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RESEARCH ARTICLE

Studies on Gastroselective Famotidine Floating Tablets for Gastric Ulcers and Effect of Polymeric Excipients on Drug Release.

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ABSTRACT

The present investigation was planned to formulate effervescent floating, gastroretentive guar gum tablets containing famotidine, which can be useful in the treatment of gastric ulcer. The investigations carried out on various formulations resulted in totally four formulations obeying zero order kinetics. The study on rheological characteristics of powder bed indicated that, all the granules were freely flowing and compressible; density of all the tablets was less than 1, thereby assisting in floating of the dosage form on the surface of the simulated gastric fluids *in vitro*. Studies on compression characteristics indicated that, the tablets float over the surface and remain over the surface for a period of more than 10 h, except FS and FS1, which stay over the surface little lesser time than other tablets. Drug content was fairly uniform and consistent. The floating guar gum tablets containing HPMC K4M and Xanthan gum as binders follow zero order drug release kinetics. The increasing the amounts of magnesium stearate does not significantly alter the drug release kinetics; it improves the flowability of the granule bed. Tablets swell when in contact with water and the swelling index is highest with xanthan gum gel followed by the order, followed by FH> FX1> FC>FH1> FC1>FS>FS1. Stability studies at 45ºC and 75 % RH indicates that there is decrease in drug content, amounting to 30%, when observed for a period of 3 months.

KEYWORDS: Famotidine, Effervescent gastroretentive tablet, Release kinetics, Stability studies

INTRODUCTION:

Oral controlled delivery of drugs at the target site helps in better absorption and improved bioavailability. A buoyant tablet is made to float over the surface of the gastric fluids and remain in the stomach for a long time, thereby increasing the gastric retention time (GRT) of the drug. It is an established fact that, when GRT of a drug, whose therapeutic window is in the upper GIT, is increased bioavailability and hence therapeutic efficacy is highly improved. Famotidine has an oral bioavailability of 40-45% and it undergoes minimal first pass metabolism and has a half-life of 3 h.[1-3] Famotidine has been successfully used in the treatment of gastric ulcer and is available only as a conventional medication, as tablets and capsules. Therefore it was planned in this investigation to formulate 'floating' tablets of famotidine and to develop the formulae using various excipients so that, controlled delivery of the drug is achieved. Also, it was planned to evaluate such tablets for their various pre-compression and compression characteristics, *in vitro* drug release kinetics and stability studies of the formulated tablet dosage forms.

MATERIALS AND METHODS:

Famotidine was purchased from Alkem laboratories, Mumbai, Calcium carboxymethyl cellulose from by Zydus Cadila, Ahmedabad, Hydroxypropylmethyl cellulose by Himedia laboratories, Pvt. Ltd, Mumbai. Xanthan gum purchased from Danmed pharmaceuticals, Hyderabad, Guar gum from Himedia laboratories, Pvt. Ltd, Mumbai. Sodium bicarbonate from Nice chemicals Pvt. Ltd, Cochin. The Starch insoluble, Citric acid, Talc and Magnesium stearate obtained from S.D. Fine chemicals limited Mumbai.

ANALYTICAL METHOD FOR THE ESTIMATION OF DRUG EITHER IN BULK OR IN TABLETS:

Famotidine wavelength scan: The drug was dissolved in distilled water to get 10 µg /ml solution. Further diluted with the same and scanned for absorbance maxima in a Hitachi U-2000 U.V spectrophotometer (double beam) from 200 to 400 nm against distilled water as blank.

CALIBRATION CURVE OF FAMOTIDINE:

100 mg of famotidine drug was accurately weighed and dissolved in distilled water and volume was adjusted to 100 ml with the same solution. The above prepared clear respective stock solutions of drug was subsequently diluted with distilled water to get 2 µg, 4µg, 6 µg, 8µg and 10 µg of drug per ml of the final solution. Then the absorbance of these dilute solutions was measured at 266.5 nm by using double beam U.V. spectrophotometer against a blank of distilled water. The analytical method so developed was validated for precision, accuracy and linearity. Melting point determination: Melting point of the drug was determined by taking a small amount of drug in a capillary

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tube closed at one end and is placed in Theil's melting point apparatus and the temperature at which the drug melts was noted. Average of triplicate readings was noted. Solubility studies: The solubility of all drugs was determined in distilled water and ethanol according to the method proposed by Diez et.al.,[4] Triplicate readings were taken for and average was calculated.

Ingredients (mg)	FS	FC	FH	FX	FS1	FC1	FH1	FX1
Famotidine	80	80	80	80	80	80	80	80
Starch paste (10% w/w)	40	-	-	-	40	-	-	-
CaCMC (10% w/w)	-	40	-	-	-	40	-	-
HPMCK4M (10% w/w)	-	-	40	-	-	-	40	-
Xanthan gum (10% w/w)	-	-	-	40	-	-	-	40
$NaHCO_3$	60	60	60	60	60	60	60	60
Citric acid	45	45	45	45	45	45	45	45
Talc (% w/w)	8	8	8	8	6	6	6	6
Mg. Stearate (% w/w)	4	4	4	4	6	6	6	6
Guar gum	163	163	163	163	163	163	163	163
Total tablet weight (mg)	400	400	400	400	400	400	400	400

Table No. 1. Formulation chart of gastroretentive famotidine tablets with various polymers

PREPARATION OF FAMOTIDINE GRANULES BY WET GRANULATION:

All the powders as obtained in table 4.3 were weighed accurately and passed through # 100 mesh sieve. The smaller particles were granulated with water either starch paste (10% w/w) or CaCMC (10% w/w) or HPMC-K4M (10% w/w) or xanthan gum (10% w/w) as binder and guar gum as diluent/ filler. The wet mass was passed through mesh # 16, dried in an oven at 40°C and again passed through mesh # 20. Later the talc and magnesium stearate as required were incorporated. The granules were stored in air tight container than compressed into tablets. Prepared granules were dried at 40°C and evaluated for various rheological properties like bulk density, compressibility index, flow properties (angle of repose) by using standard procedures. All studies were carried out in triplicate and average values were reported.

BULK DENSITY:

Bulk density was determined (bulk density apparatus, konark instruments, India) by placing the dried granules in a measuring cylinder and the total volume was measured and total weight of granules was measured. Bulk density was given by total weight of granules/total volume of granules [5].

COMPRESSIBILITY INDEX:

Compressibility index was determined by placing the dried granules in a measuring cylinder and the volume (V_0) was noticed before tapping. After 100 tappings again volume (V) was noticed. Compressibility index = $(1- V/ V_0) X 100$. Where V_0 is volume of granules before tapping and V is volume of granules after tapping [5].

ANGLE OF REPOSE (°θ):

Angle of repose was determined by measuring the height, radius of the heap of the granules. A cut stem funnel was fixed to a stand and bottom of the funnel was

fixed at a height of 3 cm from the plane. Granules were placed in the funnel and allowed to flow freely and measured the height and radius of the heap of granules. Similar studies were carried out after incorporating lubricants / glidants. tan ø = h /r. Where h is height of heap of granules and r is radius of heap of granules [5].

PREPARATION OF TABLETS:

After adding lubricants (talc), and anti-adherents (Mg.sterate), granules were compressed into tablets on 10 station pilot press rotary tablets compression machine by using 10 mm diameter, flat faced punches. (PP1D, Chamunda, India)

DETERMINATION OF DRUG CONTENT:

Tablet was crushed into powder in mortar and 100 mg of powder was taken in a volumetric flask and kept aside with constant shaking for 24 hours to extract the total drug present in the tablet. Then the absorbance of the solutions was measured after suitable dilution at 266.5 nm against drug devoid ethanol as blank. Average of triplicate readings was taken. The content of drug was calculated using standard graph [5].

HARDNESS TEST:

The prepared tablets were evaluated for hardness by Pfizer hardness tester [5].

DENSITY MEASUREMENT:

The apparent density of the tablets was calculated from their volumes and masses. The volumes V of the tablets were calculated from their height h and radius r. Height and radius were determined by using micrometer. Volume of the tablets was calculated by using the following equation $V = \prod x r^2 x h$[6].

SWELLING STUDIES:

The swelling study was conducted in petridish containing small amount of water. At regular time intervals of 2 hrs tablet was removed from the petridish, removed the excess of water by placing on filter paper and weighed the tablet. Studies were carried out for 24 h. The % Swelling index is given by as (Weight of the swollen tablet-initial weight of tablet/ Initial weight of the tablet) x100[7].

BUOYANCY LAG TIME DETERMINATION:

The buoyancy of tablets was studied at 37 ± 0.5 °C, in 100 ml 0.1N HCl. A glass beaker contains 100 ml of 0.1N HCl was taken, in which a tablet was placed for observation. The time taken by the tablet to float was observed visually[5].

DURATION OF FLOATING TIME:

A glass beaker contains 100 ml of 0.1N HCl was taken, in which a tablet was placed for observation. Total floating time was studied in 100 ml 0.1N HCl. The total floating time was recorded[5].

***IN VITRO* DISSOLUTION STUDIES:**

Sodium chloride 2.0 g and 3.2 g of purified pepsin was dissolved (porcine stomach mucosa with an activity of 800 to 2500 units per mg of protein) in 7.0 ml of hydrochloric acid and sufficient water to make 1000 ml. Method: A modified dissolution apparatus [9] was fabricated by attaching an S-shaped side arm (glass tube), capable of holding 70 ml of dissolution medium (simulated gastric fluid), to a 100- ml glass beaker. The medium was stirred by a magnetic stirrer. A burette was mounted above the beaker to deliver the dissolution medium SGF at a flow rate of 2 ml/min. The tablet was put in the modified beaker containing 70 ml of dissolution medium (after flotation of the tablet); the medium was stirred at 50 rpm and at 37 ± 0.5 ºC. Samples of 1 ml were collected at predetermined time intervals for 12 hr. All the studies were carried out in triplicate[8].

KINETICS OF DRUG RELEASE:

Attempts to modify drug release from tablets have been reported by kinetic treatment of data, which was assumed that the drug release was conformed to zero order. One indication of the mechanism can be obtained using a plot of the cumulative amount of drug release from the matrix against time. A zero order release would be a linear in such plots indicating that the release rate is independent of concentration. The rate of release of drug can be described mathematically as follows: Rate of release = $dC_s/dt = k$ --- (1). Where C_s is Concentration of drug present in the matrix, k is reaction rate constant and t is time. Since C_s is a constant, x- amount of drug released is described as $dx/dt = k$ --- (2). Integration of equation (2) yields $X = kt + Constant$ - (3). A plot of **'x'** Vs **'t'** results in a straight line with a slope k. The value of k would indicate the amount drug released per unit time and the intercept of the line at time 0 is equal to constant to the equation[10].

PEPPA'S EQUATION:

Peppa's et.al used a simple empirical equation to describe general solute behaviour from controlled release polymer matrices: $M_t / M_\infty = k x t^n$. Where M_t / M_∞ are fraction drug released, k is kinetic constant, t is release time and n was the diffusional exponent for drug release. Peppas claimed that, the above equation could adequately describe the release of solutes from slabs, spheres,

cylinders, and tablets (discs), regardless of release mechanism. The value of 'n' gives an indication of release mechanism. When n = 0.87 to 0.91 zero order release; when n = 0.447- 0.454 the drug release follows fickian diffusion; and the value of n is 0.45< n > 0.85 then anomalous non fickian release would be implicated. Where n is the slope value, of log M_t / M_∞ vs log time curve. In the present work, the *in vitro* data was analyzed by both zero order kinetics equation as well as korsemeyer's equation to understand the release profile and release mechanism[12].

RESULTS AND DISCUSSION:

Famotidine U.V. absorption maxima in water were found to be 266.5 nm which is same as literature value 266 nm. [12] Melting point was found to be 158°C which corroborates with the literature. [12] Solubility of famotidine was found to be 1.28 mg/ml in distilled water and in ethanol 1.32 mg/ml at 20°C, but in ether and ethyl acetate famotidine was found to be insoluble. pH of 2% solution was found to be 8.79. It was optimized that for a 400 mg tablet containing 80 mg of famotidine, 60 mg and 45 mg of sodium bicarbonate respectively were required; to float the tablet within 9 min and to make the tablet stay buoyant for > 10 h. Guar gum was used as a diluent showing desirable results. In this study it was planned to control the release of the active ingredient for more than 10 h. Therefore guar gum alone was selected as a diluent in this study. Guar gum also swells in the presence of fluids. While optimizing sodium bicarbonate: citric acid ratio, minimum floating lag time 9 min and maximum period of floatation > 10h was observed with 1:0.75 ratio, hence the ratio was optimized. This result is in confirmation with a previous work by Sanjay Garg et.al. [13]

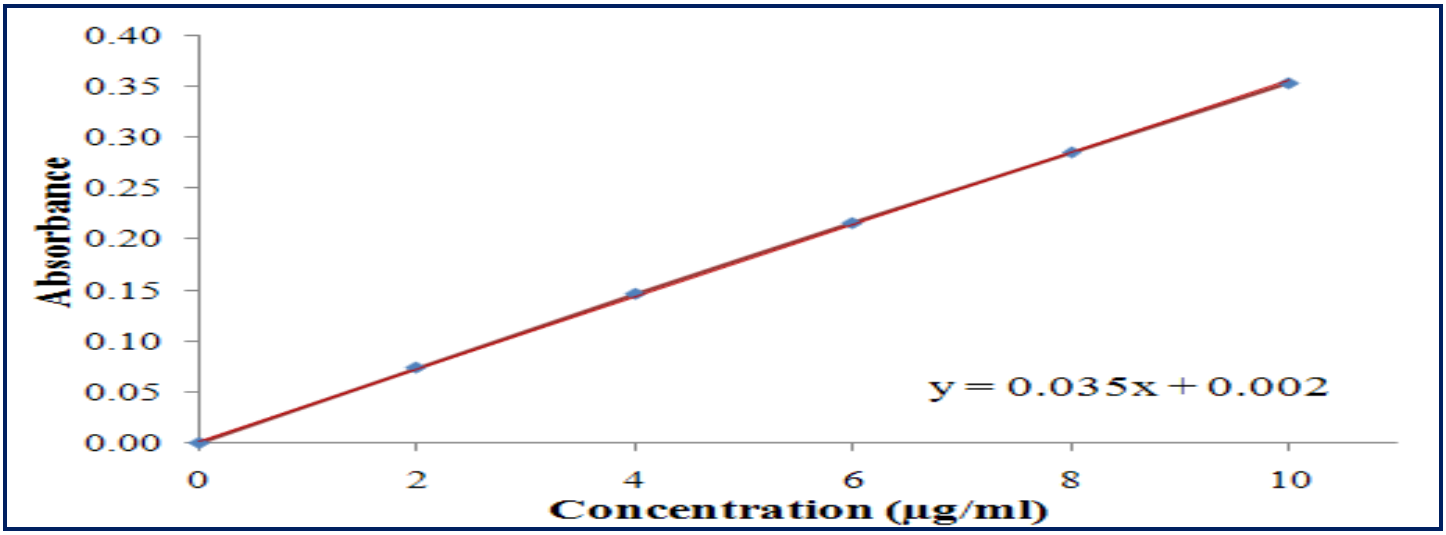

Figure No. 1. Calibration cure of famotidine in distilled water

Code	Accuracy (%)	Precision	Repose angle(° θ)	BD (g/cm^3)	CI (%)	Thickness (mm)	Hardness (Kg/cm^2)	Density (g/cm^3)	Flt. lag time (min)	Float time (h)	DC (mg)
FS	98.93	0.0498	29.52	0.598	3.35	5.2	4.2	0.971	8.17	6	78.23
FC	101.64	0.0774	30.24	0.625	4.08	5.18	4.2	0.976	8.17	12	78.28
FH	103.19	0.0686	29.65	0.632	4.86	5.12	4.4	0.958	8.50	15	78.56
FX	101.64	0.0669	29.86	0.672	5.72	5.12	4.6	0.934	9.00	16	77.21
FS1	99.56	0.0521	28.78	0.628	4.25	5.13	4.2	0.989	8.50	8	78.46
FC1	99.98	0.0450	28.29	0.632	4.26	5.08	4.2	0.968	8.50	12	78.28
FH1	100.02	0.0532	28.56	0.645	4.78	5.12	4.4	0.958	8.80	15	78.90
FX1	99.95	0.0351	28.25	0.686	5.26	5.12	4.6	0.954	9.00	16	76.68

Table No. 2. Rheological properties of various formulations containing famotidine

The granules bulk density was found to be the highest with FX and least with FS, and the order was found to be FX> FH> FC>FS. Similar studies were conducted for talc: magnesium sterate 1:1 the results for this were found to be similar and the order was found FX1> FH1> FC1>FS1. It was observed that, bulk density of granules containing talc: magnesium stearate 1:1 was always higher with all the binders used in the study, as compared to talc: magnesium stearate 2:1. Angle of repose (°θ) was found to be decreasing when lubricants/ glidants were incorporated and it also decreased further upon increasing their amount. The hardness of tablets was found to be between 4.2 Kg/cm^2 to 4.6 Kg/cm^2. The strength of the tablet with xanthan gum as binder was found to be the highest 4.6 Kg/cm^2 followed by HPMC-K4M 4.4 Kg/cm^2, CaCMC and starch 4.2 Kg/cm^2. The densities of compressed tablets were calculated from their respective mass and volume. The densities of all compressed formulation are of less than 1 g/cm^3. All the formulations showed lag time of less than 9 min. The formulation prepared using guar gum as diluent floated to simulated gastric fluid surface within 9 min and when the same tablets were allowed to stand on the surface of the fluid, they did not sink nor disintegrate within 10 h. The tablets were swollen; shape was not significantly distorted and did not disintegrate for at least 10 h.

Code	Floating tablet matrix percent swelling index							
	1 hr	2 h	4 h	6 h	8 h	10 h	12 h	18h
FS	0.44	1.08	1.27	1.36	1.42	1.96	1.96	2.21
FC	1.26	1.46	2.52	2.68	3.46	3.87	3.87	4.38
FH	1.54	1.68	2.96	2.96	3.68	4.46	4.46	5.21
FX	1.72	2.23	3..45	3.45	3.45	4.10	4.84	5.67
FS1	0.38	0.96	1.26	1.26	1.38	1.54	1.54	1.86
FC1	1.18	1.26	1.98	1.98	2.46	3.24	3.24	3.47
FH1	1.36	1.45	2.28	2.28	2.78	3.56	3.56	4.16
FX1	1.52	1.78	2.62	2.62	3.12	3.92	3.92	4.87

Table No. 3. Swelling studies for different formulations of famotidine floating tablets

The FS formulation released 90.74% of drug in 12 h. As the solvent seeps in and brings out the drug on its return path into the media with peppa's r value 0.938 and the n value was found to be 0.83 indicated drug release other than zero order, owing to both polymer relaxation and diffusion mechanisms. The FC showed 94.04% of drug release in 12 h and according to Peppa's equation r is 0.941 and n value was found to be 0.82. Erosion of particles might occur from the swollen matrix. The drug release kinetics therefore follows other than zero order due to polymer relaxation and diffusion. The dissolution of FH released 86.41% of drug at the end of 12 h. The data obtained was subjected to, regression analysis by least squares method (r), and ANOVA, a value of $p< 0.05$ was considered to be significant. More solvent seeps in and solubilize the drug in the matrix and brings out the drug on its return path into the media. For peppa's equation r is 0.943 with n value was found to be 0.88. The drug release kinetics therefore follows exact zero order. Where the FX formulation released 89.00% of drug and the data obtained was subjected to, regression analysis by least squares method (r). From the peppa's plot the value of 'n' was found to be 0.87. The drug release kinetics therefore follows exact zero order.

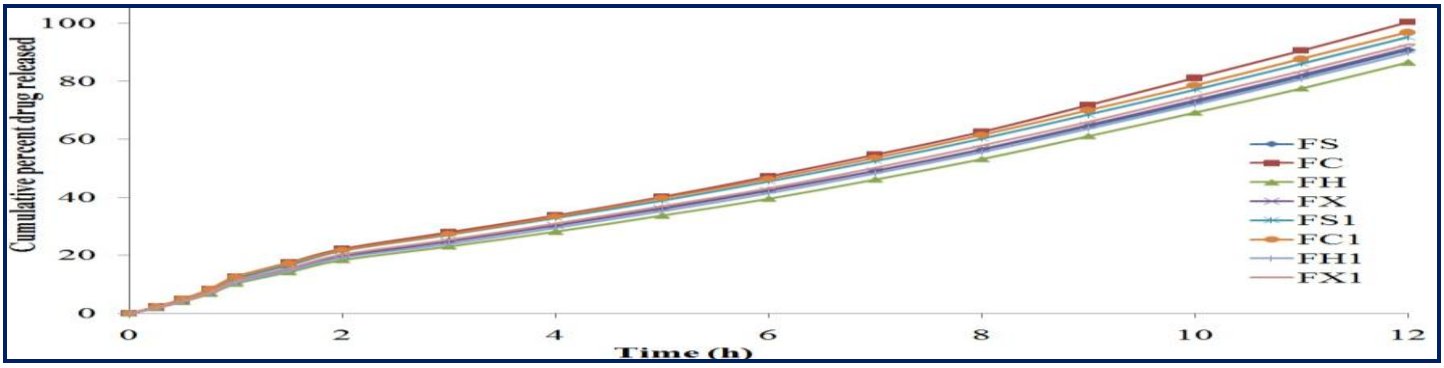

Figure No. 2. *In vitro* drug release of famotidine from gastroretentive tablets

The FS1 containing starch 10%w/w as binder and guar gum as filler released 95.41% of drug. Plot of cumulative amount of drug release (mg) vs time (h) showed linear curve with an r value 0.997. The peppa's value of 'n' was found to be 0.82 indicate erosion of particles from the swollen matrix. The drug release kinetics therefore follows other than zero order, due to polymer relaxation and diffusion. Later the FC1 released 97.33% of drug into the dissolution media. The data obtained was subjected to, regression analysis by least squares method. More solvent seeps into the core of the tablet and reaches the drug, solubilize the drug in the matrix and brings out the drug on its return path into the media. For such a plot according to Peppa's equation showed r value of 0.941 and n value 0.82. Erosion of particles might occur from the swollen matrix. The drug release kinetics therefore follows other than zero order. The results of FH1 formulation revealed that the drug released from 15 min onwards and upto 12 h with 89.04% of drug into the dissolution media. The r value of 0.943 and n value of 0.88 indicated zero order drug release kinetics. The FX1 formulation containing xanthan gum (10%w/w) as binder and guar gum as diluent/ filler released 92.008% drug in 12h. The n value of 0.87 and 0.994 r indicated zero order release kinetics.

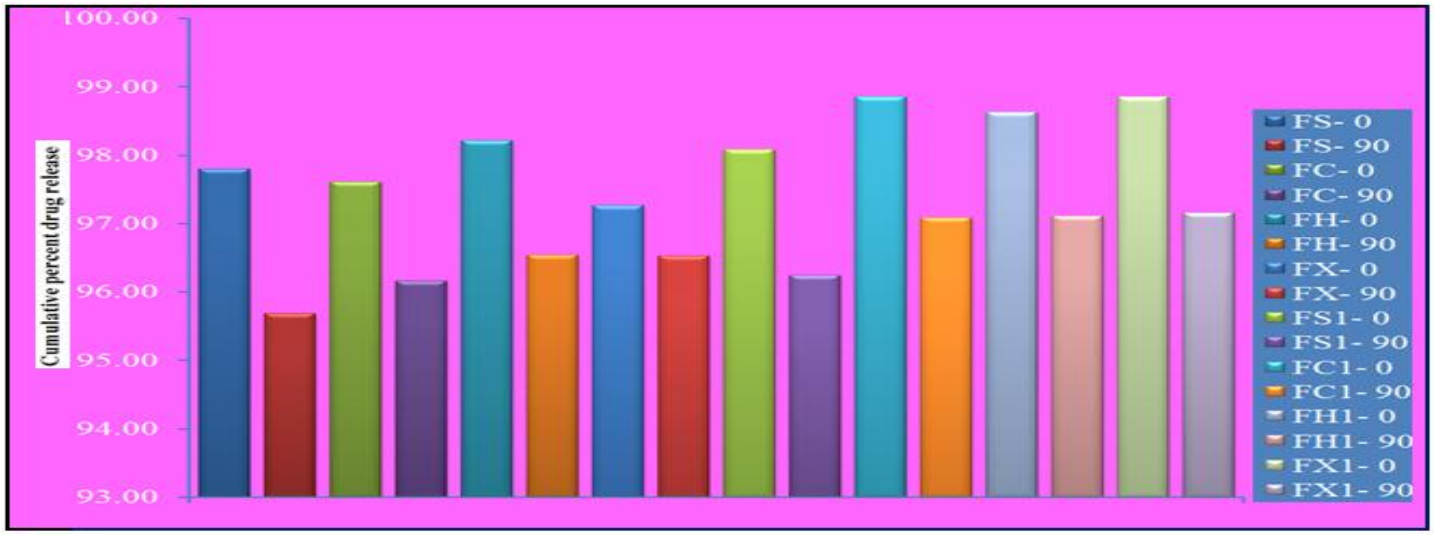

Figure No. 3. Stability studies of famotidine floating tablets at 45°C and 75% RH

Stability studies were conducted according to ICH protocol at 45°C/ 75% RH for a period of 90 days. Results indicated that there is slight decrease in drug content after every 24 h, and in total there is a decrease of 10% drug content at the end of the stress studies.

CONCLUSIONS:

The study has indicated that, gastro retentive floating tablets of guar gum can be tailored to release famotidine by zero order using HPMC-K4M and Xanthan gum at 10% w/w as binders. Thus, study of pre compression and compression characteristics, *in vitro* release and stability studies concluded the objective of the investigation.

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