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Formulation and Evaluation of Gastro retentive Floating Tablets of Famotidine

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Abstract

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 gastro retentive 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 gastro retentive floating Tablets of Famotidine containing 40mg HPMCK100M and Xanthan gum provides a better option for controlled release action and improved bioavailability.

Keywords: Famotidine, HPMC K4M, HPMC K100M, Gastric residence time, swelling index.

Contents

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1. Introduction

The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. 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 [1-3]. 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[3] .Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior. Drugs that could take advantage of gastric retention include: furosemide, cyclosporine, allopurinol ciprofloxacin and metformin [4-6]

2. Materials and Methods

Table1: List of Chemicals Used

Materials	**Company Name**
Famotidine	Micro lab,Hosur
HPMC K4M	Colorcon Asia Pvt. Ltd., Goa
HPMC K100M	Colorcon Asia Pvt. Ltd., Goa
Xanthan gum	Micro lab,Hosur
Sodium bicarbonate	Nice chemicals laboratory
Citric acid (anhydrous)	Nice chemicals laboratory
Polyvinylpyrollidine-k-30	Nice chemicals laboratory
Avicel PH-102	Signet Chem. Ltd
Talc	Loba Chemie
Magnesium Stearate	Loba Chemie
Hydrochloric acid LR	S.D. Fine Chem. Ltd.

Experimentation

Preformulation Studies: It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies [7-9].

Determination of Melting Point: Melting point of Famotidine was determined by capillary method.

Solubility: solubility of Famotidine was determined in water, 0.1N HCl, practically insoluble in ethanol (95%), chloroform and ether.

Compatibility Studies:

Table 2: Drug Excipient compatibility studies

API and Excipients	**Ratios**	**Observations**			
		Storage condition/duration			
		60°C/75%RH		40°C/75%RH	
		Initial	1week	15 days	30 days
Famotidine		White to off white color	NCC	NCC	NCC
Famotidine +HPMC K4M	1:5		NCC	NCC	NCC
Famotidine +HPMC K100M	1:5		NCC	NCC	NCC
Famotidine +Xanthan gum	1:1		NCC	NCC	NCC
Famotidine +Sodium bicarbonate	1:1		NCC	NCC	NCC
Famotidine +Citric acid(anhydrous)	1:0.5		NCC	NCC	NCC
Famotidine +PVP-K-30	1:1		NCC	NCC	NCC
Famotidine +Avicel PH-102	1:0.5		NCC	NCC	NCC
Famotidine +MagnesiumStearate	1:0.5		NCC	NCC	NCC
Famotidine + Talc	1:0.5		NCC	NCC	NCC

Evaluation of powder blend

The following flow properties were evaluated [10-13].

Angle of repose

The angle of repose of powder blend was determined by 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) was determined. By 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} x 100

All the results are listed in table No:-5

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. 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 [14-16].

Table 4: Composition of Famotidine Floating Tablets

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	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

Evaluation of Tablets [17-21]

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. All the results are listed in table 6.

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/cm^2. Three tablets were randomly picked and hardness of the tablets was determined. All the results are listed in table 6.

Thickness

The thickness of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated. All the results are listed in table 6.

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.

All the results are listed in table 6.

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

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. All the results are listed in table 6.

In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time method described by Dave B.S.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). All the results are listed in table 7.

***In Vitro* dissolution studies**

The release rate of Famotidine from floating tablets was determined using *TheUnited 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 8 h, 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 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:

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

Where, W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet.

All the results are listed in table No:-8

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. All the results are listed in table No:-9

Stability study

An ethical drug manufacturer is committed to provide to his consumers drug products, which are efficacious and safe. This can be ensured only by instituting a sound programme to study the stability of a product during its various phases of development and to arrive at the proper storage conditions and the expiry period under those conditions. This is a requirement in most of the countries and is stipulated by the regulatory agencies of those countries. These studies would very quickly identify the need, if any, to stabilize the active substance or the formulation, and save invaluable time and effort from being spend on an unmarketable formulation. With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing worldwide under various climatic conditions including tropical, subtropical and temperate.

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^oc and 4^oc a period up to 30 days. The samples were withdrawn after periods of 15 days, and 30 days and were analyzed for its appearance, hardness, friability, floating time, drug content and in vitro release. All the results are listed in table 11.

3. Results and Discussion

Melting point of Famotidine was found to be in the range 162-164^{o}C, which complied with BP standards, indicating purity of the drug sample. Famotidine was found to be soluble in water, 0.1NHCl, and practically insoluble in ethanol (95%), chloroform and ether. Compatibility studies were performed using IR spectrophotometer. The IR

spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of were obtained at 3504.66cm^{-1}, 1591.27cm^{-1}, 981.77cm^{-1}.Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between Famotidine and the polymers used. Drug has given peaks due to furan ring and secondary diamine groups. From the figure no.14, 15,16,17,18. It was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. The peaks obtained in the spectra's of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

Table 5: Micromeritic properties of powder blend

Powder blend	Angle of Repose (^{0})	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

Post-Compression Parameters

Table 6: Evaluation of Physical Parameters of Floating Tablets

Tablets Batch	% deviation in Weight	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

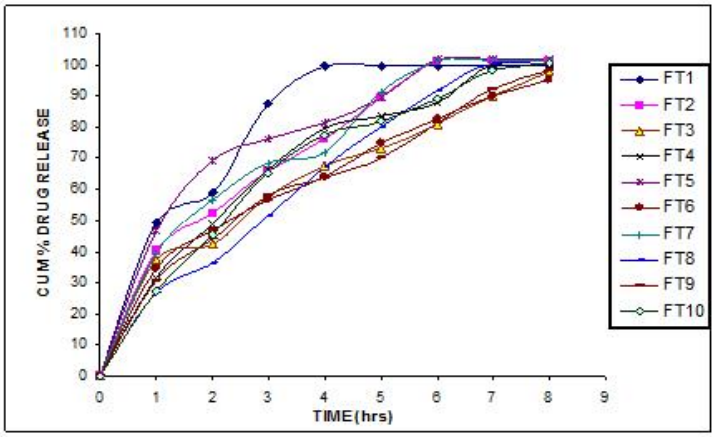

Figure 1: In Vitro Buoyancy Study

Table 8: Swelling Index of Tablets of Batch FT1 to FT10

Time	Swelling Index of Tablets of Batch FT1 to FT10									
	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

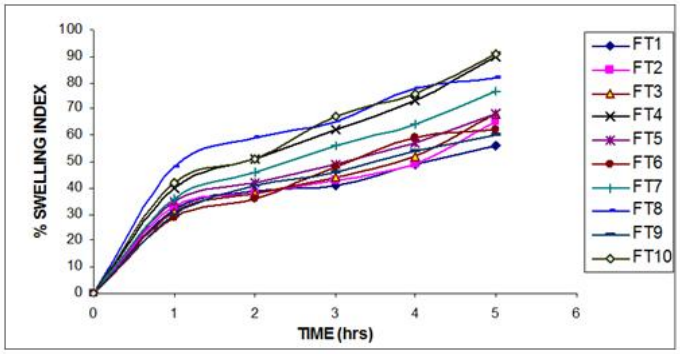

Figure 2: Swelling Index for Tablets of Batch Ft1 To FT10

Table 9: Effect of Hardness On Buoyancy Lag Time

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

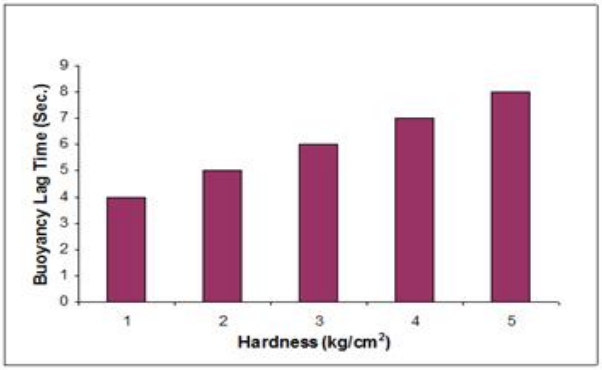

Figure 3: Plot of Hardness V/S Buoyancy Lag Time

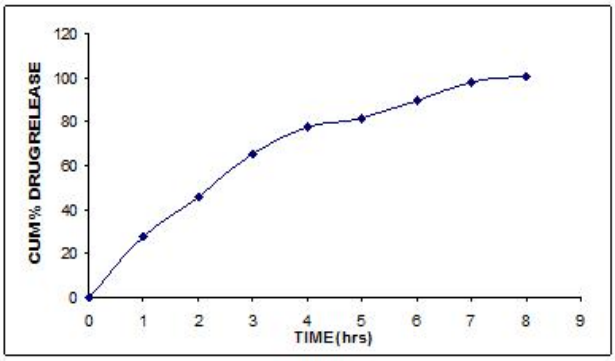

Figure 4: Zero Order Release Profile

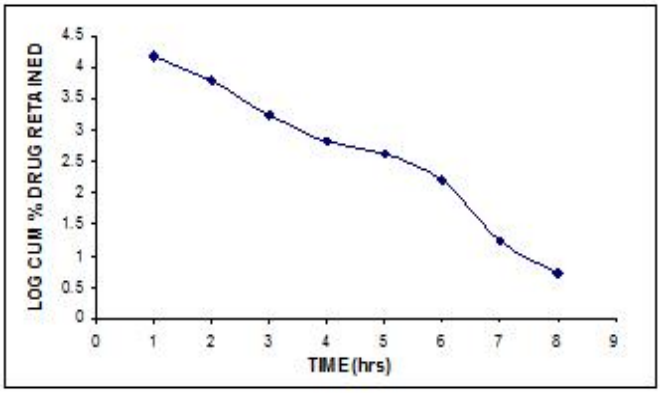

Figure 5: First Order Plots

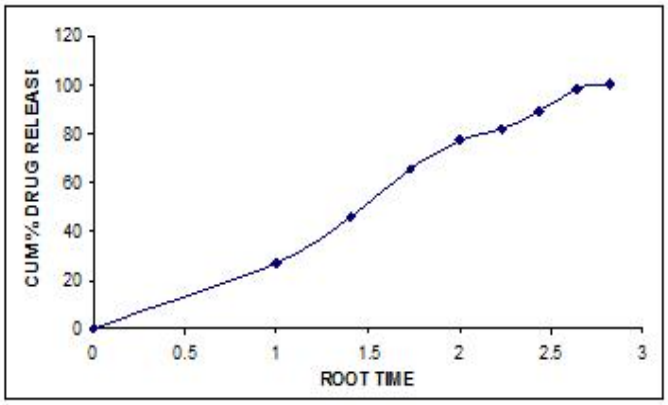

Figure 6: Higuchi Plot

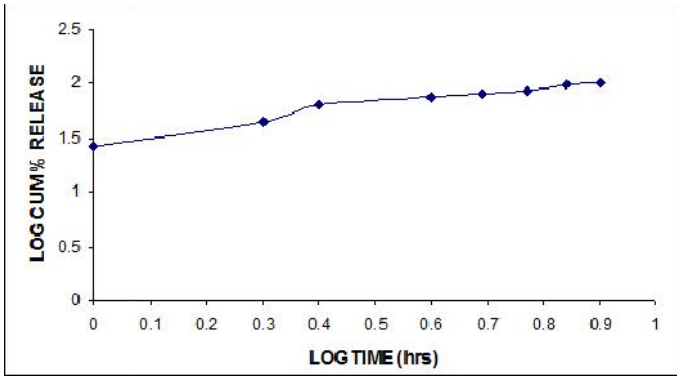

Figure 7: Korsmeyer peppas plot

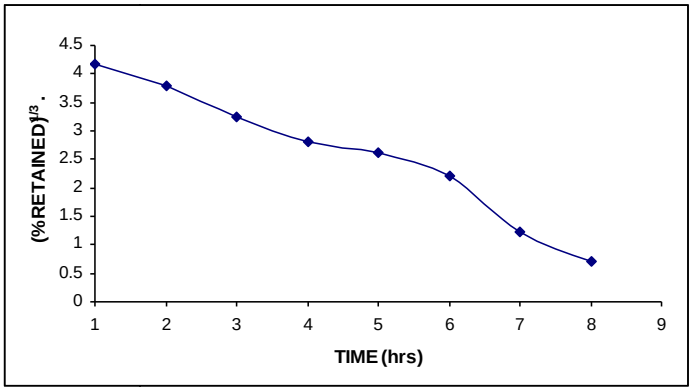

Figure 8: Hixson-Crowell Plot

Table 10: Stability Studies of Formulation Ft10 Stored At Room Temperature

Time (hrs)	**Cumulative % Drug release**		
	Initial	**After 15 Days**	**After one months**
0	0.0	0	0
1	27.09	30.51	31.89
2	45.68	48.54	46.74
3	65.51	57.96	56.92
4	77.48	69.45	66.45
5	81.80	75.23	73.93
6	89.07	83.98	84.98
7	98.12	96.87	95.75
8	100.36	98.63	98.45
FLT (sec)	45	49	51
TFT(hrs)	>12	>12	>12
Hardness(kg/cm^2)	4.3	4.1	4.6
Friability (%)	0.75	0.78	0.81
Drug Content (%)	99.69	99.76	99.89

Table 11: Stability Studies Of Formulation Ft10 Stored At Temperature 40^{O}C

Time (hrs)	**Cumulative % Drug release**		
	Initial	**After 15 Days**	**After one months**
0	0.0	0	0
1	27.09	28.51	26.89
2	45.68	45.54	45.74
3	65.51	67.96	67.92
4	77.48	79.45	77.45
5	81.80	85.23	83.93
6	89.07	89.98	86.98
7	98.12	96.87	97.70
8	100.36	99.83	99.75
FLT (sec)	45	45	48
TFT(hrs)	>12	>12	>12
Hardness(kg/cm^2)	4.3	4.0	4.4
Friability (%)	0.75	0.75	0.75
Drug Content (%)	99.69	99.59	99.45

Table 12: Stability Studies Of Formulations Ft10 Stored At Temperature (2-8^{O}C)

Time (hrs)	**Cumulative % Drug release**		
	Initial	**After 15 Days**	**After one months**
0	0.0	0	0
1	27.09	35.51	36.98
2	45.68	46.34	46.64
3	65.51	57.69	55.23
4	77.48	69.54	69.84
5	81.80	79.32	72.92
6	89.07	84.99	82.89
7	98.12	96.78	93.73
8	100.36	98.36	98.75
FLT (sec)	45	49	54
TFT(hrs)	>12	>12	>12
Hardness(kg/cm^2)	4.3	4.9	4.1
Friability (%)	0.75	0.65	0.74
Drug Content (%)	99.69	99.90	99.53

4. Conclusion

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.

5. 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., 1996, 136, 117-139.
2. Reddy, L., Murthy, R., "Floating dosage systems in drug delivery", Crit. Rev. Ther. Drug Carrier Syst., 2002, 19, 553-585.
3. Deshpande, A.A., Shah, N.H., Rhodes, C.T., Malick, W., "Development of a novel controlled release system for gastric retention", Pharm. Res., 1997, 14, 815-819.
4. Chien, Y.W., "Novel drug delivery system", Marcel Dekker, 2nd Edi. Rev. Expand., 50, 139-196.
5. Chungi, V.S., Dittert, L.W., Smith, R.B., "Gastrointestinal sites of furosemide absorption in rats", Int. J. Pharm., 1979, 4, 27-38.
6. Sheth, P.R., Tossounian, J., "The Hydrodynamically balanced system (HBS™): a novel drug delivery system for oral use", Drug Dev. Ind. Pharm., 1984, 10, 313-339.
7. Gutierrez-rocca, J., Omidian, H., Shah, K., "Progress in Gastro retentive drug delivery systems", Business Briefing, Pharmatest, 2003, 152-156.
8. Hou, S.Y., Cowles, V.E.,Berner, B., "Gastric retentive dosage forms: a review", Crit. Rev. Ther. Drug Carrier Syst., 2003, 20(6), 459-97.
9. Cremer, K., "Drug delivery: gastro-remaining dosage forms", The Pharm. Journal 1997, 259, 108.
10. Robinson, J., Lee, R., "In Controlled drug delivery", 2nd edition, 1987, 418.
11. Kalus, Florey, "Analytical profile of drug substances", Academicpree, Florida, l-9, 1987, 87.
12. Timmermans, J., Moes, A.J., "Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy", J.Pharm.Sci., 83, 1994, 18-24.
13. Mojaverian, P., Vlasses, P.H., Kellner, P.E., Rocci, M.L., "Effects of gender, posture and age on gastric residence time of an indigestible solid: pharmaceutical considerations", Pharm.Res., 10, 1988, 639-644.
14. Kormeyer, R.W., J. Pharm.Sci., 1983, 72, 1189-1191.
15. Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C., Falson, F., "Gastroretentive dosage forms: Overview and special case of Helicobacter pylori", J. Control. Rel., 2006, 111(1-2), 1-18.
16. Roche, R.C., Sheskey, P.J, Weller, P.J., "Handbook of pharmaceutical excipients", 4th edition, Pharmaceutical Press, London, 2003.
17. S.P.vyas Roop K.Khar, **"**Controlled Drug Delivery Concepts and Advances", (1stedn) VallabhPrakashan, Delhi, (2002), 257-261.
18. Bramhankar D.M. and Jaiswal S.B., "Biopharmaceutics and Pharmacokinetics A Treatise", (1stedn) Vallabh Prakashan, Delhi, (2002), 335-337.
19. RoopK.Khar, Alka Ahuja and Javed Ali, Jain N.K.Eds., "Controlled and Novel Drug Delivery", (1stedn), CBS publication, Delhi, (2002), 353-365.ICH Q1A (R2), Stability Testing Guidelines, Stability testing of a new drug product and new drug substance.
20. Cobby J. Mayersohn M, Walker GC. Influence of shape factors on kinetics of drug release from matrix tablets. II. Experimental. J Pharm Sci. 1974; 63; 732 – 737.