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Der Pharmacia Lettre, 2009, 1 (2) 102-114
(<http://scholarsresearchlibrary.com/archive.html>)



ISSN 0975-5071

Studies on formulations and evaluation of floating tablets containing anti-ulcer drugs

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Abstract

Floating drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Different approaches for gastroretentive dosage forms include floating, raft, expanding or swelling, bioadhesive or mucoadhesive and high/low-density systems. Famotidine, an anti-ulcer drug, suffers from poor bioavailability (50%), as famotidine is very less soluble in alkaline P^H. Famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases bioavailability at the stomach wall receptor site and increases the efficacy of drugs to reduce acid secretion. Thus, the present work is aimed to formulate floating tablets of famotidine using an effervescent approach for gastroretentive drug delivery system. Floating tablets were prepared using directly compression technique using polymers like HPMC K4M and HPMCK100M for their gel-forming properties. The HPMC alone polymer unable to controlled on release rate it release drug >90% in 4-6 hrs while in combination with Xanthan gum it release >90% in 8 hrs. The results indicate that gas powered gastroretentive floating Tablets of famotidine containing 40mg HPMCK100M and Xanthan gum provides a better option for controlled release action and improved bioavailability.

Key words: Famotidine, HPMC K4M, HPMC K100M, Gastric residence time, Swelling index.

Introduction

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit

time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed¹. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine). The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS). To date, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit hydro dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems. The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions. Recently, various efforts are being made to design gastro retentive systems such as, floating, swelling and expanding, bioadhesive/mucoadhesive, modified shape, low density/high density and raft systems etc. These systems are advantageous in improving GIT absorption of drug with CR due to specific site absorption limitations. Famotidine is a histamine H₂-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The recommended adult oral dosage of famotidine is 20 mg twice daily or 40 mg once daily. The effective treatment of erosive esophagitis requires administration of 20 mg of Famotidine 4 times a day. a conventional dose of 20 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 40 mg leads to plasma fluctuations; thus a sustained release dosage form of famotidine is desirable. The short biological half-life of drug (~2.5-4 hours) also favors development of a sustained release formulation. The gastro retentive 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 the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. The objective of the present study was preparation and evaluation of floating tablet of famotidine based on low density polymer that

retains the dosage form in the stomach. Provide an increased gastric residence time resulting in prolonged drug delivery in gastrointestinal tract using HPMCK4M, HPMCK100M and Xanthan gum as sustain release polymers. To study the various formulation and process variables that ultimately affects the drug release. Selection and optimization of polymer concentration, type of filler and amount of low density polymer that has pronounced effect on tablet properties and drug release profile as well as buoyant properties of the formulations.

Materials and Methods

Famotidine was procured by Micro lab, Hosur, HPMC K4M, HPMC K100M, Xanthan gum were gifted by Colorcon Asia Pvt. Ltd., Goa, Sodium bicarbonate, Citric acid (anhydrous), Polyvinylpyrrolidone-k-30 procured by Nice chemicals laboratory, Avicel PH-102 was gifted by Signet Chem. Ltd, Mumbai, Talc, Magnesium Stearate, Hydrochloric acid LR procured by Loba Chemie.

Preparation of gastro retentive floating tablets

Floating tablets containing Famotidine were prepared by direct compression technique using variable concentrations of HPMC K4M, HPMCK100M, and Xanthan gum with sodium bicarbonate. Different tablets formulations were prepared by direct compression technique. All the powders were passed through 60 mesh sieve. Required quantity of drug, and low-density polymer were mixed thoroughly.

All quantities were in milligrams, # All the batches contained 1% w/w talc and 0.5% w/w magnesium stearate

Table 1→ Composition of Famotidine Floating Tablets

INGREDIENTS	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
Famotidine	40	40	40	40	40	40	40	40	40	40
HPMC K4M	40	-	-	-	80	-	40	-	40	20
HPMC K100M	-	40	-	80	-	-	40	40	-	40
Xanthan gum	-	-	40	-	-	80	-	40	40	20
Sodium bicarbonate	20	20	20	20	20	20	20	20	20	20
Citric acid (anhydrous)	10	10	10	10	10	10	10	10	10	10
PVP-K-30	20	20	20	20	20	20	20	20	20	20
Avicel PH-102	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2

Talc and magnesium stearate were finally added as glident and lubricant respectively. The blend was directly compressed (9mm diameter punches) using tablet compression machine. Each tablet contained 40mg of famotidine and other pharmaceutical ingredients as listed in table 6 in each section.

Evaluation of tablets

⇒ *Weight variation test*

To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

⇒ *Drug content*

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1 N HCl, the drug content was determined measuring the absorbance at 266.2 nm after suitable dilution using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer.

⇒ *Hardness*

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets were determined.

⇒ *Thickness*

The thickness of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated.

⇒ *Friability Test*

The friability of tablets were determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_{initial}) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by –

$$\%F = 100 (1 - W_0/W)$$

% Friability of tablets less than 1% are considered acceptable.

⇒ *Tablet Density*

Tablet density is an important parameter for floating tablets. The tablet will float when its density is less than that of 0.1N HCL (1.004). The density was determined using following formula.

$$V = \pi r^2 h$$
$$d = m/v$$

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (cm)

m = mass of tablet

In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time method described by Dave B.S.⁶⁰ The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

In Vitro dissolution studies

The release rate of famotidine from floating tablets was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at $37 \pm 0.5^\circ\text{C}$ and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 266.2 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Swelling index

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index } WU = \frac{(W_1 - W_0)}{W_0} \times 100$$

Where, W_t = Weight of tablet at time t.
 W_0 = Initial weight of tablet

Effect of hardness on Buoyancy Lag Time:-

Formulation FT10 was selected to study the effect of hardness on buoyancy lag time. The tablets of batch 10 were compressed at different compression pressures to get the hardness of 5kg/cm^2 , 6kg/cm^2 , 7kg/cm^2 , 8kg/cm^2 and 9kg/cm^2 . The tablets were evaluated for Buoyancy Lag Time. The method followed is same as that of Buoyancy test.

Results and Discussion

Hydrodynamically balanced tablets of famotidine (gastroretentive drug delivery systems) were prepared and evaluated to increase its local action and bioavailability. In the present study, 10 formulations with variable concentration of polymer were prepared and evaluated for physico-chemical parameters, invitro buoyancy studies, invitro release studies and stability studies.

Preformulation studies:**⇒ Melting Point Determination:**

Melting point of famotidine was found to be in the range 162-164°C, which complied with BP standards, indicating purity of the drug sample.

⇒ Solubility:

Famotidine was found to be soluble in water, 0.1N HCL, and practically insoluble in ethanol (95%), chloroform and ether.

Evaluation of tablet formulations:**1. Pre-compression Parameters:**

- a. *Angle of Repose (θ):*- The angle of repose for the formulated blend was carried out and the results were shown in table 2. It concludes all the formulations blend was found to be in the range 24⁰.88' to 29.30'.
- b. *Compressibility Index:* - Compressibility index was carried out, it found between 12.34% to 16.30% indicating the powder blend have the required flow property for compression.

2. Post-compression Parameters:**a) Shape of the tablet:-**

Microscopic examinations of tablets from FT1 to FT10 were found to be circular shape with no cracks.

b) Hardness test:-

The measured hardness of tablets of each batch ranged between 4.3 to 6.4 kg/cm². This ensures good handling characteristics of all batches.

c) Friability Test:-

The values of friability test were tabulated. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

d) Weight Variation Test:-

The percentage weight variations for all formulations were tabulated. All the formulated (FT1 to FT10) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of $\pm 7.5\%$ of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

e) Drug Content Uniformity:-

The percentage of drug content for FT1 to FT10 was found to be between 97.11% to 99.69% of famotidine, it complies with official specifications.

) Tablet density:-

When tablet contacts the test medium, tablet expanded (because of swellable polymers) and there was liberation of CO₂ gas (because of effervescent agent, NaHCO₃). The density decreased due to this expansion and upward force of CO₂ gas generation. This plays an important role in ensuring the floating capability of the dosage form.

To provide good floating behavior in the stomach, the density of the tablets should be less than that of the gastric contents the density below (1.004 g/cm³) than of gastric fluid. For formulation FT1-FT10 density were found to be less than that of the gastric content.

In vitro Buoyancy Study:-

On immersion in 0.1N HCl solution pH (1.2) at 37⁰C, the tablets floated, and remained buoyant without disintegration. Table shows the results of Buoyancy study and Fig shows Buoyancy character of prepared tablet.

From the results it can be concluded that the batch containing only HPMC polymer showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation containing HPMC K4M, HPMC K100M and Xanthan gum showed good BLT of 45 sec, while the formulation containing Xanthan gum(alone) did not float more than 1.5 hrs. This may be due to the nature of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

Swelling Study:-

Swelling study was performed on all the batches (FT1 to FT10) for 5 hr. The results of swelling index against time (hr) plotted in Fig. 3

From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch FT10 containing HPMC K4M, HPMC K100M and Xanthan gum having nominal viscosity of more than 1, 04,000 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

Effect of hardness on Buoyancy Lag Time:-

The effect of hardness on buoyancy lag time for batch FT10 was studied. The results of floating lag time of tablets with hardness of 4 kg/cm², 5kg/cm², 7kg/cm² and 8 kg/cm² were 47,58,76,89 and 186 sec respectively, Buoyancy lag time (sec) V/s hardness (kg/cm²) plotted and shown in Fig. 1.

Buoyancy of the tablet were influenced by both the swelling of the hydrocolloid particle on surface when it contacts the gastric fluid which in turn results in an increase in the bulk volume and porosity buoyancy lag time will increases when the hardness increases, at high compressed, reduces of porosity of tablets occurs, the compacted hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablet reaches the gastric fluid and as a result, the capability of the tablet to float is significantly reduced.

Table 2 → Micromeritic properties of powder blend

Powder blend	Angle of Repose ($^{\circ}$)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Total Porosity (%)
FT1	24°.30'	0.130	0.155	16.13	15.78
FT2	26°.77'	0.110	0.130	15.67	20.00
FT3	25°.28'	0.090	0.102	14.48	37.50
FT4	28°.56'	0.105	0.126	16.30	26.31
FT5	29°.88'	0.129	0.146	15.41	27.77
FT6	25°.30'	0.114	0.135	14.30	12.50
FT7	26°.47'	0.132	0.148	12.76	35.00
FT8	24°.28'	0.135	0.154	13.47	13.04
FT9	26°.56'	0.144	0.162	12.34	20.83
FT10	28°.88'	0.106	0.120	15.91	10.00

Table 3 → Evaluation of Physical Parameters of Floating Tablets

Tablets Batch	Weight variation test (%)	Friability (%)	Hardness (kg/cm²)	Thickness (mm)	Drug content (%)
FT1	± 1.75	0.92	5.6 ±0.47	3.08 ± 0.2	98.02
FT2	±3.52	0.72	4.5 ±0.63	3.16 ±0.010	97.01
FT3	±2.15	0.91	6.4 ±1.27	3.14 ±0.012	99.53
FT4	±1.56	0.86	5.1 ±0.03	3.12 ±0.06	98.01
FT5	±3.54	0.79	4.3 ±0.83	3.16 ±0.011	97.04
FT6	±1.42	0.86	5.1±0.03	3.18 ±0.012	98.40
FT7	±2.11.	0.78	4.3 ±0.83	3.15 ±0.010	97.11

FT8	± 1.89	0.81	6.4 ± 1.27	3.10 ± 0.012	99.55
FT9	± 2.56	0.96	5.1 ± 0.03	3.11 ± 0.06	99.01

Table 4 → Effect of different polymers on drug release by paddle method

Cumulative % Drug release										
Time (hrs)	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	49.19	40.30	37.41	31.44	46.66	34.51	39.47	26.66	30.66	27.09
2	58.92	52.35	42.36	48.91	69.47	46.85	56.52	36.59	44.31	45.68
3	87.47	65.94	57.71	66.18	76.41	56.61	68.48	51.56	57.96	65.51
4	99.68	76.14	67.49	79.62	81.56	64.17	71.83	67.34	63.49	77.48
5	-	89.57	73.06	83.67	89.58	74.90	91.35	80.11	70.06	81.80
6	-	101.16	80.84	88.04	101.83	82.62	100.16	92.02	81.34	89.07
7	-	-	90.07	100.1	-	89.98	-	100.30	92.07	98.12
8	-	-	97.98	-	-	95.35	-	-	98.18	100.36
FLT (sec.)	175	102	NO	95	136	NO	100	78	190	45
TFT (hrs)	8	8	NO	12	12	NO	>12	6	8	>12
FT10	± 2.04		0.75		4.3 ± 0.83		3.20 ± 0.011		99.69	

All the values are expressed as mean \pm SE.**Table 5** → Effect of hardness on Buoyancy Lag Time of formulation FT10

Hardness in kg/cm^2	Buoyancy Lag Time (sec)
4	47
5	58
6	76
7	89
8	186

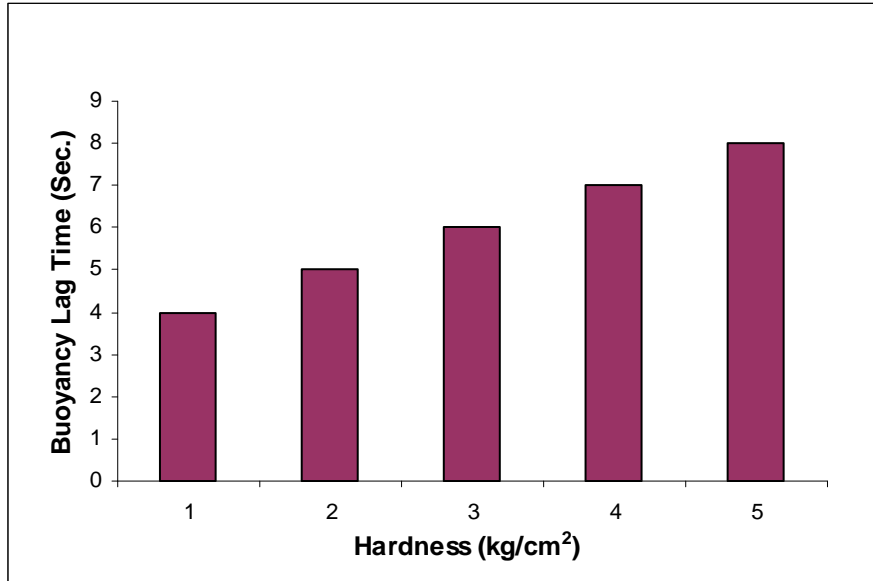


Fig 1: Plot of hardness v/s buoyancy lag time

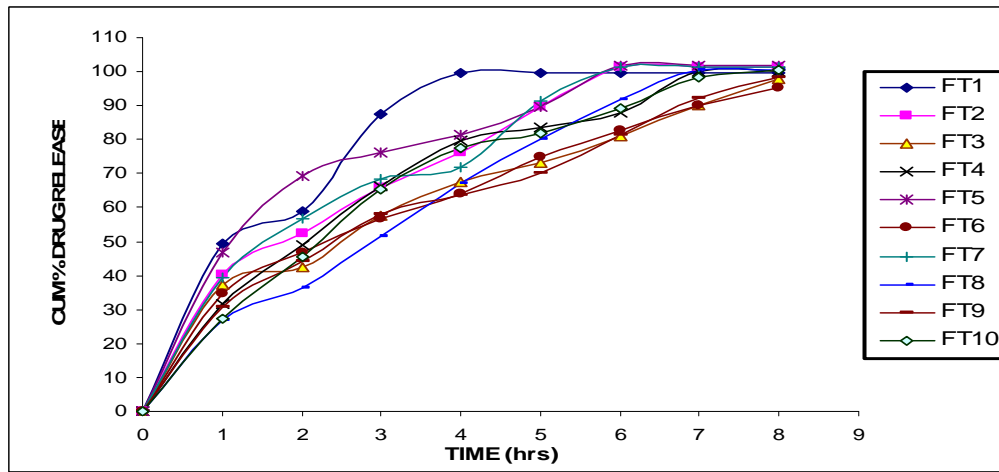


Fig 2: *In-vitro* dissolution profile for tablets of batches ft1 to ft10 (using dissolution apparatus)

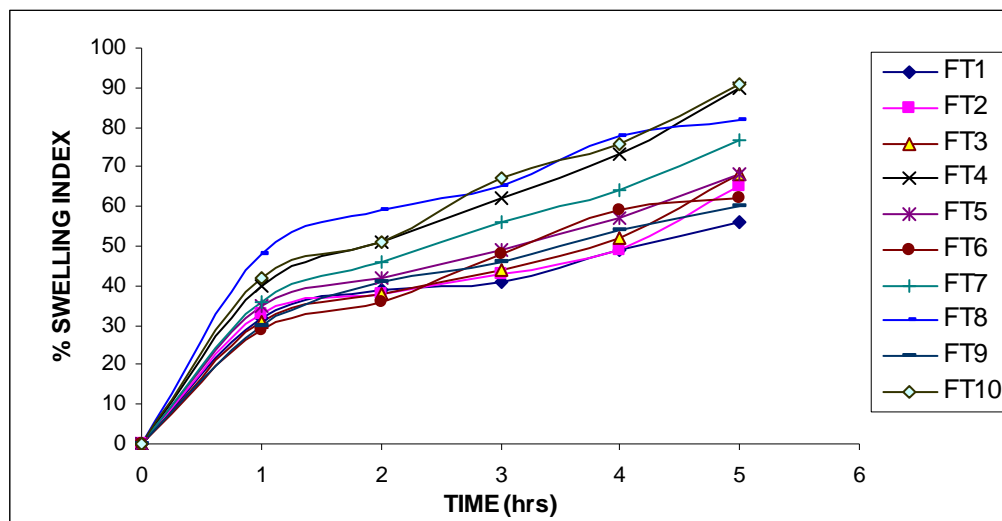


Fig: 3 swelling index for tablets of batch ft1 to ft10

Conclusion

The aim of the study was to develop and physico-chemically characterized gastro retentive matrix tablet of Famotidine based on a low density polymer. Famotidine has a short biological half-life (2.5–4hours) and 50 % absolute bioavailability. Development of sustained release formulation of Famotidine can be advantageous, that can provide prolong gastric retention and increase efficacy of the dosage form. A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. Famotidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability. Moreover, less solubility in alkaline PH of Famotidine is partly responsible for the poor bioavailability of Famotidine from the colon. These properties of Famotidine do not favor the traditional approach to sustained release delivery. Hence, clinically acceptable sustained release dosage forms of famotidine prepared with conventional technology may not be successful. Different types of matrix forming polymers were studied: HPMC K4 M, HPMC K100 M, Xanthan gum, for the study. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former. The release rate could effectively be modified by varying the “matrix-forming polymer/low density polymer” ratio, the tablet geometry (radius), the type of matrix-forming polymer, the use of polymer blends and the addition of water-insoluble fillers (such as Avicel PH-102). The floating behavior of the low density drug delivery systems could successfully be combined with accurate control of the drug release patterns. The batch optimization was done using HPMC K4M, HPMC K100 M and Xanthan gum as matrixing polymers as they gave optimum FLT as well as long acting effect and no/ least eroding effect. It was also found that the tablet formulations released more than 90 % drug in 8 hours as desired. Gastro retentive (low density) tablets of Famotidine were prepared using polymer which not only imparted buoyancy to the formulations but also reduced floating lag times to a great extent. The use of HPMC K4 M, HPMC K100 M polymer in matrix tablets as density reducing agent has given a different

look while Xanthan gum used as release retardant polymer. Faster release of the drug from the hydrophilic matrix was probably due to faster dissolution of the water-soluble drug from the core and its diffusion out of the matrix that fast release of drug retarded by use of Xanthan gum. So, we can obtain a formulation that has desired release profile by adjusting different parameters that ultimately effect release behavior of the matrices. Thus it is summarized and concluded that HPMC K4M, HPMC K100 M and Xanthan gum can be successfully used in formulation of Famotidine sustained release gastro retentive floating drug delivery system using low density polymer.

Acknowledgement

Authors are thankful to Prof.(Dr.) B.Jayakar, Dean & principal Vinayaka missions college of pharmacy, Vinayaka mission University Salem, Tamilnadu and providing all the facilities for this research Project.

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