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Design, Evaluation and Study of Effect of Hydrophilic Polymers on Release Rate of Antiulcer Floating Tablets

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ABSTRACT

Gastro retentive 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 gastro retentive dosage forms include floating, raft, expanding/swelling, bioadhesive/ mucoadhesive and high/low density systems.Famotidine, an anti-ulcer drug, suffers from poor bioavailability (50% as famotidine is less soluble in alkaline pH. 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. This study aim to formulate floating tablets of famotidine using an effervescent approach for gastroretentive drug delivery system. Floating tablets were prepared using direct compression techniques using polymers like HPMC K4M and HPMCK100M for their gel-forming properties. The HPMC polymer alone is unable to control release rate. It releases drug >90% in four to six hours. In combination with Xanthan gum it release >90% in eight hours. The results indicate that gas generated gastroretentive floating tablets of famotidine containing HPMCK100M and Xanthan gum provide better options for controlled release action and improved bioavailability.

Key words: Famotidine, HPMC K4M, HPMC K100M, xanthan gum, swelling index

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INTRODUCTION

Effective oral drug delivery may depend upon several 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 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; 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 observed.[1] 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 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.[2] The retentive characteristics of the dosage form are not significant for the drugs that:

1. Are insoluble in intestinal fluids
2. act locally

exhibit site-specific absorption.

MATERIALS AND METHODS

Famotidine and Xanthan gum was gifted from Micro lab Hosur, HPMC K4 and HPMC K100 was gifted by Colorcon Asia Pvt. Ltd., Goa. Avicel PH-102 was obtained as gift sample from signet Chem Ltd, Mumbai and other reagents were obtained from the laboratory.

Preparation of gastro retentive floating tablets

Different tablet formulations were prepared by direct compression technique. All the powders were passed though 60 mesh sieve. The required quantity of drug, and low-density polymer were mixed thoroughly. Talc and magnesium stearate were finally added as glidant and lubricant respectively. The blend was directly compressed (9mm diameter punches) using tablet compression machine. Each tablet contained 40mg of famotidine and others pharmaceutical ingredients used as shown in Table 1.

Evaluation of powder blend[5-8]

Angle of repose: The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to a 10 ml measuring cylinder. The initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index: The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V)

Porosity (%) $= V_{bulk}-V/V_{bulk} \times 100$

Evaluation of Tablets

Drug content[9]

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.

Friability test

The friability of tablets was 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.

In vitro buoyancy studies[10]

The in vitro buoyancy was determined by floating lag time method described by Dave B.S.[10] The tablets were placed in a 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) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

In Vitro dissolution studies[4]

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 ± 0.5°C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for eight hours, and the samples were replaced with fresh dissolution medium. The samples were 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[11]

The swelling index of tablets was determined n 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:

Swelling index WU = $(W_1 - W_0)/ W_0$ x 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.

Stability study[12-14]

Gastro retentive tablets of famotidine formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40^{o}c and 4^{o}c for a period up to 30 days. The samples were withdrawn after periods of 15 days and 30 days; analyzed for its appearance, hardness, friability, floating time, drug content and in vitro release.

RESULTS AND DISCUSSION

Evaluation of tablet formulations

Pre-compression parameters

a. Angle of Repose (θ): The angle of repose for the formulated blend was carried out. It concludes all the formulations blend were found to be in the range 24^0.88' to 29.30'.

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

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

b. Compressibility Index: Compressibility index was carried out and found to be 12.34% to 16.30% indicating the powder blend has the required flow property for compression.

Post-compression parameters

a. Friability Test: The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.
b. Drug Content Uniformity: The percentage of drug content for FT1 to FT10 was found to be in between 97.11% to 99.69% of famotidine, it complies with official specifications as shown in Table 2.

In vitro buoyancy study

On immersion in 0.1N HCl solution pH (1.2) at 37^{0}C, the tablets floated, and remained buoyant without disintegration. From the results it can be concluded that the batch containing only HPMC polymer showed good total floating time (TFT). Formulation containing HPMC K4M, HPMC K100M and Xanthan gum showed good FLT 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 FLT and TFT.

Swelling study

Swelling study was performed on all the batches (FT1 to FT10) for five hours. The results of swelling index were shown in Table 3 and in Figure 1.

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/cm^2, 5kg/cm^2, 7kg/cm^2 and 8 kg/cm^2 were 47,58,76,89 and 186 sec respectively as shown in Table 4 and. Buoyancy lag time (sec) vs. hardness (kg/cm^2) plotted and shown in Figure 2.

In vitro dissolution study and kinetic modeling of drug release

From the *in vitro* dissolution data it was found that

Table 2: Evaluation of physical parameters of floating tablets

Tablets Batch	Weight variation test (%)	Friability (%)	Hardness (kg/cm^2)	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
FT10	±2.04	0.75	4.3 ±0.83	3.20±0.011	99.69

All the values are expressed as mean ± SE.

Table 3: Swelling Index of Tablets of Batch FT1 to FT10

Time	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
1 hr	32	33	31	40	35	29	36	48	30	42
2 hrs	39	38	38	51	42	36	46	59	41	51
3 hrs	41	43	44	62	49	48	56	65	46	67
4 hrs	49	49	52	73	57	59	64	78	54	76
5 hrs	56	65	68	90	68	62	77	82	60	91

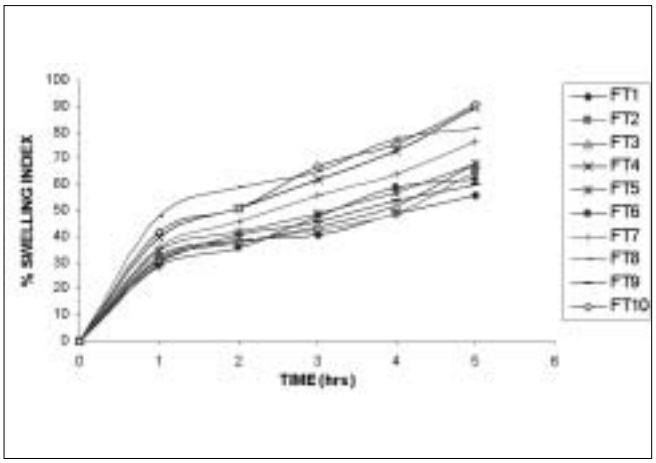

Figure 1: Swelling index for tablets of batch Ft1 to Ft10

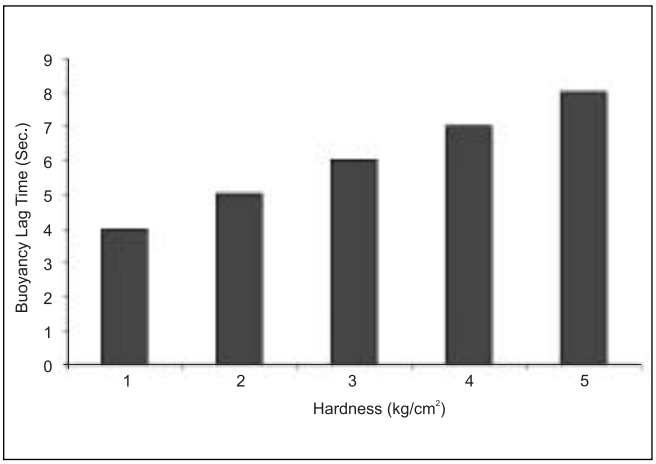

Figure 2: Plot of hardness v/s buoyancy lag time

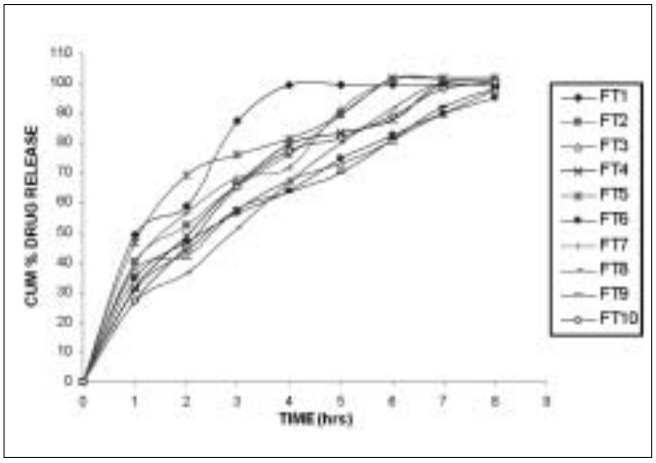

Figure 3: *In vitro* dissolution profile of batches Ft1 to Ft10 (using dissolution apparatus)

formulation FT1 to FT9 released more than 90% of drug before eight hours of the study indicating that the polymer amount is not sufficient to control the drug release. While FT8 and FT10 containing Xanthan gum and HPMC K100M released more than 90% of drug with in eight hours. It concludes that F10 had better controlled release than the other formulation.

Table 4: Effect of hardness on buoyancy lag time of formulation FT10

Hardness in kg/cm²	Buoyancy lag time (sec)
4	47
5	58
6	76
7	89
8	186

The release data obtained for formulations FT1 to FT10 were tabulated in Table 5, Figure 3 shows the plot of cumulative per cent drug released as a function of time for different formulations. The results obtaining *in vitro* release studies were plotted in different models of data treatment as follows: zero order rate kinetics, first order rate kinetics, Higuchi's classical diffusion equation, Peppas exponential equation, Hixson–Crowell erosion equation. The kinetic values obtained for formulation FT10 were shown in Table 6.

Table 5: *In vitro* cumulative % drug release of all batches by paddle method

Time (hrs)	Cumulative % drug release									
	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

Table 6: Kinetic values obtained from *in vitro* released data of formulation FT10

Kinetic model	Intercept	Slope	R^2
Zero-order plot	17.177	10.120	0.9942
First-order plot	4.7579	-0.4795	0.9850
Higuchi plot	-3.6818	37.99	0.9880
Hixson Crowell	4.7579	-0.4795	-0.9936
Peppas-korsmeyer	1.4767	0.6214	0.9555

Stability study

The stability study results obtained were shown in Table 7 and 8. The results revealed that no significant changes in appearance, floating time, drug content, hardness, friability, and *in vitro* release for FT10 formulation when it was stored at the three different storage conditions.

CONCLUSION

The aim of the study was to study the effect of various hydrophilic polymers on *in vitro* release rate from gastro retentive floating tablet of famotidine based on a low density polymer.

Different types of matrix forming polymers - HPMC K4 M, HPMC K100 M, Xanthan gum were studied. 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.

The use of HPMC K4 M, HPMC K100 M polymer in matrix tablets as density reducing agents has given a different look, Xanthan gum was used as release retardant polymer. During the study with the polymer various characteristics of the material observed include: highly porous spherical structure, good compressibility, good flow property with drug and other polymers, no significant effect on drug release and compatibility with drug and other polymers as seen through IR spectra.

Thus the above studies reveals that HPMC K4M, HPMC K100 M and Xanthan gum can be successfully used in the formulation of famotidine sustained release gastro

Table 7: Stability studies data of formulation FT10

Time (hrs)	Cumulative % drug release						
	Initial % drug release	At room temperature		At 40° C temperature		At 2-8° C temperature	
		After 15 days	After 1 month	After 15 days	After 1 month	After 15 days	After 1 month
1	27.09	30.51	31.89	28.51	26.89	35.51	36.98
2	45.68	48.54	46.74	45.54	45.74	46.34	46.64
3	65.51	57.96	56.92	67.96	67.92	57.69	55.23
4	77.48	69.45	66.45	79.45	77.45	69.54	69.84
5	81.80	75.23	73.93	85.23	83.93	79.32	72.92
6	89.07	83.98	84.98	89.98	86.98	84.99	82.89
7	98.12	96.87	95.75	96.87	97.70	96.78	93.73
8	100.36	98.63	98.45	99.83	99.75	98.36	98.75

Table 8: Results of physical parameters after stability studies of formulation FT10

Parameters	Initial	At room temperature		At 40° C temperature		At 2-8° C temperature	
		After 15 days	After 1 month	After 15 days	After 1 month	After 15 days	After 1 month
FLT (sec)	45	49	51	45	48	49	54
TFT (hrs)	>12	>12	>12	>12	>12	>12	>12
Hardness (kg/cm^2)	4.3	4.1	4.6	4.0	4.4	4.9	4.1
Friability (%)	0.75	0.78	0.81	0.75	0.75	0.65	0.74
Drug Content (%)	99.69	99.76	99.89	99.59	99.45	99.90	99.53

retentive floating drug delivery system using low density polymer.

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