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PREPARATION AND EVALUATION OF A GAS FORMATION-BASED MULTIPLE UNIT GASTRO RETENTIVE FLOATING DRUGDELIVERY SYSTEM OF FAMOTIDINE

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ABSTRACT

Gastro retentive Famotidine floating mini-tablets-in-capsule were prepared using three different natural polymers HPMC K4M, HPMC K15M and Guar gum in different ratios by direct compression method in order to achieve maximum local bioavailability. Buoyancy of mini-tablets was achieved for about 12 hours by an addition of optimized gas generating mixture consisting of sodium bicarbonate and citric acid to the formulations. The prepared mini-tablets were evaluated for various precompression parameters i.e., angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio including Drug Excipients compatability studies by using FT-IR studies. The prepared formulations were evaluated for various post compression parameters like weight variation, thickness, friability, hardness, floating lag time, floating buoyancy studies and in-vitro dissolution studies. The *In-vitro* dissolution data confirmed the success of the optimized formula F5, which contains HPMC K15M, has shown desired percentage drug release in 12 hours. The release of drug from optimized formulation followed Fickian diffusion. FT-IR studies indicated that there is no positive evidence for the interaction between Famotidine and excipients of the optimized formula. Famotidine floating mini-tablets based on HPMC K15M is a promising formulation as an effective anti-ulcerative. The developed formulation overcome and alleviates the drawback and limitation of conventional dosage forms.

Keywords: Gastro retentive; Floating; Mini-tablets; Famotidine; Hydroxypropylmethylcellulose (HPMC); FT-IR.

INTRODUCTION

Oral sustained release dosage forms deliver the drug for longer period and helps in producing the therapeutic effect for 24 h for those drugs which are having low plasma half life. Drugs that have narrow absorption window in the gastro intestinal tract (GIT) will have poor absorption (1,2). For these drugs, gastroretentive drug delivery systems (GRDDSs) have been developed. Oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract (3). GRDDSs help in maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy and thereby reduce the total dose of administration.

Recently several gastroretentive approaches like swelling devices (4,5), floating systems (2,6), bioadhesive systems (7), low density systems (8), high density systems (9), expandable systems (10), superporous, biodegradable hydrogels (2,11,12), and magnetic systems (13) have been developed. To increase the gastric retention time (GRT), one should have a thorough knowledge about the physiology of GIT, and all the limitations should be well understood. To justify the in vitro studies, in vivo studies must be conducted.

The excellent floating system is effective only in the presence of sufficient fluid in the stomach; otherwise, buoyancy of the tablet may be hindered. This limitation can be overcome by using a combination

of a floating system with other gastroretentive approaches. GRDDSs are formulated as floating microparticles, tablets, pellets, capsules, etc. among which the multiparticulate systems are more effective than the single unit dosage forms.

Famotidine is histamine receptor (H2) antagonist used in a treatment of zollinger ellision syndrome, gastro esophageal reflux disease and peptic ulcer in the dose ranging from 10 to 80 mg.[13] Half life of a drug is about 2.5−3.5 h and the oral bioavailability is 45 ± 14% indicating its promising candidature for sustained release formulation.[14] Oral treatment of gastric disorders with H2 receptor antagonist such as famotidine or ranitidine in combination with antacids promotes local delivery of these drugs to the receptor of parietal cell wall. Local delivery also increases a bioavailability and the efficacy of drug to reduce acid secretion.[15]

In the present investigation floating tablets of Famotidine by direct compression technique using varying concentrations of different grades of polymers (HPMC K4 M and HPMC K15 M) and Guar gum with sodium bicarbonate and citric acid were evaluated for their gel forming and release controlling properties. The aim of the work was to evaluate the effect of gel forming polymer on floating properties and release characteristics of Famotidine tablets.

MATERIALS AND METHODS

Materials

Famotidine was received as a gift sample from Nulife Pharmaceuticals Ltd, Pune, India. Hydroxypropyl methylcellulose K4M (HPMC K4M) was obtained from Signet Chem. Products, Mumbai, India. Sodium bicarbonate and magnesium stearate were obtained from Loba Chemie Pvt.Ltd, Mumbai, India. Lactose and talc were obtained from Chemdyes Corporation, Ahmedabad, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Methods

Formulation of floating tablets of Famotidine:

The composition of different formulations of Famotidine floating tablets are shown in Table no 10**.** Famotidine, HPMC K4M, HPMC K15M, Guar gum were passed through sieve no. 80 separately. Sodium bicarbonate was passed through sieve no. 44. All the ingredients were mixed in the proportions as shown in Table 10. The powder blends were lubricated with Magnesium stearate and Talc and mixed for two to three minutes. These lubricated blends were compressed into tablets using 4 mm punch on a multiple punch rotary tablet machine. The compression force was adjusted to obtain tablets with hardness in the range of 4.5 to 5 kg/cm. Each mini tablet contained 50 mg. Mini tablets were placed in capsule, each capsule containing 4 tablets and capsule size is Zero. Prior to compression, powder blends were evaluated for pre-compression parameters like Hausner's ratio [tapped/bulk density ratio using a tapped volumeter apparatus (Copley Scientific, UK)], Carr's compressibility index, and static angle of repose. To measure the angle of repose, 10 gm of powder was poured through a glass funnel onto a flat surface and the angle to the horizontal was measured. The measurements were performed in triplicate.

Characterization of tablets

Physical properties of the tablets were determined according to the USP 24 methods [5]. Weight variation was performed on 20 tablets selected at random. Hardness of the tablets was measured by recording the force to fracture a tablet on a hardness tester for 6 tablets from each formulation (SCHNEUNIGER). Friability was determined using Roche Friabilator for 20 tablets at 100 rpm for 4 minutes.

Drug content

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopeia. This test is performed by taking twenty tablets were selected randomly, weighed and powdered. A quantity of powdered tablet equal to 40 mg of Famotidine was dissolved in 0.1 N HCL in 100ml volumetric flask. The so formed sample was diluted and the absorbance was measured at 288 nm using 0.1 N HCL as blank.

***In vitro* dissolution studies:**

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Labindia) rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium (900ml). It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Famotidine at 288 nm by using a double beam UV spectrophotometer (Labindia-3000). Each dissolution study was performed for three times and the mean values were taken.

***In vitro* Buoyancy study**

In vitro Buoyancy was determined by floating lag time as per method prescribed by (Roasa M, Zia H,Rhoeds T 1994) the tablet was placed in a 100ml beaker containing 0.1N Hcl. The time required for the tablet raise to surface and float was determined as floating lag time.

Preliminary screening

Preliminary screening was performed to optimize amount of sodium bicarbonate and total amount of polymer in a formulation. Tablets were prepared by direct compression method using 20% of total concentration of polymers and varying amount of sodium bicarbonate (5%, 10%, 15%) as shown in Table 1. Prepared tablets were tested for in vitro buoyancy studies and intactness. Tablets were prepared using 10% of sodium bicarbonate and varying amount (10%, 20%, 30%) of polymer (HPMC K15M, HPMC K4M and Gaur gum) as shown in Table 2. Tablets prepared with varying amount of polymer were tested for in vitro buoyancy studies, intactness and in vitro drug release.

Kinetic modeling of dissolution data

Dissolution profile of all batches were fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsemeyer, and Peppas to ascertain kinetics of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release.

RESULTS AND DISCUSSION

The powder blends of floating tablets were evaluated for their flow properties, the results were shown in Table 3. Angle of repose was in the range from 24.8 to 27.74 which indicates good flow of the powder for all formulations. The values of bulk density were found to be in the range from 0.48±0.08 to 0.57±0.05 gm/cc; the tapped density was in the range of 0.56±0.05 to 0.66±0.07 gm/cc. The Carr's index was found to be in the range from 12.29±0.07 to 17.24±0.04, the Hausner's ratio was found to be in the range less than < 1.20. These values indicate that the powdered blend exhibited good flow properties and have good compressibility.

The prepared tablets were subjected to various evaluation parameters like hardness, friability, weight variation, drug content estimation, floating lag time and total floating time results as shown in table 4. The thickness of floating tablets was measured by vernier callipers and was ranged between 4.01±0.11 and 4.89±0.03 mm. The weight variation for different formulations (F1 to F12) showed satisfactory results as per United States Pharmacopoeia (USP) limit (average weight ± 7.5%). The hardness of the floating tablets was measured by Monsanto tester and was found to be ranged from 4.1 ± 0.10 to 4.9 ± 0.27 kg/cm2. The friability was found in be ranged from 0.47 to 0.68 which was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F12 was found to be in between 95.5 ± 0.58 to 103.3 ± 0.46 of Famotidine. In vitro buoyancy studies indicated that the formulations containing Sodium bicarbonate showed decrease in floating lag time. The generated gas was entrapped into the matrix of swollen polymer matrix and was well protected by gel formed by hydration of polymers, which led to floating of the dosage forms. All the prepared batches shows the total floating time more than 12 hours except the F1, F3,F4,F7 and F10 batches shows only more than 6 hours.

In vitro drug release studies exhibited a decrease drug release with an increase in polymer concentration which may be due to increase in viscosity of the gel as well as the gel layer with longer diffusional path. The variation in drug release was due to different types of polymers and different concentrations of polymer in all the formulations. Among these formulations (fig.1), formulation F5 gave desired release in first hour for loading dose and also retarded the drug release for 12 hours (98.75%). Hence, the formulation F5 was considered as most promising formulation among all the formulations. The release data of optimized formulation (Table no .5) seem to fit better with the zero order and higuchi model.

CONCLUSION

From the results of the study it is evident that the gastro retentive floating tablets of Famotidine can be successfully developed by using cellulose derivatives in combination with gas generating agents and this would be a feasible alternative to conventional oral dosage form of Famotidine in order to retain the drug at the site of its absorption and to increase the bioavailability of the drug thereby reducing dose or dosing interval.

Table No 1: Optimization of gas generating agent

Ingredients	F1	F2	F3
Famotidine	40	40	40
HPMC K15 M	40	40	40
NaHCO3	5	10	15
Citric acid	5	5	5
Mg.stearate	5	5	5
Talc	5	5	5
MCC pH 102	QS	QS	QS

Table No 2: Composition of different floating tablet formulations of Famotidine

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Famotidine	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K4M	20	40	60	-	-	-	-	-	-	20	-	20
HPMC K15M	-	-	-	20	40	60	-	-	-	20	20	-
Guargum	-	-	-	-	-	-	20	40	60	-	20	20
$NaHCO_3$	15	15	15	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

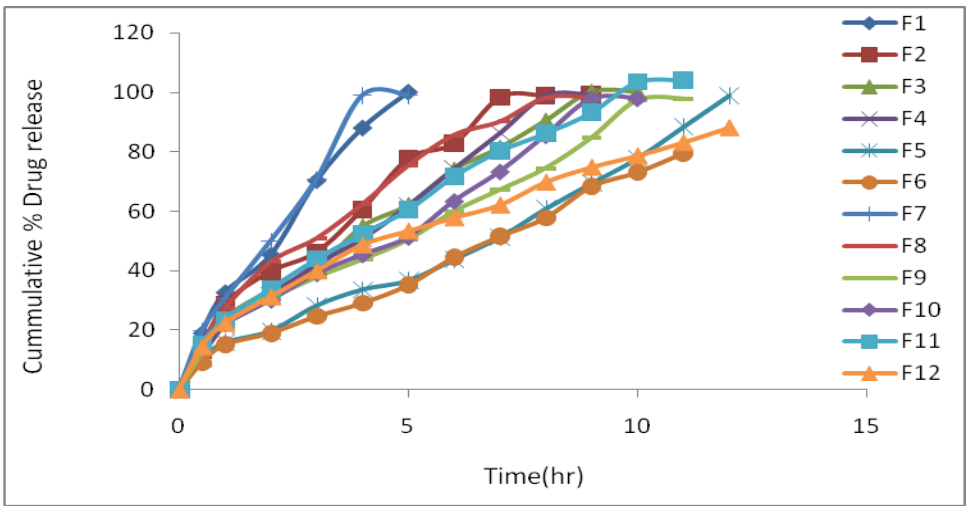

Fig .1 Percentage of drug release of Famotidine

Table No 3: Pre compression Flow Properties of Famotidine

Formulation code	Angle of repose (Ɵ)	Bulk density(gm/cm 3) /cm3) (gm/cm3)	Tapped density(gm/cm3)	Carr's index (%)	Hausner's ratio (HR)
F1	26.01	0.48±0.06	0.58±0.02	17.24±0.04	1.20±0.05
F2	24.8	0.54±0.02	0.63±0.04	14.28±0.06	1.16±0.06
F3	27.74	0.53±0.04	0.62±0.06	14.51±0.02	1.16±0.04
F4	25.33	0.55±0.05	0.63±0.07	12.29±0.07	1.12±0.05
F5	26.24	0.50±0.07	0.61±0.08	18.0±0.06	1.22±0.03
F6	26.12	0.55±0.04	0.63±0.05	12.69±0.05	1.17±0.09
F7	27.08	0.57±0.05	0.66±0.07	13.63±0.04	1.18±0.03
F8	25.12	0.49±0.06	0.59±0.03	16.94±0.03	1.18±0.09
F9	25.45	0.53±0.07	0.63±0.04	15.87±0.08	1.17±0.02
F10	26.14	0.52±0.08	0.61±0.06	14.75±0.07	1.17±0.03
F11	25.89	0.48±0.08	0.56±0.05	14.28±0.05	1.16±0.06
F12	24.78	0.51±0.08	0.60±0.08	15.02±0.03	1.18±0.05

Table No 4 : Post Compression Properties Famotidine of Floating Tablets

Formulation Code	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug Content (%)	Weight variation(mg)
F1	4.81±0.03	4.4±0.21	0.50	99.89±0.75	199.6±0.89
F2	4.85±0.04	4.3±0.22	0.53	98.93±0.71	195±1.22
F3	4.79±0.05	4.4±0.20	0.48	102.63±0.42	198.8±0.14
F4	4.86±0.06	4.2±0.06	0.64	95.56±0.58	199.8±0.88
F5	4.89±0.03	4.3±0.11	0.48	106.96±0.57	204.7±1.18
F6	4.5±0.01	4.6±0.21	0.68	101.5±0.65	201.8±0.80
F7	4.7±0.02	4.1±0.29	0.47	98.7±0.50	202.05±1.17
F8	4.80±0.05	4.8±0.27	0.64	99.51±0.55	197.85±1.10
F9	4.83±0.9	4.6±0.16	0.55	98.9±0.47	200.24±0.63
F10	4.25±0.14	4.1±0.10	0.59	103.3±0.46	203.78±0.58
F11	4.12±0.13	4.3±0.13	0.49	101.1±0.47	204.56±0.89
F12	4.01±0.11	4.5±0.11	0.52	99.5±0.42	201.25±0.45

Table no 5: Release kinetic models of optimized formulation (f5).

S.No	RELEASE KINETIC MODELS	REGRESSION COEFFICIENT (R^2)
1	Zero Order Release	0.982
2	First Order Release	0.861
3	Higuchi Model	0.984
4	Korsemeyer-Peppas Model	0.969

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