Research Article **CODEX: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

PREPARATION AND *IN VITRO* EVALUATION OF FAMOTIDINE FLOATING TABLETS BY USING DIFFERENT HYDROPHILIC POLYMERS

T.V. Thulasiramaraju*[1], S. Ravendra Reddy[2], B. Tejeswar Kumar[1], A. Kartik Kumar[1]

[1*]Department of Pharmaceutics, Sri Sai Aditya Institute of Pharmaceutical Sciences and Research, Surampalem, East Godavari, Andhra Pradesh, India.

[2]Department of Pharmaceutics, Aditya Institute of Pharmaceutical Sciences and Research, Surampalem, East Godavari, Andhra Pradesh, India.

ABSTRACT

Famotidine has been the most widely used drug for the treatment of peptic ulcer for many decades. Famotidine, an anti-ulcer drug, Poor bioavailability (50%) and Famotidine is less soluble in intestinal pH. 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 HPMC K100M and Xanthan Gum for their gel-forming properties. The tablets were evaluated for *in vitro* buoyancy and dissolution studies. Tablets were evaluated for physical characteristic viz. hardness, floating capacity, thickness, swelling index, and weight variation. From the above results the HPMC polymer alone is unable to control release rate. It releases drug >100% within 6 to 8 hours. In combination with Xanthan gum it release >80% in 12 hours. The results indicate that gas generated gastroretentive floating tablets of famotidine containing HPMC K4M, HPMC K100M and Xanthan gum provide better options for controlled release action and improved bioavailability.

KEYWORDS

Famotidine, HPMC K4M, HPMC K100M, Xanthan gum, I*n vitro* buoyancy and dissolution studies.

Author for Correspondence:
T.V. Thulasiramaraju,
Department of Pharmaceutics,
Sri Sai Aditya Institute of Pharmaceutical Sciences and Research, Surampalem, East Godavari,
Andhra Pradesh, India.
Email: thulasiramaraju912@gmail.com.

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].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Gastroretentive 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 for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Famotidine is histamine H2 -receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastro esophageal reflux disease. In the management of benign gastric and duodenal ulceration the dose is 40 mg daily by mouth at bed time, for 4 to 8 weeks. In gastro esophageal reflux disease the recommended dose is 20 mg by mouth twice daily for 6 to 12 weeks; where gastro esophageal reflux disease is associated with esophageal ulceration, the recommended dosage is 40 mg twice daily for a similar period. For the short term symptomatic relief of heartburn or non-ulcer dyspepsia a dose of 10 mg up to twice daily is suggested. In the Zollinger-Ellision syndrome the initial dose by mouth is 20 mg every 6 hours, increased as necessary; dose up to 80 mg daily have been employed. The low bioavailability (40-45%), short biological half-life (2.5-4.0 hours) [3].

MATERIAL AND METHOD

MATERIALS

Famotidine and Xanthan gum was gifted from Micro lab Hosur, HPMC K4 and HPMC K100 was gifted from Apex Laboratories Pvt.Ltd, Chennai. Avicel PH-102 was obtained as gift sample from SDF Chem Ltd, Mumbai and All other chemicals and reagents used were of analytical grade.

METHOD [4]

Preparation of gastro retentive floating tablets of Famotidine

Different tablet formulations were prepared by direct compression technique. All the powders were passed through 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 No.1.

EVALUATION PARAMETERS [4-9]

Precompression studies of granules

Bulk density

5gms of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal (Table No.2).

$$\theta = \tan^{-1}(h/r)$$

Where,

θ = Angle of repose,

h = Height of the powder cone,

r = Radius of the powder cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density (Table No.3).

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density

BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules (Table No.4).

Hausner's Ratio = Tapped density/Bulk density

Postcompression studies of gastro retentive floating tablets of Famotidine

Hardness or Crushing strength Test

Hardness of the floating tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10kg ; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg) [7].

Thickness Test

The thickness of the floating tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten floating tablets were randomly selected from each tablet thickness was determined using a Vernier calliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed floating tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The floating tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight

F - Final weight

Weight variation test

Weights of 20 individual floating tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula (Table No.5),

Percentage deviation = [X-*X/ X] × 100**

X - Actual weight of the tablet

X* - Average weight of the tablet

Estimation of Drug Content

Ten floating tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 250ml volumetric flask, it was shaken with 150 of distilled water and volume was adjusted to 250ml with water. The solution was filtered, suitable dilutions were made and absorbance was recorded by using U.V. spectrophotometer (Labindia, Hyderabad) at 266nm. The experiment was repeated three times.

Calculation

The amount of Famotidine present in tablet can be calculated using the formula

A_t/As x S_w/100 x 100

Where, A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Famotidine working standard (mg)

***In vitro* buoyancy studies** [7]

The *in vitro* buoyancy was determined by floating lag time method described by Dave B.S [7]. The tablets were placed in a 250 ml beaker containing 0.1N 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 0.1N 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).

Swelling index [9]

The swelling index of tablets was determined in 0.1N 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_t - W_0)/ W_0 x 100

Where, W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet

***In vitro* drug release study** [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 0.1N 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 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.

RESULTS AND DISCUSSION

Preformulation studies

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated tablets, pure drug and polymers was recorded. The tablets were taken in a KBr pellet using SHIMADZU, 8400s, Japan, FTIR Instrument. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the pure drug and polymers. Then all the functional groups found in the IR spectrum of pure drug and polymers.

Precompression studies of granules

Bulk density

The packing properties of the drugs and their formulations widely depend upon bulk density. It has been stated that bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow. From the result it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow

characteristics of the granules. Values showed Table No.6.

Tapped density

The tapped density was determined by cylindrical method. The tapped density values indicate good flow characteristics of the granules. Values showed Table No.6.

Angle of Repose

Angle of repose can be observed from Table No.6 that the angle of repose for various batches of the granules is found to be less than 40^0, it indicates good flow properties of the granules.

Compressibility Index or Carr's Index

The Carr's Index for various batches of the granules is found to be less than 37; it indicates good flow properties of the floating tablets. Values showed Table No.6.

Hausner's Ratio

Hausner's Ratio can be observed from Table No.6 that the Carr's Index for various batches of the floating tablets is found to be less than 1.35; it indicates good flow properties of the floating tablets.

Postcompression studies of Famotidine floating tablets

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the tablets. Values showed Table No.7.

Thickness Test

The floating tablets mean thicknesses were almost uniform in the all formulations and were found to be in the range of 3.2mm. Values showed Table No.7.

Friability Test

The floating tablets Friability values are found to be less than 1% in all cases and considered to be satisfactory. Values showed Table No.7.

Weight variation test

All this floating tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. Values showed Table No.7.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range (97.26-99.52) which shows the proper mixing of the drug with the excipients. Values showed Table No.7.

***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. Formulation containing HPMC K4M, HPMC K100M and Xanthan gum (FM-7) showed good FLT of 48 sec (Table No.8) (Figure No.1).

Swelling index study

Swelling index study was performed on all the batches (FM-1 to FM-7) for five hours. The results of swelling index were shown in (Table No.9) and in (Figure No.2). In the present study, the higher swelling index was found for tablets of batch FM-7 containing combination of HPMC K4M, HPMC K100M and Xanthan gum. 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.

***In vitro* dissolution study**

From the *in vitro* dissolution study it was found that formulation FM-7 has more than 98% of drug release for 12 hours, when compared with other formulation. It concludes that the formulation FM-7 had better controlled release than the other formulation (Table No.10) (Figure No.3).

Table No.1: Formulation of different batches of Famotidine floating tablets (mg/tab)

S.No	Formulations	Drug (Famotidine)	Polymers			Citric acid	Sodium bicarbonate	PVP -K_{30}	MCC	Mg-stearate	Talc
			HPMC K_4M	HPMC K100M	Xanthan Gum						
1	FM-1	40	90	--	--	15	20	Q.S	Q.S	3	2
2	FM-2	40	--	90	--	15	20	Q.S	Q.S	3	2
3	FM-3	40	--	--	90	15	20	Q.S	Q.S	3	2
4	FM-4	40	45	45	--	15	20	Q.S	Q.S	3	2
5	FM-5	40	--	45	45	15	20	Q.S	Q.S	3	2
6	FM-6	40	45	--	45	15	20	Q.S	Q.S	3	2
7	FM-7	40	30	30	30	15	20	Q.S	Q.S	3	2

Total weight of the tablet – 160 mg/Tab.

Table No.2: Angle of Repose I.P limits

S.No	Angle of Repose	Powder flow
1	< 25	Excellent
2	25 – 30	Good
3	30 – 40	Passable
4	> 40	Very poor

Table No.3: Carr's Index I.P limits

S.No	Carr's Index	I.P Limits value
1	Excellent	<10
2	Good	11 – 15
3	Fair	16 – 20
4	Possible	21 – 25
5	Poor	26 – 31
6	Very poor	32 – 37
7	Very very poor	>38

Table No.4: Hausner's Ratio I.P Limits

S.No	Hausner's Ratio	I.P Limits value
1	Excellent	1.00 – 1.11
2	Good	1.1 – 1.18
3	Fair	1.19 – 1.25
4	Possible	1.26 -1.34
5	Very poor	1.35 -1.45
6	Very very poor	>1.60

Table No.5: Weight variation test for Tablets

S.No	Average weight of Tablets(mg)	Maximum % difference allowed
1	130 or less	± 10
2	130-324	±7.5
3	More than 324	±5

Table No.6: Precompression studies of granules

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
1	FM-1	0.623	0.678	32.68	8.112	1.088
2	FM-2	0.652	0.692	32.43	5.780	1.061
3	FM-3	0.636	0.682	33.86	6.744	1.072
4	FM-4	0.612	0.664	32.36	7.831	1.084
5	FM-5	0.643	0.692	34.52	7.080	1.076
6	FM-6	0.652	0.687	32.45	5.094	1.053
7	FM-7	0.648	0.694	34.24	6.628	1.070

Table No.7: Postcompression studies of Famotidine floating tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (mm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content (%)
1	FM-1	13.25	3.2	0.523	99.5	97.26
2	FM-2	13.36	3.2	0.654	99.6	97.32
3	FM-3	13.54	3.2	0.664	99.5	97.84
4	FM-4	13.65	3.2	0.486	99.6	98.18
5	FM-5	13.85	3.2	0.452	99.9	98.56
6	FM-6	14.10	3.2	0.434	99.8	99.06
7	FM-7	14.65	3.2	0.423	99.9	99.52

Table No.8: *In vitro* buoyancy study

S.No	Formulations	*In vitro* buoyancy study (TFT in hrs)
1	FM-1	>12
2	FM-2	>12
3	FM-3	>12
4	FM-4	>12
5	FM-5	>12
6	FM-6	>12
7	FM-7	>12

Table No.9: Swelling index study

S.No	Time in hrs	Swelling index study (%)						
		FM-1	FM-2	FM-3	FM-4	FM-5	FM-6	FM-7
1	1 hr	24	26	14	28	31	34	40
2	2 hrs	31	34	20	39	42	48	52
3	3 hrs	46	49	26	53	57	62	68
4	4 hrs	54	57	32	64	68	74	79
5	5 hrs	62	65	38	72	79	82	87

Table No.10: Comparative dissolution study of different formulations of Famotidine floating tablets

S.No	Time (hrs)	FM-1	FM-2	FM-3	FM-4	FM-5	FM-6	FM-7
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	28.36	23.16	8.653	18.26	10.29	14.53	14.78
3	2	47.65	34.12	12.47	25.52	17.24	21.56	23.61
4	3	65.32	46.64	17.23	37.24	23.12	28.42	32.84
5	4	80.46	58.35	23.15	50.18	29.86	36.14	41.92
6	5	94.24	70.25	29.34	64.28	36.74	42.05	49.64
7	6	109.7	81.56	35.62	76.84	42.06	49.24	58.15
8	7	--	92.72	41.23	87.42	49.52	57.82	65.42
9	8	--	103.4	47.94	98.67	56.32	63.37	72.18
10	9	--	--	53.75	108.9	63.27	70.64	79.26
11	10	--	--	58.12	--	70.13	76.58	86.43
12	11	--	--	64.34	--	76.48	83.12	92.08
13	12	--	--	70.25	--	82.32	90.55	98.72

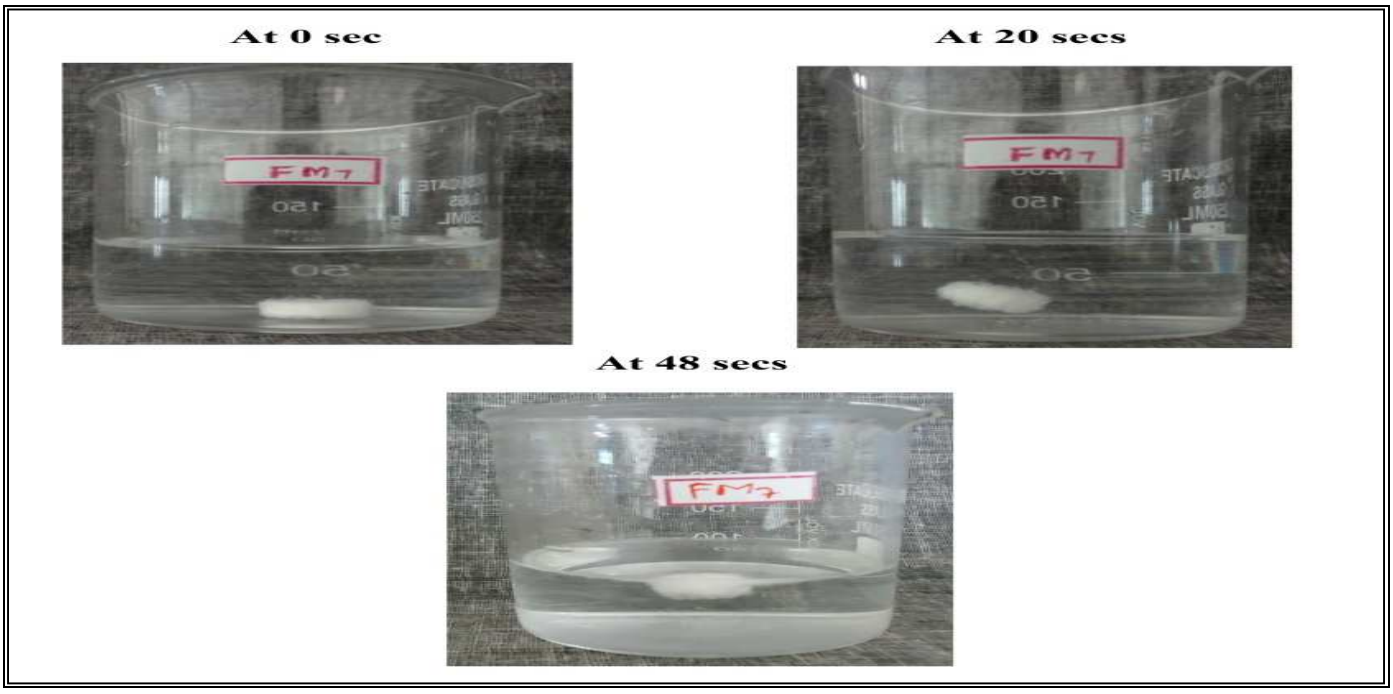

Figure No.1: *In vitro* buoyancy study

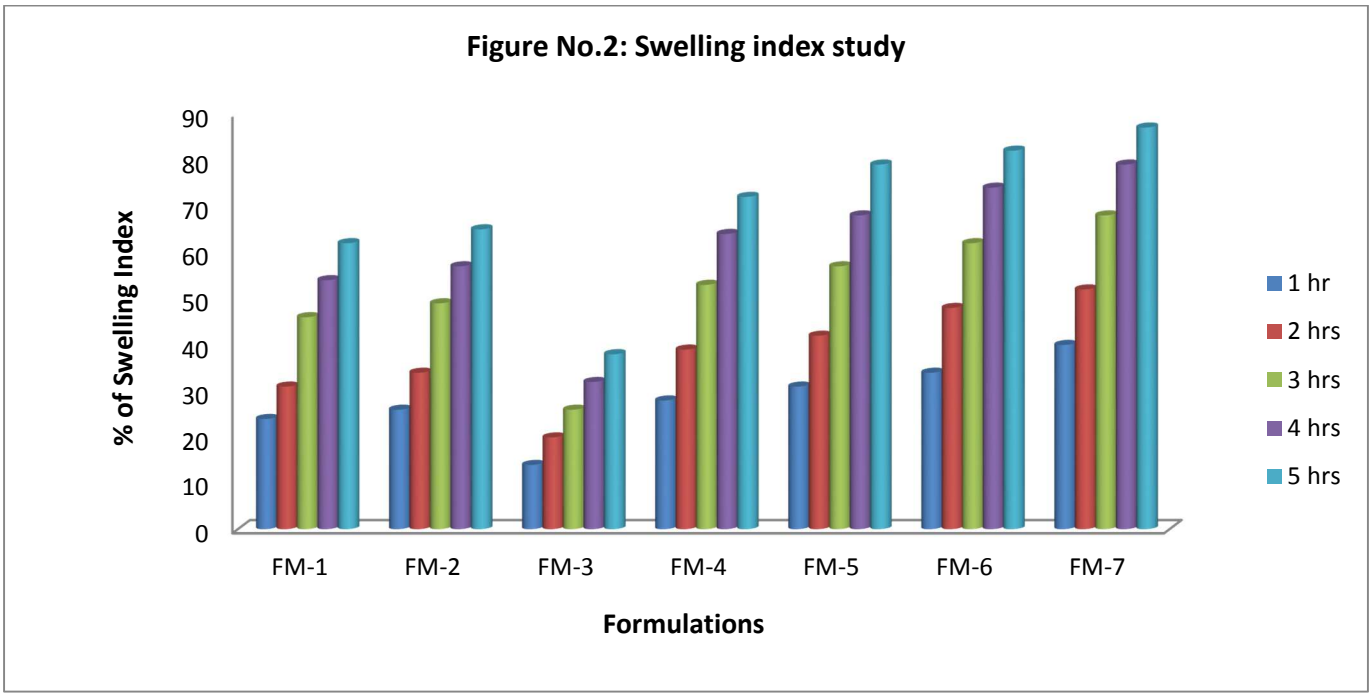

Figure No.2: Swelling index study

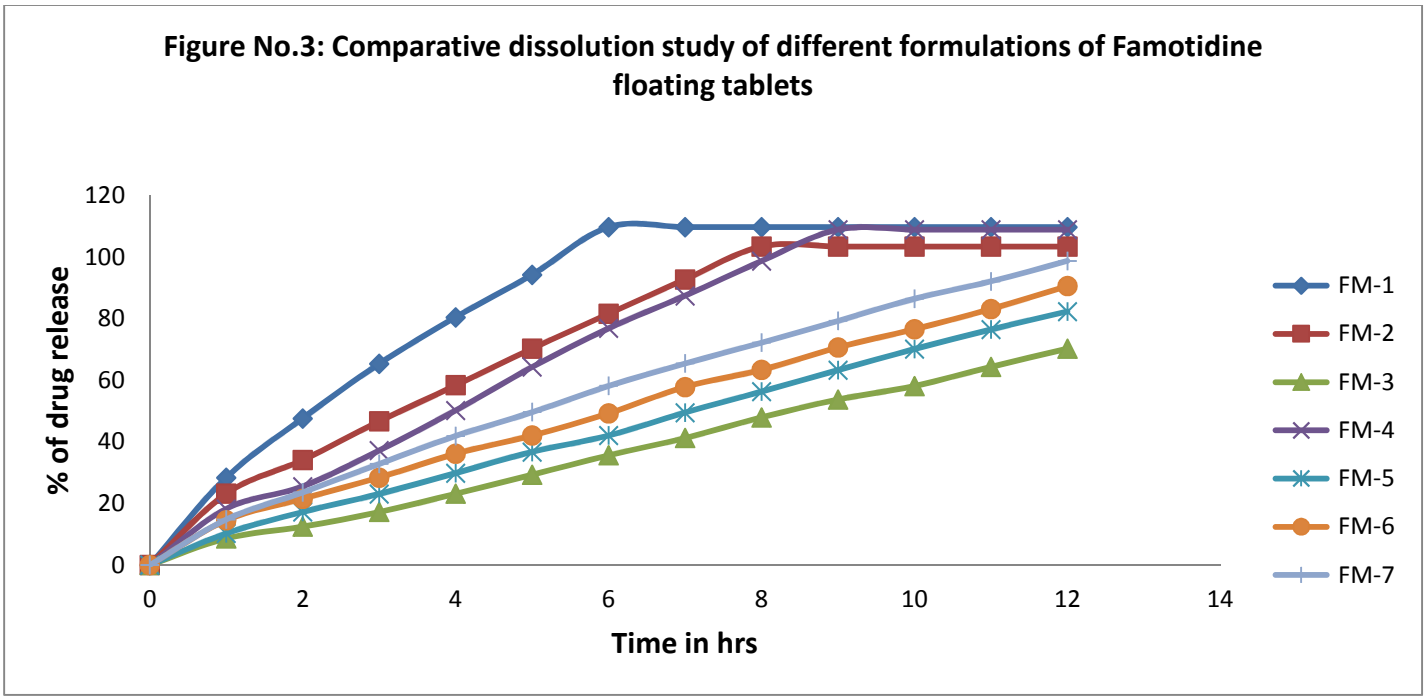

Figure No.3: Comparative dissolution study of different formulations of Famotidine floating tablets

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, and 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 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 98% drug in 12 hours as desired. Thus the above studies concluded that the combination of HPMC K4M, HPMC K100M and Xanthan gum formulation (FM-7) can be successfully. and used in the formulation of famotidine controlled release gastro retentive floating drug delivery system using low density polymer.

ACKNOWLEDGEMENT

The authors are sincerely thanks to Sri Sai Aditya Institute of Pharmaceutical Sciences and Research, Surampalem, East Godavari, Andhra Pradesh, India for providing the facilities to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, *Int J Pharm*, 136(1-2), 1996, 117-139.

2. Deshpande A A, Shah N H, Rhodes C T, Malick W. Development of a novel controlled-release system for gastric retention, *Pharm Res*, 14(6), 1997, 815-819.
3. Reynolds J E F. "Martindale the Extra Pharmacopoeia", *The Royal Pharmaceutical Society: London*, 31st edition, 1996, 1218-20.
4. Raju D B, Sreenivas R and Varma M M. Formulation and evaluation of floating drug delivery system of Metformin Hydrochloride, *J.Chem.Res*, 2(2), 2010, 274-278.
5. Patel V F, Patel N M, Yeole P G. Studies on formulation and evaluation of Ranitidine floating tablets, *Ind J Pharm Sci*, 67(6), 2005, 67, 703-9.
6. Arunachalam A, Sudhakar Babu A M S, Varatharajan P. Preparation and *in vitro* evaluation of sustained release tablets of Aceclofenac, *International Journal of Research in Pharmaceutical and Nano Sciences*, 1(1), 2012, 1-10.
7. Dave B S, Amin A F, Patel M M. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation, *AAPS Pharm Sci Tech*, 5(2), 2004, 34.
8. Anonymous. Hardness or Crushing strength, *Pharmainfo.net*, 1, 2008, 1-4.
9. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time, *Int J Pharm*, 195(1-2), 2000, 125-35.

Please cite this article in press as: Thulasiramaraju T V. *et al*. Preparation and *in vitro* evaluation of famotidine floating Tablets by using different hydrophilic polymers, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(3), 2013, 382-393.