ml of 0.1N HCl solution. All the tablets showed floating time of more than 12 hrs.

Swelling Index The tablets swelled 87.9 % to 99.5 % in the specific time period.

In-vitro dissolution profile of famotidine tablets containing different drug to polymer ratios

The figure no. 1 demonstrates the dissolution profiles of tablets F1, F2, F3, F4 and F5 in which Drug:Polymer (D:P) ratios are 1:1, 1:1.5, 1:2, 1:2.5, 1:3 respectively. Formulation F3 gave the best sustained release profile of Famotidine.

The comparative study of the dissolution profile of the marketed formulation with the floating matrix tablets of Famotidine as shown in figure no. 2 shows that the floating matrix tablets of Famotidine sustained the drug release for prolonged time period than the marketed formulation. The marketed formulation needs to be administered 2 to 3 times in a day. But the Famotidine Floating tablet can release drug for 12 hrs. hence one tablet daily is sufficient to reduce gastric acidity.

DISCUSSIONS

Oral sustained release dosage forms have been extensively used to improve therapy of many important medications. However, in case of narrow absorption window drugs, this pharmaceutical approach cannot be utilized. Floating drug delivery systems are designed to be retained in the stomach for a prolonged time and release their active materials and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract.

Famotidine, the drug used in present study, is a H_2 receptor antagonist & widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. It blocks the H_2 receptors present on the parietal cells in the stomach region. Thus local delivery of this drug to the receptor of parietal cell wall (stomach) is desired. Also it has low oral bioavailability of 30 % to 35 % & short biological half-life of 2.5 to 3.5 hrs. Hence, to improve patient compliance and to minimize the frequency of dosage as well as to improve therapeutic efficacy of drug it was decided to formulate the sustained release floating matrix tablet of Famotidine.

In the present work initially the physiochemical characterization of drug was carried out by determining its melting point, λmax (UV spectroscopy), IR spectroscopy, which complied with the result of official books. Drug polymer interaction study was carried out using FT-IR, which showed no drug polymer interaction. Evaluation of powder blends showed good flow properties and compressibility index. All the formulated tablets passed the official tests given in IP. Firstly the effect of Sodium bicarbonate on floating properties of Famotidine tablets was evaluated, it was found that 16% of sodium bicarbonate was necessary to achieve desired floating lag time (1-2 min.) and floating time (>12). Secondly, the effect of different polymer to polymer ratio on release of Famotidine from floating tablet was evaluated. After carrying out the dissolution study it was found that Chitosan:Xanthan gum in ratio 1:1 sustained the drug release for longer period of time. Hence this ratio was used for further study. Later Famotidine tablets were formulated using different drug to polymer ratio, to see the effect of increasing polymer concentration on drug release. & to find out the best combination of drug to polymer ratio which would sustain the drug release for the desired time period. It was found that Drug to polymer ratio of 1:2 gave desired floating properties as well as gave constant drug release for 12 hrs.

Finally, it is concluded that Famotidine can be formulated with Chitosan and Xanthan gum polymers to achieve gastric retention and sustained release by employing direct compression technique.

FUTURE PROSPECTS

In the present work the floating tablets of Famotidine were formulated using natural gums such as Chitosan and Xanthan gum by direct compression method. In this work only physiochemical characterization, formulation and *in-vitro* evaluation of floating tablets of Famotidine was done. Along with *in-vitro* release study *in-vivo* release behavior of drug is also important. So in future *in-vivo* release study using different models are required to set the *in-vitro in-vivo* correlation which is necessary for development of successful formulation and also long term stability studies are necessary.

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Table No. 1 Evaluation of Floating Properties of Famotidine Containing Varying Quantity of Sodium bicarbonate

Formulations	Floating Lag Time (mins.)	Total Floating Time (hrs.)
A1	No floating	-
A2	12 ± 0.55	8 ± 0.22
A3	06 ± 0.42	10 ± 0.25
A4	02 ± 0.65	12 ± 0.12
A5	01 ± 0.78	10 ± 0.35

Table No. 2 Formulae for the Preparation of Powder Blend of Famotidine Tablet Containing Different Drug to Polymer Ratios

Ingredients (mg/tablet)	Formulations				
	F1(1:1)	F2(1:1.5)	F3(1:2)	F4(1:2.5)	F5(1:3)
Famotidine	40	40	40	40	40
Chitosan	20	30	40	50	60
Xanthan gum	20	30	40	50	60
Sodium bicarbonate	12.8	16	19.2	22.4	25.6
Magnesium stearate	0.82	1.16	1.39	1.62	1.85

Table No. 3 Evaluation of Famotidine Tablet Containing Different Drug to Polymer Ratios

Parameters	Thickness (in mm)	Wt.Variation (mg)	Hardness (kg/cm^2)	Friability (%)	*DrugContent* (%)
Formulations	(mean ± S.D., n = 3)				
F1	1.41 ± 0.025	100.9 ± 0.56	4.1 ± 0.15	0.74 ± 0.09	99.62 ± 0.54
F2	1.59 ± 0.03	116.1 ± 0.44	4.2 ± 0.63	0.67 ± 0.05	100.20 ± 0.45
F3	1.68 ± 0.015	139.4 ± 0.65	4.3 ± 0.34	0.61 ± 0.07	99.96 ± 0.67
F4	1.83 ± 0.02	162.6 ±0.43	4.5 ± 0.56	0.56 ± 0.06	99.42 ± 0.55
F5	1.95 ± 0.05	185.8 ± 0.32	4.7 ± 0.24	0.45 ± 0.04	99.14 ± 0.78

Table No. 4 Evaluation of Floating & Swelling Behavior of Famotidine Tablets Containing Different Drug to Polymer Ratios

Parameters	Floating Lag Time (min.)	Total Floating Time (min.)	Swelling Index (%)
F1	1.06 ± 0.45	10.30 ± 0.35	87.9 ± 0.45
F2	1.15 ± 0.66	11.45 ± 0.25	90.8 ± 0.45
F3	1.22 ± 0.55	12.30 ± 0.42	95.6 ± 0.45
F4	1.36 ± 0.88	12.15 ± 0.54	97.9 ± 0.45
F5	1.44 ± 0.54	12.20 ± 0.22	99.5 ± 0.45

Table No. 5 Cumulative % Release of Famotidine from Tablets Containing Different Drug to Polymer Ratios

Time (hr)	Cumulative % Release of Famotidine (mean ± S.D., n = 3)				
	Formulations				
	F1	F2	F3	F4	F5
1	24.75±0.55	22.80±0.56	12.85±0.98	09.59±0.66	07.65±0.88
2	39.80±0.88	29.26±0.65	21.40±0.66	19.20±0.76	14.63±0.67
3	55.35±0.78	40.24±0.55	38.45±0.65	31.09±0.68	18.31±0.78
4	61.71±0.45	46.36±0.66	45.39±0.46	38.38±0.56	26.24±0.55
5	72.50±0.77	58.69±0.22	56.87±0.88	48.19±0.45	35.33±0.44
6	79.94±0.55	68.01±0.46	68.28±0.76	55.31±0.65	45.95±0.56
7	84.58±0.66	82.56±0.78	78.29±0.66	63.34±0.54	52.71±0.76
8	95.92±0.35	93.97±0.89	84.77±0.45	73.72±0.78	58.61±0.66
9	99.36±0.22	98.16±0.45	94.60±0.34	79.65±0.66	65.75±0.45
10	99.96±0.36	99.94±0.98	96.68±0.56	84.81±0.55	69.32±0.89
11	-	100.08±0.85	98.27±0.55	86.61±0.42	77.14±0.86
12	-	-	99.87±0.78	88.35±0.89	81.66±0.56

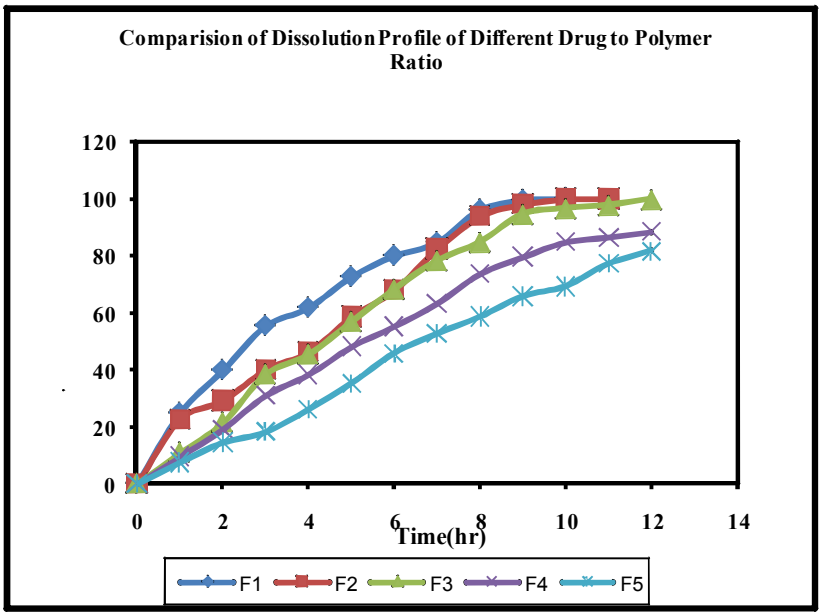

Figure No. 1 CUMULATIVE % DRUG RELEASE

The following figure no. 1 shows the comparative release of Famotidine from all formulations. Formulation F3 gave more constant release and for desired period of time, hence it was considered as optimized formulation

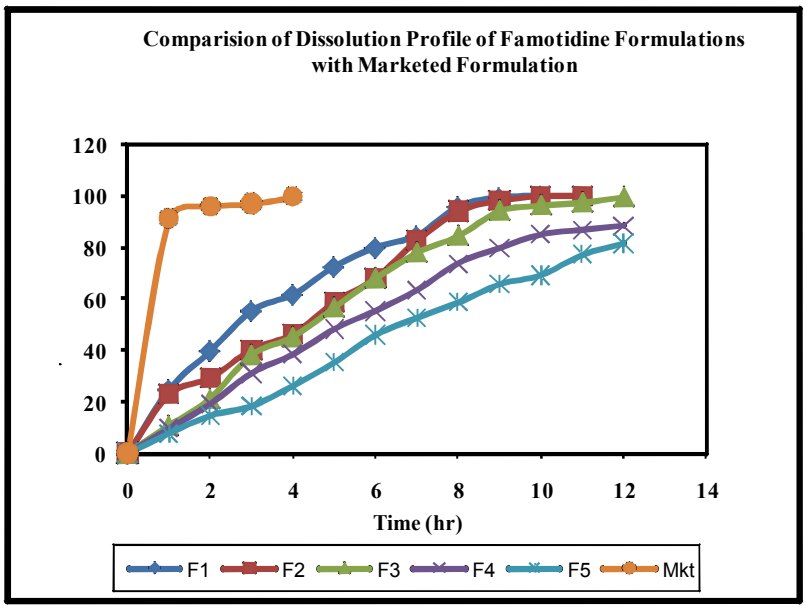

Figure No. 2 COMPARISION OF DISSOLUTION PROFILE OF FAMOTIDINE WITH MARKETED FORMULATION

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