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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING MATRIX SUSTAINED RELEASE TABLETS OF LAFUTIDINE USING NATURAL AND SEMISYNTHETIC POLYMERS

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ABSTRACT

The purpose of the present investigation is to develop floating matrix sustained release tablets of lafutidine to prolong the gastric residence time of the drug as well as to deliver the drug over prolonged periods of time to maximize therapeutic efficacy and improve the bioavailability of the drug. Lafutidine is a newely developed second generation histamine H_2-receptor antagonist were prepared by direct compression method using different concentration of semisynthetic gel forming hydrophilic polymers HPMC K15 M, HPMCK4M and freshly prepared natural tamarind seed polysaccharides powder. The prepared tablets of various formulations were evaluated for a total floating time, buoyancy lag time, swelling index and percentage drug released. Compatibility studies were performed by FTIR and DSC methods, it confirms that there is no interaction between the drug and polymer. The formulation code F4 having HPMCK4 showed better results it may be useful for prolonged drug release (97.81±1.407 in 12 hrs) in the stomach to improve the bioavailability and reduced the dose frequency. Non- fickian diffusion was confirmed as the drug release mechanism from optimize formulation by zero order kinetics. *In-vivo* study was performed using the rabbits by x-ray imaging technique, radiological evidences suggest that, a formulated tablet was floated upto 12 hrs in rabbits stomach. Optimize formulation showed no significant changes in the physical appearance, drug content, floating lag time and also *in-vitro* dissolution pattern after storage at 40ºC±2/75%±5 relative humidity for 2 months.

INTRODUCTION

The design of floating drug delivery system (FDDS) should be aimed that to achieve more predictable and increased bioavailability of drug[1]. Floating systems are low- density systems that have sufficiently buoyancy to float over the gastric content and remain buoyant in the stomach without Affecting gastric emptying rate for a prolonged period of time, which results in a increased gastric retention time and a better control of fluctuation in plasma drug concentration. After release of drug, the residual system is emptied from stomach[2,3,4].Lafutidine is newely developed

second generation histamine H_2-receptor antagonist[5]. It is used in the treatment of gastric ulcers, duodenal ulcers and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis[6]. Lafutidine is proved that it is inhibits day-time as well as night time gastric acid secretion. Despite these promising biological effects of lafutidine, a major drawback with lafutidine is its low aqueous solubility which leads to low bioavilability and short elimination half life[7,8]. Lafutidine is absorbed in the small intestine, reaches gastric cells via the systemic circulation and rapidly binds to gastric cells H_2-receptors, resulting in immediate inhibition of gastric secretion.Lafutidine has a receptor binding affinity, which is 2-80 times higher than famotidine, ranitidine and cimetidine.[9] As per the literature study the selected tamarind seed polysaccharides a novel natural polymer with exhibit high viscosity even at low concentration, broad p^H tolerance, non-carcinogenicity, mucoadhesivity and biocompatability[10]. As it forms a strong viscos gel on contact with aqueous media, which may be useful in sustained delivery of drugs. The main objective of the present work was to formulate and evaluate floating matrix sustained release tablets of lafutidine along with freshly prepared natural Tamarind seed polysaccharides polymers, which is prepared by direct compression method using effervescent technique. Floating matrix tablets were designed such that they prolong the gastric residence time and thus increase the half-life of the drug so that it assist in improving the oral sustained delivery of drugs in gastrointestinal tract.

MATERIALS AND METHODS:

Lafutidine was procured as a gift sample from Pure Chem Pvt. Ltd, Gujarat, India. HPMC K15, K4, sodium bi carbonate and citric acid were provided as a gift sample from Fourrts India Laboratories Pvt. Ltd. Tamarind seed polysaccharide prepared with the help of Bose Clinical Laboratory, Madurai, India. Microcrystalline cellulose, Talc and Magnesium stearate were supplied from Paris Dakner Pvt. Ltd, India. All other chemicals used were of analytical grade.

FT-IR Spectroscopy Study: Fourier transform infrared spectroscopy (Shimadzu RXI Japan) was carried out to study the compatibility of pure drug of Lafutidine with the polymer used in the formulations of floating tablets. IR spectrum of pure drug and the physical mixture of drug with polymers of optimized formulation were recorded[11]. The pellets were prepared in KBr dish and scanned over the frequency range from 4000 to 450 cm^{-1}.

Differential Scanning Calorimetry Studies (DSC) : The DSC analysis of drug, and excipient physical mixture were done using Differential Scanning Calorimeter (Perkin Elmer Pyris-DSC)[12]. The specified samples is hermetically sealed in aluminum pans at temperature 20ºC/min nitrogen were purged at 50ml/m in conducted over a temperature range of 35ºC to 380ºC.

Preparation of lafutidine floating matrix tablets : Lafutidine floating matrix tablets were prepared by direct compression technique using HPMC K15M, HPMC K4M and natural polymer Tamarind seed polysaccharides as a polymer. The powder mixture containing drug, polymer, tamarind seed polysaccharides, sodium bicarbonate, citric acid, microcrystalline cellulose, magnesium stearate and talc. All the excipients were individually weighed and passed through sieve no.40. Then the drug was weighed accurately and added to the mixture. Excipients and the drug were mixed thoroughly in a mortar for 5-10 min. Then talc and magnesium stearate were weighed and added to the blend and the obtained blend was compressed using 8mm flat single punch tablet machine (Cadmach Machinery Co. Pvt, Ahmadabad)[13]. The composition of the different formulation were given in **Table 2.** All the tablets were white in color and round in shape having 8mm diameter.

Evaluation of pre-compression parameters of powder blend:

Micromeritic properties: The floating tablets were characterized by their micromeritic properties such as angle of repose, bulk density, tapped density, carr's index and hausner's ratio.[14,15,16]

Angle of repose : The flow characteristics are evaluated by determining angle of

repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle of repose is calculated using the equation.

Angle of repose (Ɵ) = $\tan^{-1}h/r$

Bulk Density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

Bulk density = Mass of powder / Bulk volume of powder

Tapped Density: It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume were noted if the difference between these two volumes is less than 2%. If it is more than 2%, then tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

Tapped density = Mass of powder / Tapped volume of powder

Percentage of compressibility index and Hausner's Ratio: Compressibility index and Hausner's ratio have become the simple, fast, and popular method of predicting powder flow properties. The Compressibility index and Hausner's ratio were determined by measured both the bulk volume and the tapped volume of a powder.

Compressibility index = 1- (Bulk density/ Tapped density)

Hausner's Ratio = Tapped density/ Bulk density

Physico chemical characterization of gastroretentive floating matrix tablets of Lafutidine

Tablet Dimension : The thickness and diameter of the tablets are carried out using digital vernier caliper . Three tablets of each formulation were picked randomly and its thickness were measured and the results are expressed in millimeter (mm).

Weight variation : Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The tablets meets the IP test if not more than 2 tablets are outside the percentage limit and if no tablets differs by more than 2 times the percentage limit.[17]

Hardness test : Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Monsanto hardness tester.[18] Three tablets were randomly picked from each batch and results are expressed in Kg/cm^2.

Friability test : Roche friabilator was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.[19]

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Drug content uniformity: Ten tablets were weighed and taken in a mortar and crushed to make powder form. 10mg equivalent weight of drug was accurately weighed and transferred into a 100ml volumetric flask. It was dissolved and made up the volume with 0.1N HCL, P^H 1.2 followed by The solution is filtered using membrane filter (0.45µm) and suitable dilutions were made and analyzed at 283nm using UV - Visible spectrometer.[19] The amount of drug present in each tablet was estimated from standard curve of drug using 0.1N HCL, P^H 1.2.

In-vitro buoyancy studies: The *in-vitro* buoyancy was characterized by floating lag time and floating duration. The *in-vitro* floating behaviour of the tablets were studied by placing them in 100 ml beaker containing 100ml 0.1N Hcl buffer, P^H 1.2, was used as a medium and the temperature was maintained to at 37^0 ±0.5C through the study. **Floating lag time** is the time required by the tablet to emerge at the

surface when introduced in the medium and the time, tablets constantly float on the surface of the medium is called **floating duration or total floating time.**[20]

Swelling index study: Weight gain or water uptake can be studied by considering the swelling behaviour of floating dosage form. The water uptake study of the floating tablets were done by immersing the dosage form in 900ml of p^H 1.2 Hcl buffer as a medium using USP dissolution apparatus type-II (paddle).The medium was maintained at 37 ± 0.5ºC throughout the study. After 8 hours the tablets were removed from their swelling media, blotted to remove excess water using filter paper and weighed.[21] The swelling index of the floating tablets was calculated by using the formula,

$$\text{Swelling index} = \frac{\text{Weight of swollen tablet - Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

***In -vitro* drug release studies:** The drug release was studied using a USP dissolution apparatus type II (Disso 2000 Lab, Mumbai, India) at 75 rpm in 0.1N hydrochloric acid, P^H 1.2 as a dissolution medium (900 ml) maintained at 37±0.5°C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at specified intervals and the samples were replaced with fresh dissolution medium to maintained sink condition.. The samples were filtered through a 0.45 µm membrane filter. Absorbance of these solutions was measured at 283 nm using UV-Visible spectrophotometer (Shimadzu 1700, Japan). All experiments were performed in triplicate for 12 hours. Cumulative percentage drug release was calculated .[22]

Kinetic modeling of drug release : To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained were fitted to various kinetic equations such as zero order, the first order, Higuchi matrix and Korsmeyer- Peppas equation. The regression co-efficient values were calculated. In this by comparing the regression coefficient values obtained, the best fit model was selected[23].

***In- vivo* floating behaviour :** Floating study was carried out on healthy albino rabbit by fasting the animal 12 h and X- ray photographs was taken to ensure absence of ratio opaque material in the stomach. The rabbit was made to swallow barium sulphate loaded floating tablets with 30ml of dextrose solution. At predetermined time intervals (0,2,4,6,8,10 &12 hrs) the radiograph of abdomen was taken using an X-ray imaging technique for finding the total residence time of the tablet in the stomach. The institutional Human Ethical Committee approved the protocol for the study.[24]

Stability Studies : Stability studies were conducted only on optimized formulation(F4). The formulation were packed with aluminum foil and subjected to stability studies at 40^0C ± 2^0C temperature and 75 ± 5% relative humidity conditions for a period of 2 months as per ICH (International Conference on Hormonization) guidelines. The samples were withdrawn at time intervals of 0, 15, 30 ,45, and 60days. The samples were tested for average weight, thickness, hardness, floating lag time, swelling index, drug content and *In-vitro* release studies.[25]

RESULTS AND DISCUSSION

Determination of λ max: The absorption maximum (λmax 283 nm) of the Lafutidine was estimated by scanning the drug solution (10µg/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λmax) was 283 nm for the Lafutidine. The result was shown in **Figure1.**

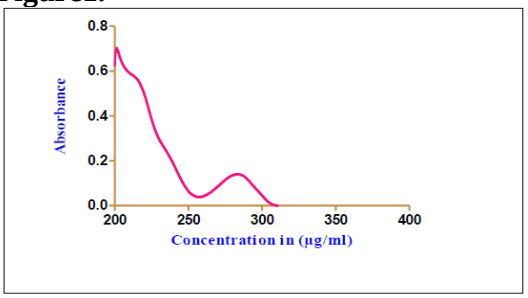


Fig 1: Absorption maximum (λ max) of drug sample

Calibration of lafutidine in phosphate buffer P^H 1.2

The Standard Calibration curves of Lafutidine were prepared using acid buffer

pH 1.2. The absorbance were measured at λmax of 283nm. The correlation coefficient was found to be 0.9995. Lafutidine obeys the beer's law within the concentration range of (5-25µg/ml). Calibration plot of lafutidine in phosphate buffer pH 1.2was shown in **Table 1 and Figure 2.**

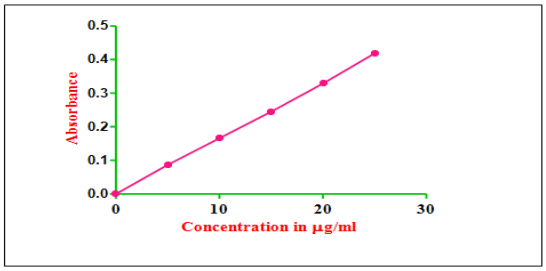


Fig 2: Standard curve of drug in 0.1 N HCL

Compatability Studies (Fourier Transform Infrared Spectroscopic (FT-IR): Drug polymer interaction was checked by comparing the IR spectra of pure drug(**Fig. 3)** and the physical mixture of the drug with the polymer used **(Fig. 4-6)** and optimized formulation (**Fig.7**). The presence of peaks confirms that no major shifting of bands or peaks was observed in both formulation and pure drug indicating no possible interaction between drug and polymers used in the study was shown in **Table 3,4.**

Differential Scanning Calorimetry (DSC) Studies : This study was carried out to detect drug- polymer interaction. The DSC thermogram of pure lafutidine showed sharp endothermic peak at 103.4ºC, which corresponding to its melting transition temperature. The thermogram of the final best formulation of lafutidine with other excipients showed the existence of drug endothermic peak within the range which indicated the absence of interaction between the drug and other excipients. The DSC thermogram of pure drug and the final best formulation was presented in **Figure 8,9**.

Evaluation of pre-compression parameters of powder blend: Prepared powder blend of all the formulations of the lafutidine ((F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12) were evaluated for their physical properties such as the angle of repose (θ) was in the range of 30-35^0 shows good flow properties: Bulk and tapped density were found in the range of 1.08 to 1.12 gm/ml and1.29 to 1.34 gm/ml respectively. Carr's index and Hausner's ratio were studied and found in range of 15.58-17.8% and 1.18-1.22% showing good flow properties, good compressibility, which allow these formulations to be directly compressed into tablets. Results of pre-compression evaluations of formulations were shown in **Table 5,6.**

Physico chemical characterization of gastroretentive floating matrix tablets of Lafutidine

The physic chemical characterization of gastroretentive floating tablets were evaluated for general appearance, tablet dimension, hardness, friability, weight variation and drug content the results were shown in **Table 6,7.** All physicochemical parameters of all the formulations (F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12,) were within the acceptance limit. The drug content was found to be within a narrow range as specified in pharmacopoeia (97.18-100.4%) in all the formulations.

***In-vitro* buoyancy study :** The **floating lag time** of all the formulations were found to be in the range of 10-60 seconds and **duration of floating time** of all formulations were upto 12 hours which is sufficient to be consider as buoyant drug delivery systems.The result were shown in **Table 8**

Swelling Index Studies: Tablets comprised of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet. Swelling mechanism to ensure floating and drug dissolution of the floating tablets .The floating tablets containing HPMCK4M showed constant increased in swelling because HPM care more hydrophilic than the another. In case of increasing concentrations of HPMCK15M showed an increase in swelling, but not to the extent of HPMCK4M. The formulation F4 containing HPMCK4M showed less swelling index at the beginning, but was found higher at end of 8 h (65.57±1.1).The results were shown in the **Table 8 and Figure 10.**

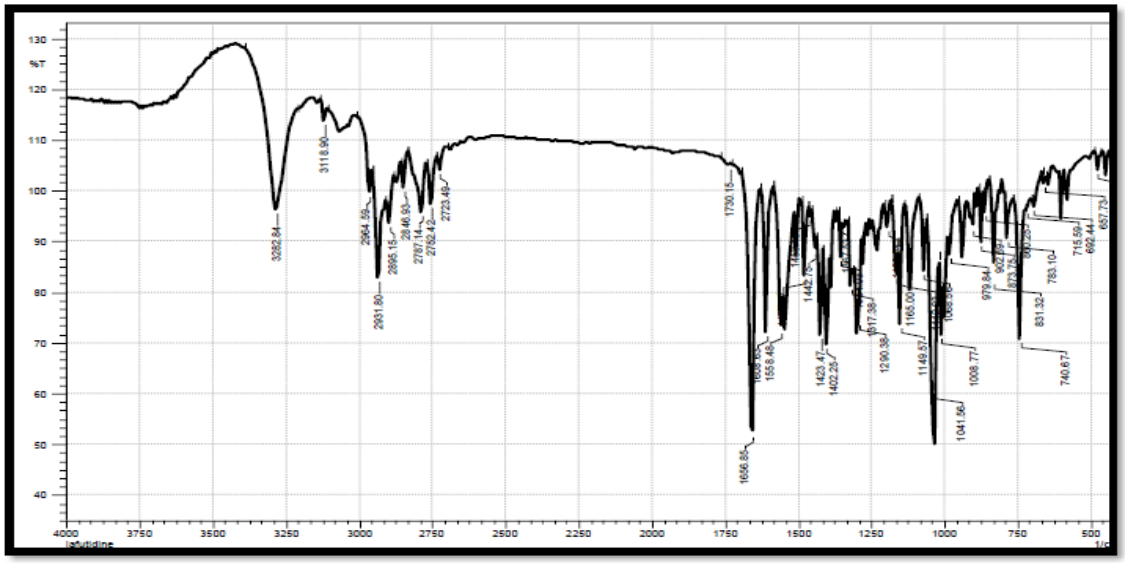


Fig 3: FTIR study of Lafutidine

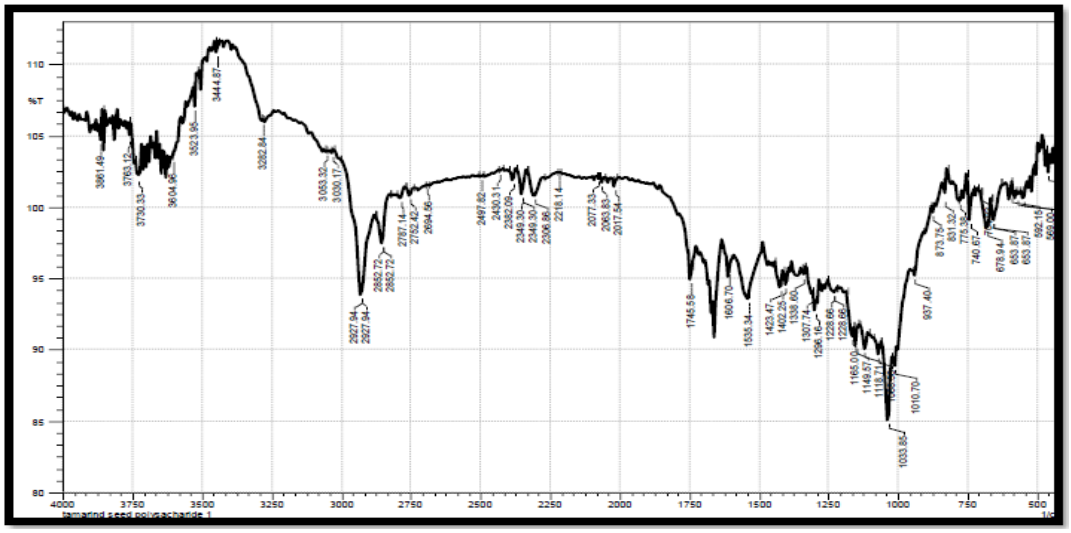


Fig 4: FTIR study of Tamarind seed polysaccharide

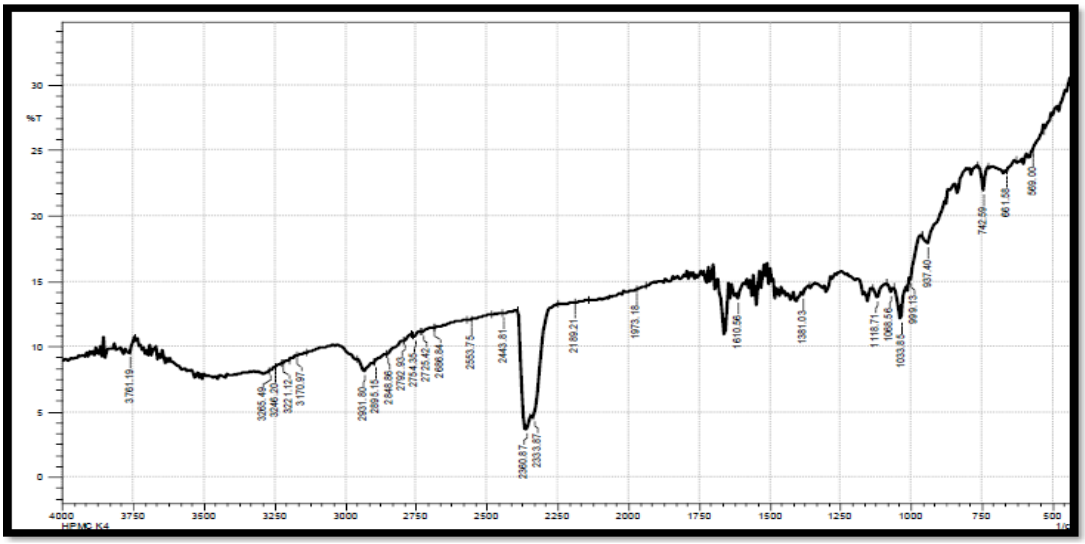


Fig 5: FTIR study of HPMCK4M

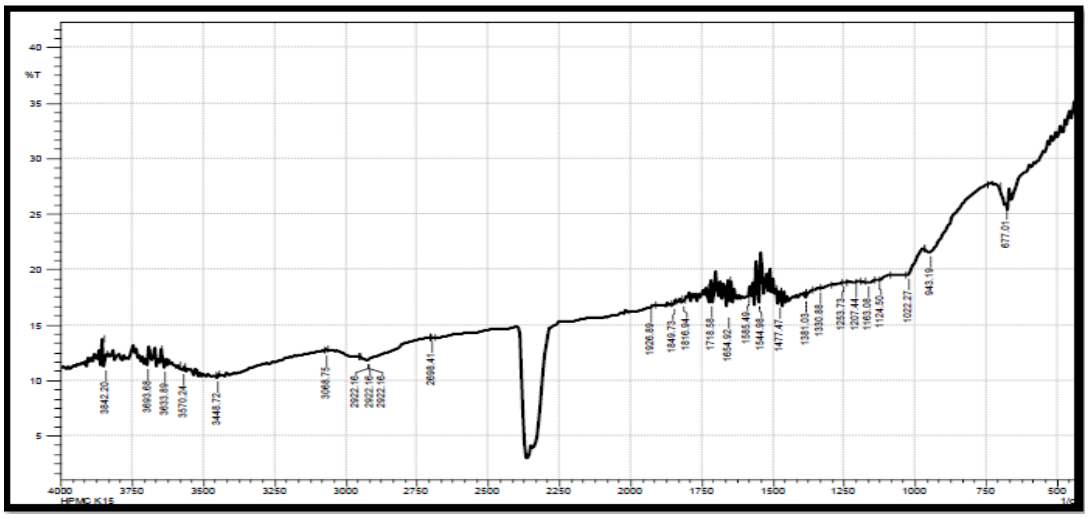


Fig 6: FTIR study of HPMCK15M.

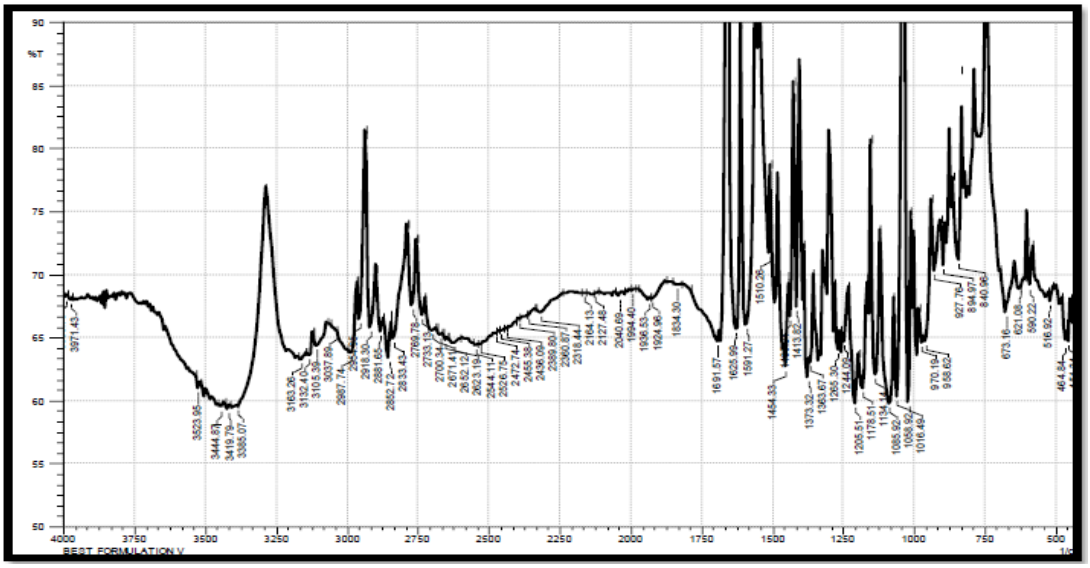


Fig 7 : FTIR study of best formulation (F4)

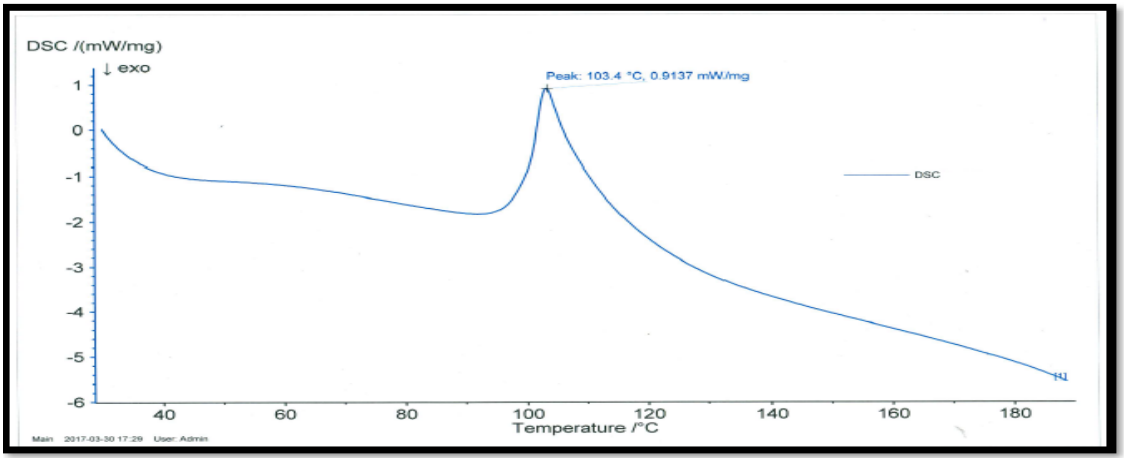


Fig 8 : DSC study of Lafutidine pure dr

Table 1: Calibration curve of Lafutidine using acid buffer p^H

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE
1	5	0.087
2	10	0.166
3	15	0.245
4	20	0.329
5	25	0.419

Regression Value –0.9995

Table 2: Composition of gastrorententive floating tablets of Lafutidine

Formulation code / Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lafutidine	10	10	10	10	10	10	10	10	10	10	10	10
Tamarind seed poly saccharides	2	4	6	8	10	12	2	4	6	8	10	12
HPMCK4	140	130	120	110	100	90	-	-	--	-	-	-
HPMCK15	-	-	-	-	-	-	140	130	120	110	100	90
Sodium bicarbonate	20	25	30	35	40	45	20	25	30	35	40	45
Citric acid	6	6	6	6	6	6	6	6	6	6	6	6
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Microcrystalline Cellulose	16	19	22	25	28	31	16	19	22	25	28	31
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Table 3: IR Spectral Interpretation of Lafutidine

Sl.No.	Functional group	Peak in cm^{-1}	Peak observed (cm^{-1})
1	N-H Stretching (Aliphatic)	3282.84	3287.03
2	C-H Stretching (Aromatic)	3118.90	3105.39
3	C=N Stretching	1656.85	1691.57
4	N=H Bending	1608.63	1652.99
5	C-H Bending	1458.18	1454.33
6	C-N Stretching	1354.03	1363.67

Table 4: IR Spectrum of best formulation F4 (HPMCK4M)

Sl. No.	Functional group	Peak in cm^{-1}	Peak observed(cm^{-1}) pure drug	Peak Observed(cm^{-1}) drug and polymer
1	N-H Stretching (Aliphatic)	3329 -3204	3282.84	3287.03
2	C-H Stretching (Aromatic)	3100-3000	3118.90	3105.39
3	C=N Stretching	1690-1640	1656.85	1691.57
4	N=H Bending	1640 -1570	1608.63	1652.99
5	C-H Bending	1450-1470	1458.18	1454.33
6	C-N Stretching	1350-1000	1354.03	1363.67

Table 5: Precompressional evaluation of powder blend

Formulation code	Angle of repose(Degree	Bulk density (gm/ml)	Tapped density (g/ml)	Compressibility index(%)
F1	$29^0$42' ± 1.11	1.11 ± 0.01	1.34 ± 0.02	16.88 ± 2.37
F2	$26^0$69' ±1.51	1.12 ± 0.01	1.35 ± 0.011	16.99 ± 0.144
F3	$33^0$47 ' ± 1.63	1.11 ± 0.01	1.32 ± 0.035	15.58 ± 1.5404
F4	$30^0$94' ± 0.56	1.12 ± 0.01	1.34 ± 0.02	15.01 ± 2.037
F5	$31^0$05' ± 1.48	1.11 ± 0.02	1.33 ± 0.023	16.45 ± 2.037
F6	$31^0$68' ± 1.82	1.12 ± 0.01	1.34 ± 0.034	16.99 ± 0.1443
F7	$34^0$29' ± 0.51	1.09 ± 0.01	1.32 ± 0.02	17.16 ± 1.015
F8	$34^0$60' ± 0.92	1.09 ± 0.01	1.32 ± 0.02	17.15 ± 1.952
F9	$29^0$72 ± 1.48	1.08 ± 0.02	1.29 ± 0.025	16.45 ± 0.514
F10	$29^0$92 ± 1.45	1.07 ± 0.01	1.32 ± 0.02	18.4 ± 2.378
F11	$30^0$63 ± 2.29	1.08 ± 0.005	1.32 ± 0.02	17.8 ± 1.500
F12	$34^0$12 ± 1.22	1.08 ± 0.02	1.29 ± 0.0251	16.45 ± 0.5146

Table 6:Physico chemical characterization of gastroretentive floating tablets of Lafutidine

Formulation Code	Hausner's ratio	Average weight in(mg)	Diameter (mm)	Thickness (mm)
F1	3.59 ± 0.035	196.83±0.153	8	3.39±0.201
F2	1.2 ± 0.300	197.17±0.045	8	3.51±0.032
F3	1.18 ± 0.020	199.08±0.055	8	3.32±0.036
F4	1.18 ± 0.030	198.46±0.061	8	3.39±0.030
F5	1.19 ± 0.0519	196.73± 0.053	8	3.26± 0.030
F6	1.20 ± 0.0115	201.00± 0.155	8	3.4± 0.081
F7	1.20 ± 0.015	195.82± 0.070	8	3.48± 0.120
F8	1.20 ± 0.321	198.24± 0.055	8	3.49± 0.035
F9	1.19 ± 0.01	198.9± 0.187	8	3.37± 0.040
F10	1.22 ± 0.035	193.42± 0.169	8	3.22± 0.05
F11	1.21 ± 0.017	201.7 ±0.178	8	3.19 ±0.045
F12	1.19 ± 0.01	199.85± 0.323	8	3.16± 0.041

n=3*

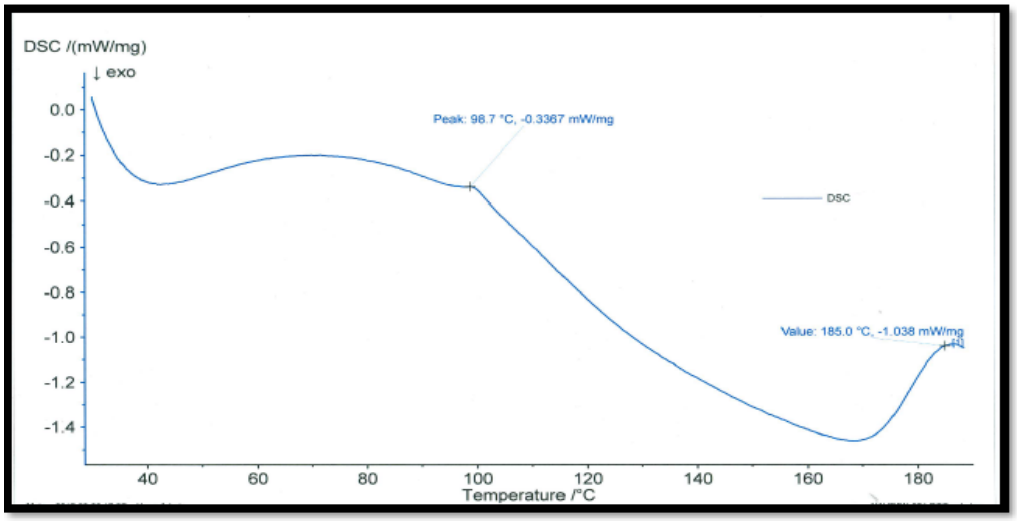


FIG 9 : DSC study of best formulation (F4)

Table 7:Physico chemical characterization of gastroretentive floating tablets of Lafutidine

Formulation code	Hardness Kg/cm^2	Friability (%) ± SD	Drug content (%)± SD
F1	6.26 ±0.378	0.529±0.038	97.18±0.352
F2	6.76±0.251	0.493±0.020	98.39±0.3464
F3	7.1±0.264	0.526±0.132	98.39±0.3464
F4	7.2±0.458	0.595±0.121	98.99±0.3464
F5	7.0±0.378	0.533±0.066	98.39±0.3464
F6	7.0±0.321	0.526±0.040	98.79±0.6
F7	6.9±0.305	0.54±0.03	97.79±0.3464
F8	6.7±0.251	0.456±0.023	99.59±0.3521
F9	7.1±0.251	0.496±0.035	99.19±0.3464
F10	6.8±0.458	0.47±0.02	100.4±0.3464
F11	7.1±0.251	0.436±0.047	98.59±0.3464
F12	7.1±0.351	0.58±0.052	99.59±0.3521

n=3*

Table 8:Physico chemical characterization of gastroretentive floating tablets of Lafutidine

Formulation code	Buoyancy lag time (in minutes)	Total floating time (in hours)	Swelling index (%) (8 hours)
F1	45 sec	< 12	60.91
F2	37 sec	<12	59.51
F3	25 sec	<12	60.82
F4	14 sec	<12	65.57
F5	16 sec	<12	59.56
F6	10 sec	>12	57.24
F7	1 mints	<12	61.97
F8	42 sec	<12	61.64
F9	35sec	<12	60.50
F10	20sec	<12	59.55
F11	Immediately	<12	59.72
F12	Immediately	>12	58.87

Table 9: *In -vitro* drug release studies of floating matrix tablets of Lafutidine

Sl.No	Time in hours	Formulation code	Drug release in (%) ± SD 12 hours
1	1	F1	61.63 ± 0.376
2	2	F2	76.89 ± 0.779
3	3	F3	86.61 ± 1.407
4	4	F4	97.81 ± 1.407
5	5	F5	95.77 ± 0.667
6	6	F6	90.28 ± 0.825
7	7	F7	63.51 ± 0.177
8	8	F8	65.91 ± 0.295
9	9	F9	73.94 ± 0.659
10	10	F10	84.08 ± 0.283
11	11	F11	80.74 ± 0.577
12	12	F12	78.8 ± 0.190

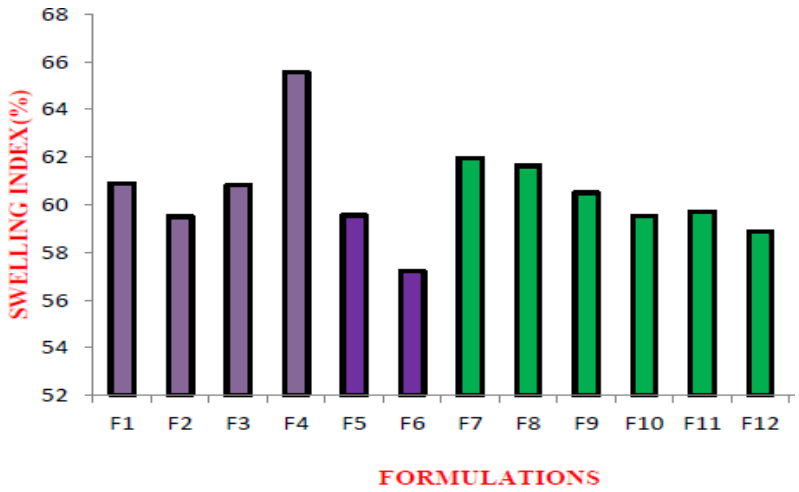


Fig 10 : Comparative study of swelling index of various formulations

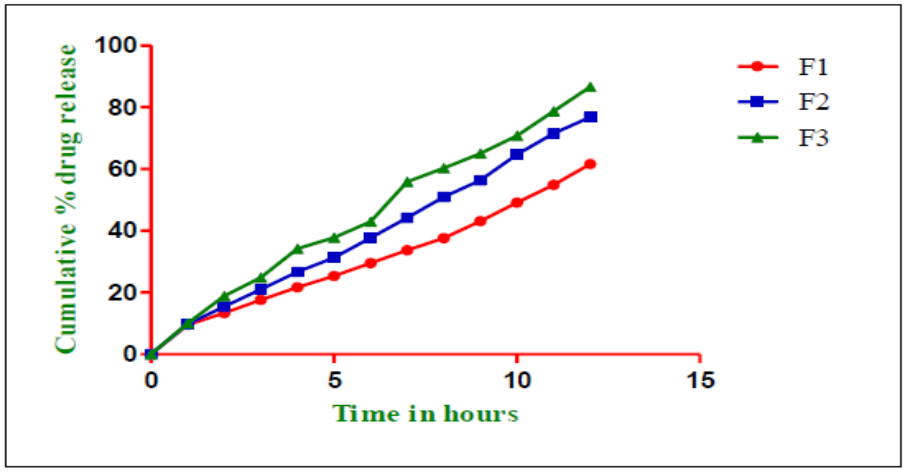


Fig 11 : *In- vitro* drug release profile of Lafutidine floating tablets

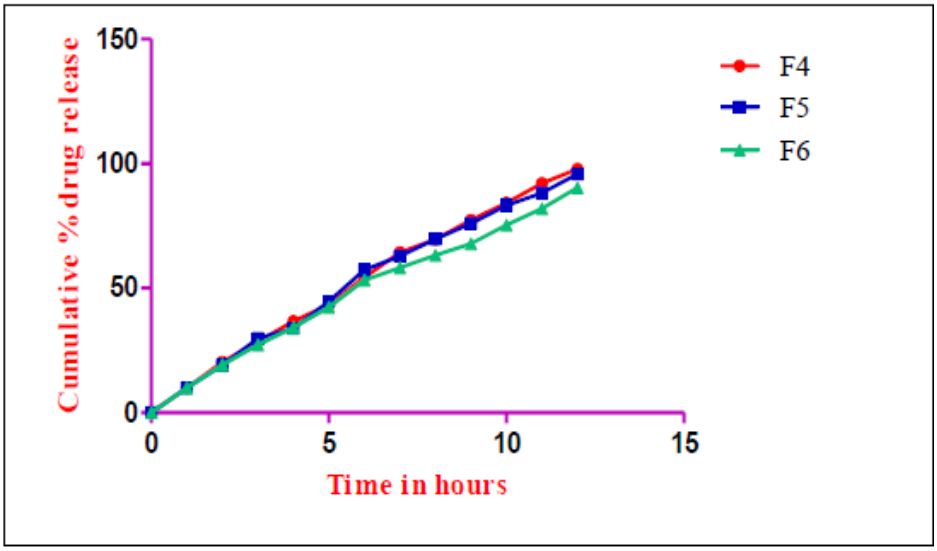


Fig 12 : *In- vitro* drug release profile of Lafutidine floating tablets

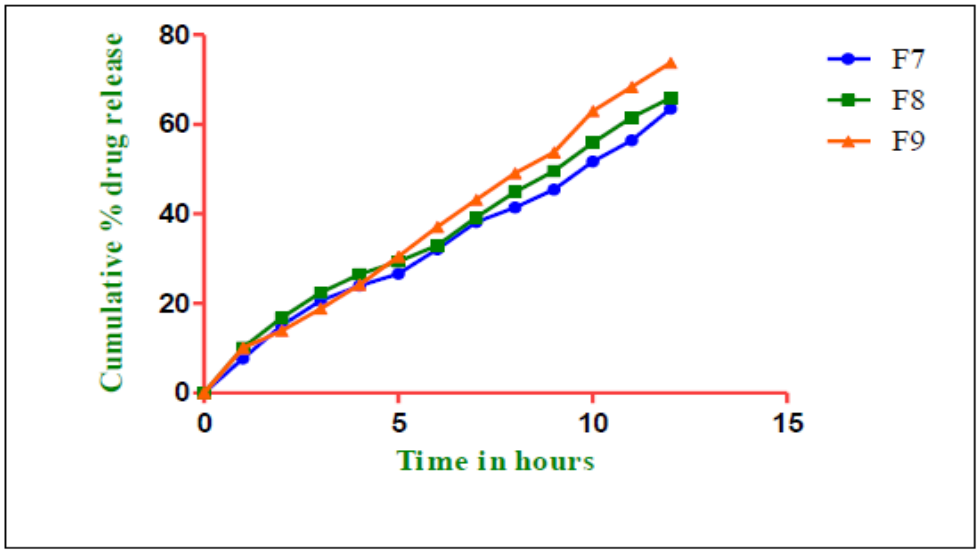


Fig 13 : *In- vitro* drug release profile of Lafutidine floating tablets

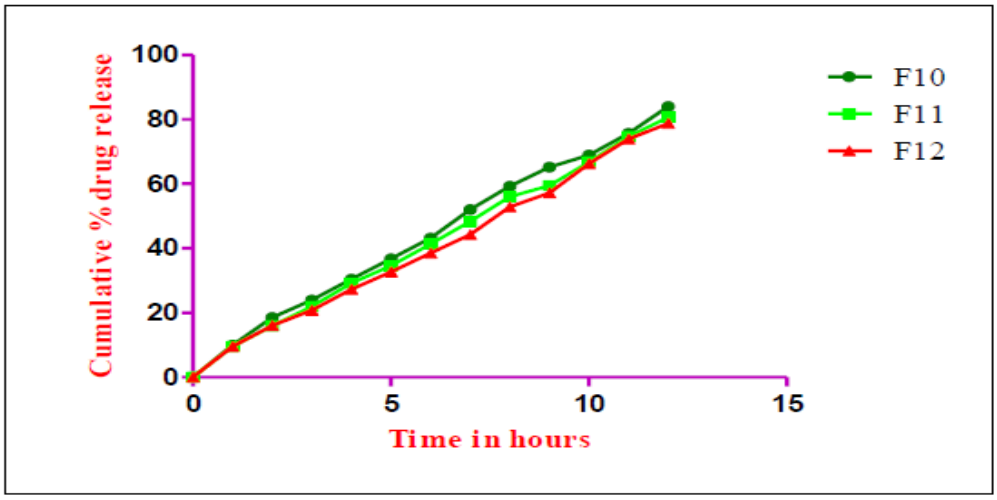


Fig 14 : *In- vitro* drug release profile of Lafutidine floating tablets

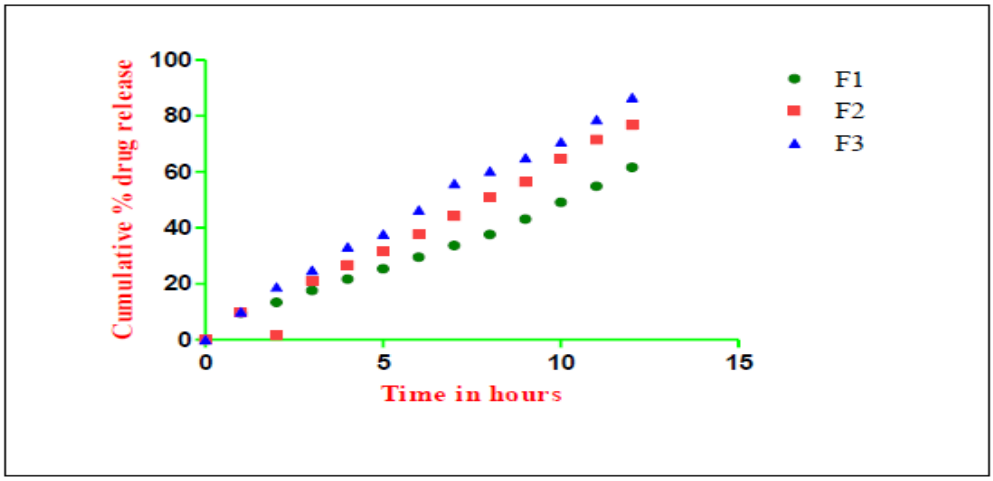


Fig 15 : Zero order kinetics release model for formulations F1-F3

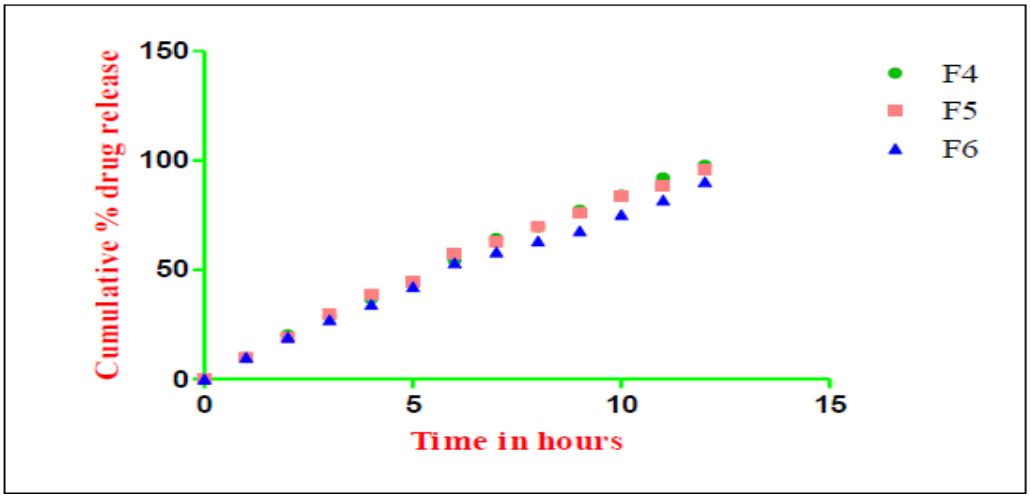


Fig 16 : Zero order kinetics release model for formulations F4-F6

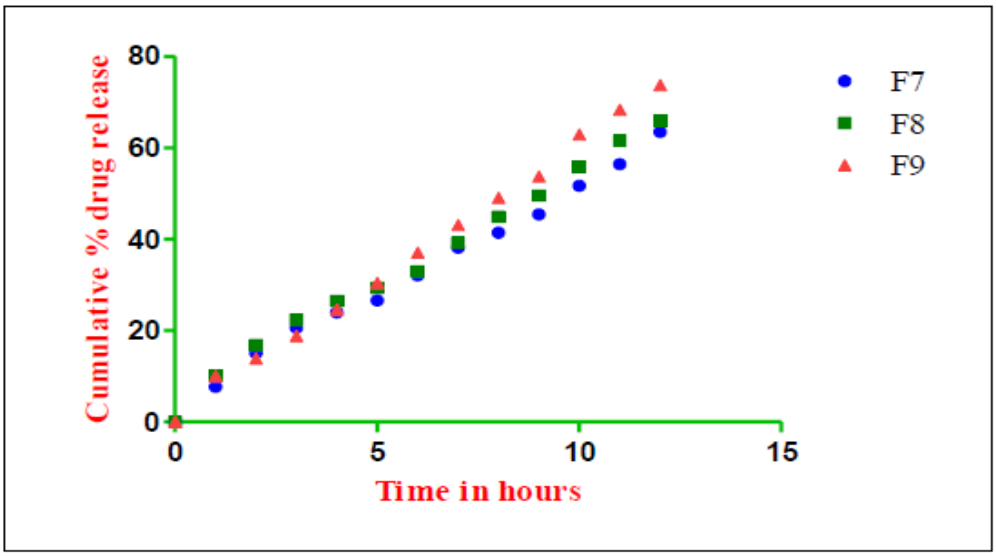


Fig 17 : Zero order kinetics release model for formulations F7-F9

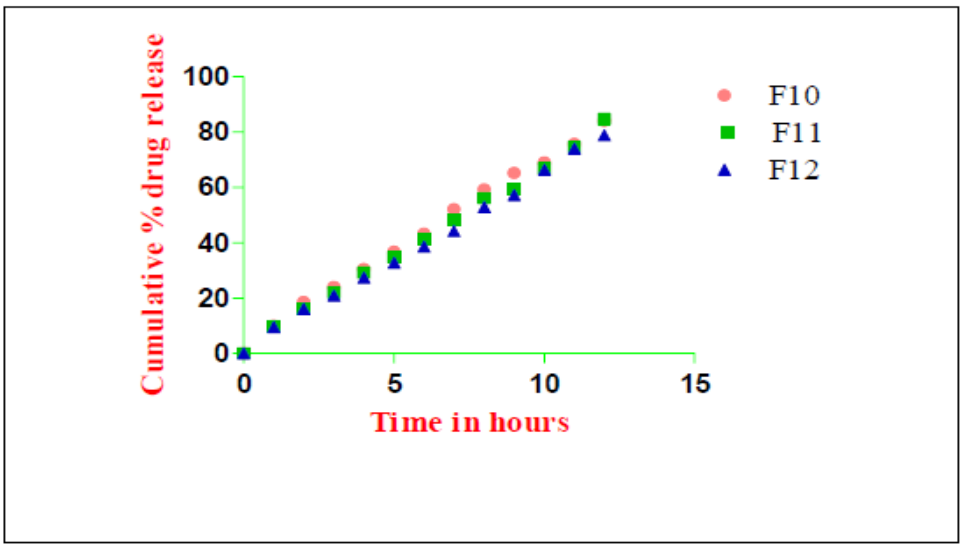
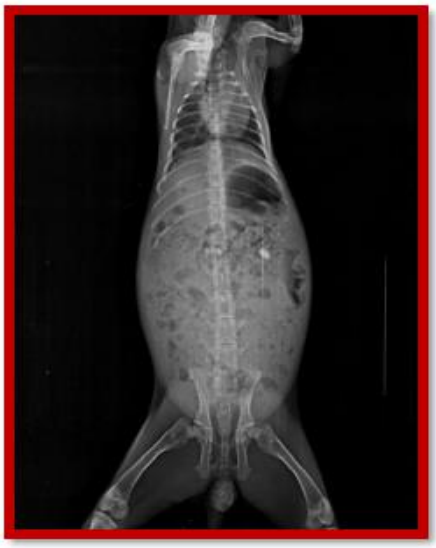
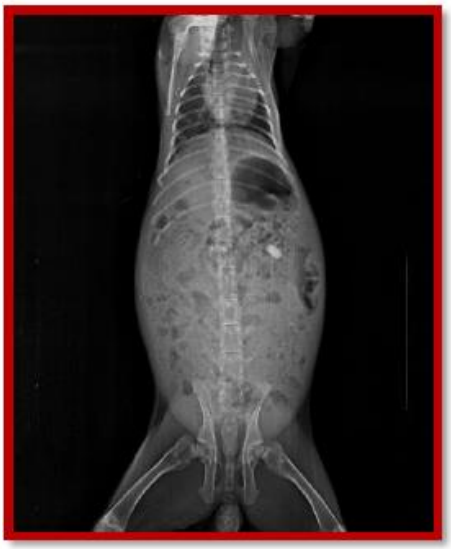


Fig 18 : Zero order kinetics release model for formulations F10-F12

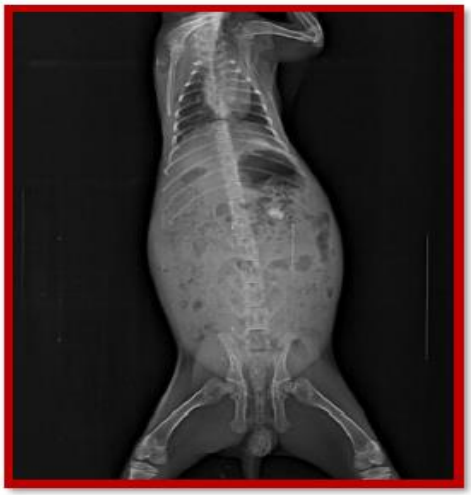


After administration

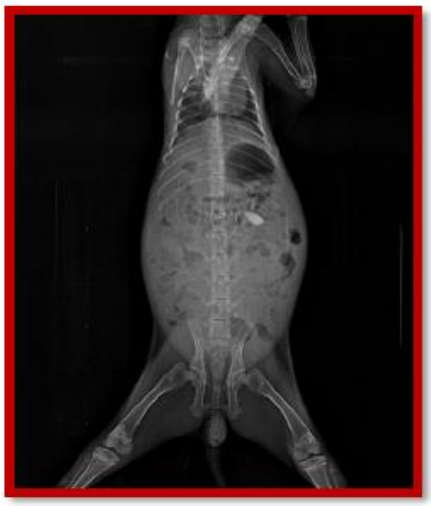


2nd hour

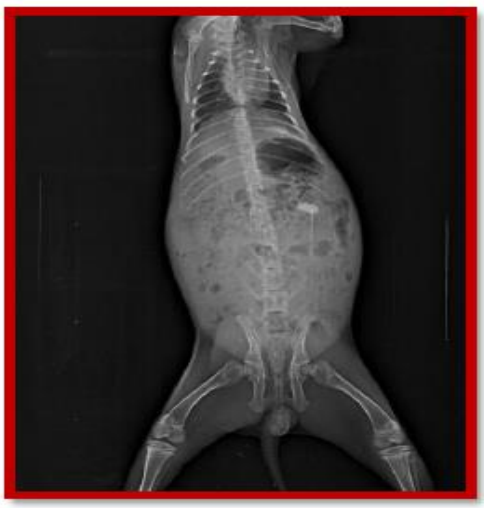
4th hour



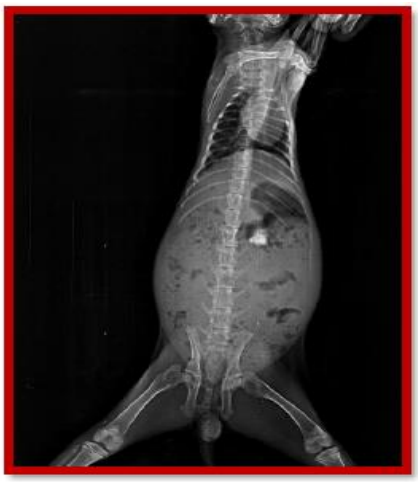
6th hour



8th hour



10th hour



12th hour

Fig 19: *In-vivo* x-ray floating study of optimized formulation F4

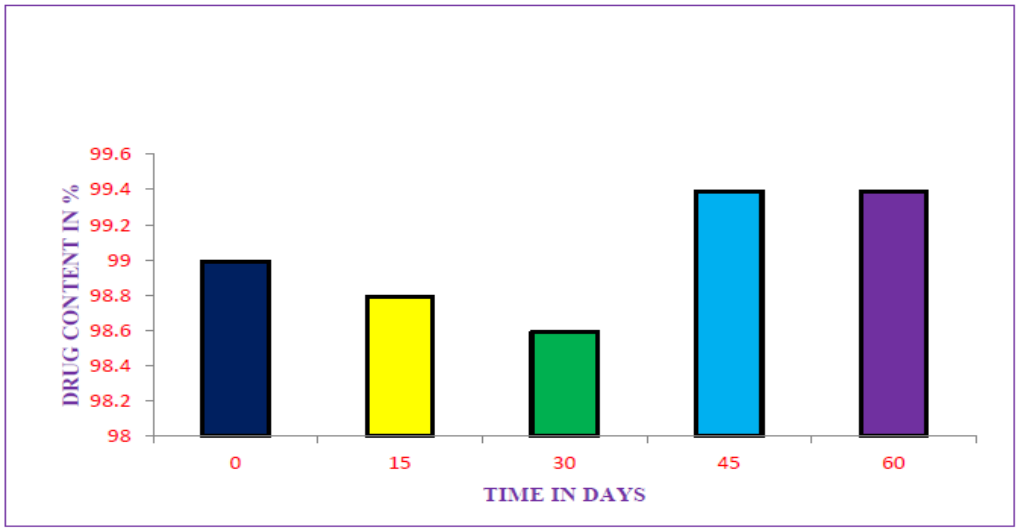


Fig 20 : % drug content of optimized formulation F4 after stability testing(60 days)

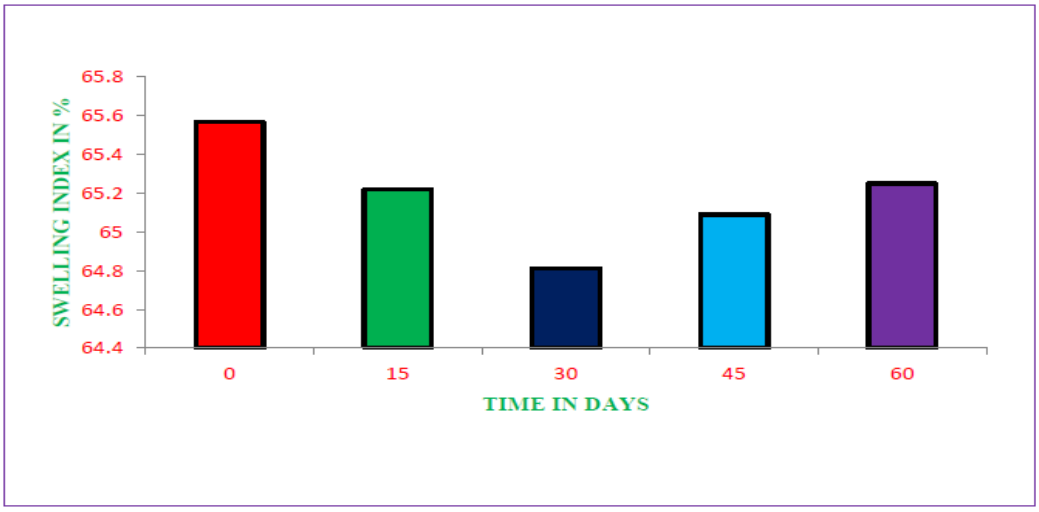


Fig 21 : % swelling index of optimized formulation F4 after stability testing(60 days)

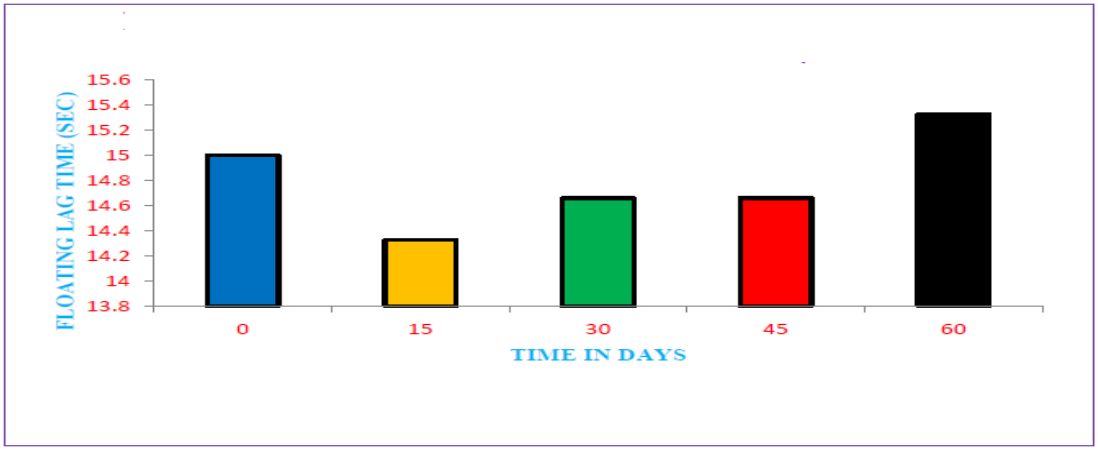


Fig 22 : Floating lag time of optimized formulation F4 after stability testing(60 days)

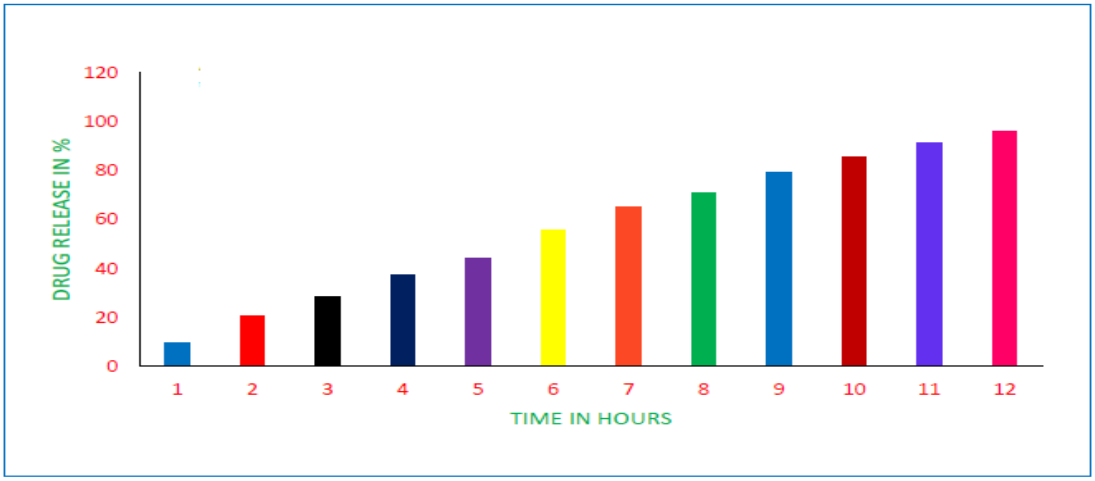


Fig 23 : % drug release of optimized formulation F4 after stability testing(60 days)

Table 10: kinetic analysis of *in-vitro* drug release data of Lafutidine floating matrix tablets

Formulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer-peppas equation		Hixsonc rowel R^2
				R^2	N	
F1	0.991	0.929	0.920	0.978	0.7572	0.9735
F2	0.982	0.949	0.923	0.991	0.8493	0.9721
F3	0.995	0.936	0.945	0.998	0.8578	0.9739
F4	0.996	0.834	0.943	0.998	0.9166	0.944
F5	0.991	0.894	0.953	0.996	0.9149	0.966
F6	0.992	0.923	0.951	0.997	0.874	0.971
F7	0.992	0.961	0.941	0.929	0.7992	0.978
F8	0.991	0.968	0.944	0.989	0.7425	0.980
F9	0.997	0.959	0.9195	0.981	0.8517	0.978
F10	0.996	0.947	0.941	0.997	0.8525	0.977
F11	0.997	0.951	0.933	0.996	0.8722	0.967
F12	0.996	0.942	0.920	0.992	0.8633	0.967

Table 11: Evaluation of floating tablets of Lafutidine kept in stability At

40^{oc} / 75% RH

Formulation Parameters	Initial	15 days	30days	45days	60days
Average weight (mg)	198.46	198.38	198.31	198.41	198.45
Thickness (mg)	3.39	3.39	3.39	3.39	3.39
Hardness (kg/cm^2)	7.2	7.13	7.16	7.2	7.16
Floating lag Time(sec)	14sec	14sec	14sec	14 sec	15sec
Swelling Index (8 Hours) (%)	65.57	65.34	65.06	64.97	64.56
Drug content in %	98.99%±0.34	98.79%±0.6	98.59%±0.346	98.39%±0.34	98.39%±0.34
% drug release at 12hrs	97.86±0.6373	-----	------	----	96.09 ±0.271

n=3*

***In -vitro* drug release studies:** The drug release was studied using a USP dissolution apparatus type II at 75 rpm in 0.1N hydrochloric acid, P^H 1.2 as a dissolution medium (900 ml) maintained at 37±0.5°C. The study was carried out for 12 hours and the data shown in **Table 9 and Figure 11-14.** Among various formulations studied, formulation F4 prepared with HPMCK4M and Tamarind seed polysaccharide showed promising results releasing 97.86±1.41 of the drug in 12 hours. By considering the *In -vitro* drug release, floating lag time, total floating time and swelling index studies, the formulation F4 was selected as the optimized formulation.

Kinetic modeling of drug release : The release data was fitted to various kinetic models in order to determine the release constant and regression coefficient(R^2). The drug release profiles for formulations (F1-F12) were fitted with zero order model based on regression coefficient which was shown in **Table 10Figure 15-18.** The highest regression coefficient (r2) value of optimized formulation F4 was obtained 0.9996 (Zero order). The value of release exponent (n) was found to be greater than 0.5 that indicates non- Fickian diffusion (anomalous) based mechanism of drug release.

***In-vivo* X-ray studies:** Based on the results of *in- vitro* buoyancy, *In* - vitro drug release and swelling index studies formulations F4 (HPMCK4M) consider a best. Hence, this formulation was selected for further *In vivo* studies. It was observed that tablets showed good floating property and sufficient integrity of Lafutidine floating matrix tablets. Radiological evidences suggest that the formulated gastroretentive floating tablets of Lafutidine was floated upto 12 hours in rabbit stomach, hence we can conclude that gastroretentive floating tablets was satisfactory floated to the rabbit stomach. The results were shown in **Figure 19.**

Stability Studies : The gastroretentive floating matrix tablets (F4) did not showed any significance changes in average weight, thickness, hardness, floating lag time, swelling index, drug content and *In-vitro* release studies. There was stable under 40^0C ± 2^0C / 75 ± 5% RH storage conditions for a period of 2 months. Formulation F4 results was found to be satisfactory were shown in **Table 11 and Figure 20-23 .**

CONCLUSION: Development of gastro retentive floating drug delivery of Lafutidine matrix tablets is to provied the action up to 12 hours. Gastro retentive floating tablets were prepared by direct compression method using various polymers like HPMCK4M, HPMCK15M and Tamarind seed polysaccharides. The use of natural polymer in pharmaceutical dosage forms is of increasing floating duration, stability and drug holding

capacity which can sustained the release of drugs. FT-IR spectra of the physical mixture showed no significant shifting of the peaks, so ingredients used in the study are suitable for the development of floating tablets. The floating tablets containing HPMCK4M (F4) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability and sustained release properties. All the formulations (F1-F12) followed zero order release kinetics and non-fickian diffusion drug release mechanism. Optimized formulation was stable at 40^0C ± 2^0C / 75 ± 5% RH for a period of 2 months results were found satisfactory. On the basis of the present study it was concluded that the floating tablets of Lafutidine can increase the gastric residence time as well as bioavailability and thereby increased therapeutic efficacy.

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