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FORMULATION, DEVELOPMENT AND EVALUATION OF GASTRO-RETENTIVE FLOATING TABLETS OF LAFUTIDINE

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ABSTRACT

The purpose of present investigation was to develop and evaluate floating drug delivery system of Lafutidine; a novel H2 receptor antagonist. The floating tablets of Lafutidine were prepared by low density and effervescent technique using HPMC K15M, Bees wax, Carnuba wax and Cetyl alcohol polymers. The pre-compression and post-compression evaluation were performed as per pharmacopoeial standards. The tablets were prepared by melt granulation method. Dissolution measurements were carried out in a (USP) dissolution testing apparatus II (Basket type). Compatibility study was performed by physical observation, FTIR. The compatibility study of the prepared Lafutidine floating tablets confirms that there is no interaction between the drug and polymers used. The release data were subjected to different models in order to evaluate their release kinetics and mechanisms. The drug release kinetics was observed by Non-fickian diffusion mechanism. The floating lag time were found to be significantly increased with the increasing concentration of the polymers. After the dissolution study of prepared Lafutidine floating tablet by low density and effervescent technique it was concluded that the formulation with Bees wax and Carnuba wax shows better sustained release effect. The release kinetic data implies that the release mechanism of all the formulations was Non-fickian. The developed floating tablets of Lafutidine may be used to prolong drug release for at least 12h, thereby improving the bioavaibility and patient compliance.

KEYWORDS: Floating Tablet, Bees Wax, Carnuba Wax, Cetyl Alcohol, Melt granulation.

INTRODUCTION

Oral sustained or controlled drug delivery system is complicated by restricted gastric residence time. Faster gastrointestinal transit can prevent complete drug release in the absorption window zone and reduce the efficacy dose since the majority of drugs are absorbed in stomach or the upper part of small intestine.[1] One of the most realistic technology for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). The Gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral sustained or controlled delivery of drugs that have an absorption window in a particular region of the gastro-intestinal tract.[2],[3] Floating drug delivery system has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the system, which results in increased gastro retentive time and reduces fluctuation in plasma drug concentration.[4],[5] There are a several approaches that can be used currently to prolong gastric retention time, such as floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, raft system, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices.[6],[7],[8] Lafutidine is 2nd generation histamine H2-receptor antagonist[9], used in the treatment of gastric ulcers, duodenal ulcers, and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis.[10],[11] It is absorbed in the stomach and small intestine, reaches gastric cells via the systemic circulation and rapidly binds to gastric cell histamine H2 receptors, resulting in immediate inhibition of gastric acid secretion.[12] Present investigation was focused on gastro retention of Lafutidine using floating technique and sustained release using low density waxy polymers.

MATERIALS AND METHODS

Materials

Lafutidine was obtained as a gift sample from Pure chem. Laboratory Pvt. Ltd, Ankaleshwar. Bees Wax and Carnuba Wax was provided by Research-Lab Fine Chem. Industries, Mumbai. HPMC K15M was provided by Wockhart Pharmaceutical Pvt. Ltd., Aurangabad and Cetyl Alcohol provided by Modern Industries, Sinner. All polymers and solvents used were of pharmaceutical or analytical grade.

Methods

1. Fourier transform infrared spectroscopy (FTIR) study: 10mg test sample mixed with the 10mg dry powder of potassium bromide. The mixture was taken in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400 cm^{-1} using FTIR spectrophotometer.[33]

2. Floating tablets of Lafutidine prepared by Melt Granulation

Lafutidine floating tablets were prepared by melt granulation technique using drug and variable concentration of polymers like Bees wax, Carnuba wax, Cetyl alcohol, HPMC K15M and gas generating agents like Sodium Bicarbonate, Citric acid and additives like MCC- 101, Mg-stearate, and Talc were used. The respective polymers except Waxes were passed through the sieve no. 40. The waxes were molten in porcelain dish on hot plate and drug was added to it then optional additives (composition listed in table-1) except Talc were added in above molten mixture. The resultant mixture was allowed to solidify at room temperature and then passed through seive no. 16 to form granules. The powder blended was then lubricated with talc and then compressed on a tablet punching machine.

Table 1: Composition of gastro retentive floating tablets of Lafutidine.

Sr. No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Lafutidine	10	10	10	10	10	10	10	10	10
2	Bees Wax	60	-	-	10	20	30	30	-	30
3	Carnuba Wax	-	60	-	20	30	10	30	30	-
4	Cetyl Alcohol	-	-	60	30	10	20	-	30	30
5	HPMC –K15M	90	90	90	90	90	90	90	90	90
6	MCC -101	40	40	40	40	40	40	40	40	40
7	Sodium Bicarbonate	75	75	75	75	75	75	75	75	75
8	Citric Acid	15	15	15	15	15	15	15	15	15
9	Magnesium Stearate	6	6	6	6	6	6	6	6	6
10	Talc	4	4	4	4	4	4	4	4	4
11	Total	300	300	300	300	300	300	300	300	300

3. Micromeritic properties: Granules were prepared by melt granulation technique and characterized by bulk density, tapped density, hausner's ratio, Carr's index and angle of repose.[18],[19]

4. Weight Variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.[20]

5. Hardness: The hardness of 10 tablets was measured using Monsanto Hardness tester.[21] for four minutes. After four minutes the tablets were weighed again.[22]

6. Friability: The % friability of the tablets was determined using Roche friabilator. 10 tablets were initially weighed and transferred to the friabilator. The friabilator was operated at 25 rpm.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

7. *In-vitro* Buoyancy studies

The tablets were placed in a beaker containing 0.1N hydrochloride solution (200 ml). The time required for the tablet to rise to the surface was determined as floating lag time and time period for which tablet remains at surface was determined as total floating time.[22]

8. Swelling Index of tablets

The swelling of floating tablets were determined by swelling the tablets in 0.1 N HCl at the room temperature. Swollen weight of the tablet determined then swelling index was calculated by following equation.[26],[27]

Swelling Index = $WT - W_O/W_O$

Where, W_0= initial weight of tablet

WT= final weight of tablet

***9. In vitro* drug release study**

Drug release was studied using six station dissolution apparatus *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (Basket method), in 900 ml of 0.1 N hydrochloric acid at 37± 1^0C and 50 rpm One tablet was placed in each vessel and the study was performed for a period of 12 hours. 5 ml of the sample was withdrawn at regular intervals and the same volume of pre-warmed (37± 1^0C) fresh dissolution medium was replaced. The samples withdrawn were filtered and drug content in each sample was analyzed after suitable dilution by UV/Vis. spectrophotometer at 281 nm. Drug release kinetics was studied using kinetics models.[24],[25]

RESULT AND DISCUSSION

Lafutidine floating tablets were fabricated to augment the gastric residence time of the active ingredient, which could be retained in the stomach for a longer time, improving the buoyancy and sustain drug release. The floating tablets were prepared by utilizing sustain release polymers, low density polymers and gas generating agents.

The FTIR spectrum of pure Lafutidine showed peaks corresponds to the functional group present in the structure of the drug. FT-IR spectrum of Lafutidine is shown in figure 1. FTIR spectra of pure Lafutidine showed characteristic sharp peaks of alkenes stretching (-CH_3, -CH_2 and –CH) vibration at 2932.86 cm^{-1}. Also exhibited C=O stretch at 1657.87 cm^{-1}. A selective stretching vibration at 1546.96 cm^{-1} and 1290.42 cm^{-1} for primary and secondary amine was also observed. For functional groups like S=O stretch and –C-S stretch showed vibrations at 1032.92 and 741.65 cm^{-1} respectively. The same peaks were also found in the spectra of the formulations of Lafutidine using various polymers, which indicated that there was no drug polymer interaction.

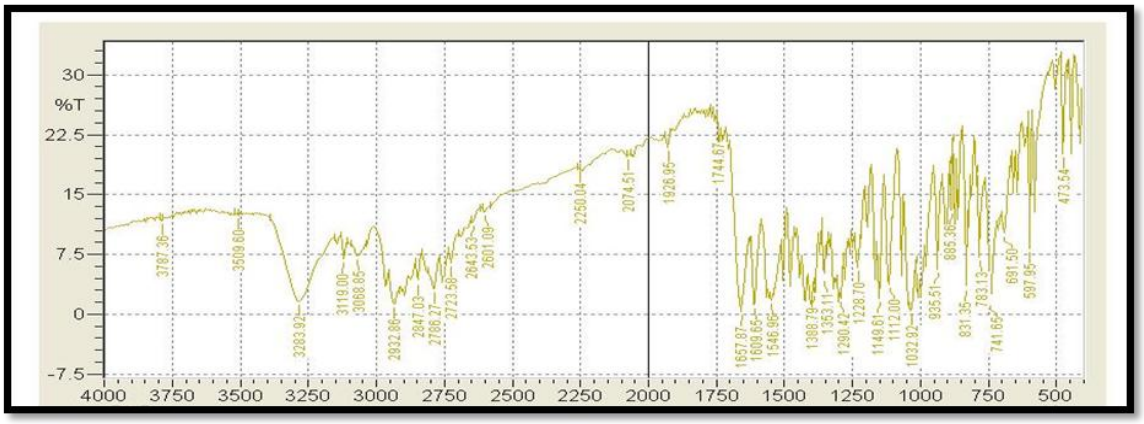

Figure 1: FT-IR spectrum of Lafutidine.

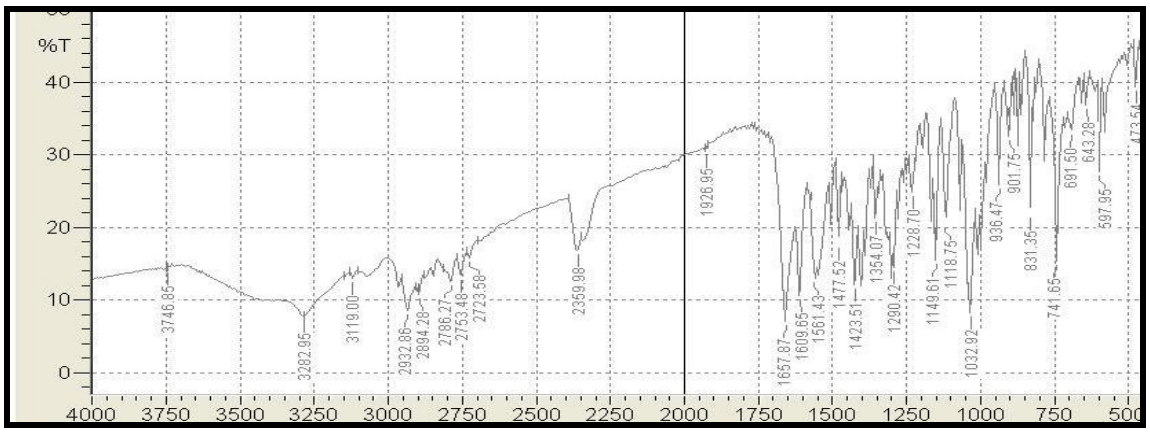

Figure 2: FT-IR spectrum of Lafutidine and all excipients in formulation (F7).

Table 2: Charaterization of pre-compressional parameters of granules of Lafutidine.

Formulation code	Angle of repose(^{0}) S	Bulk density(g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's ratio
F1	32.27 ±0.32	0.545± 0.54	0.639±0.22	14.71	1.172
F2	29.42±0.21	0.568±0.32	0.651±0.54	12.74	1.146
F3	30.17±0.12	0.542±0.67	0.618±0.21	12.29	1.140
F4	29.74±0.33	0.535±0.85	0.597±0.23	10.16	1.113
F5	27.64±0.24	0.543±0.90	0.593±0.34	7.2	1.07
F6	27.12±0.54	0.537±0.21	0.573±0.54	6.14	1.06
F7	32.57±0.76	0.584±0.32	0.674±0.65	13.35	1.154
F8	33.34±0.65	0.563±0.24	0.679±0.76	17.08	1.206
F9	31.86± 0.12	0.593±0.87	0.686± 0.52	13.55	1.156

Post compression evaluation of lafutidine floating tablets

The prepared floating tablets were compressed at constant pressure. All tablets were shown hardness between 4.1 to 6.0 kg/cm^2. All prepared tablets were shown weight variation within ±5% limit and friability within ±1% limit.

Table 3: Charaterization of post-compressional parameters of granules of Lafutidine.

Formulation Code	Hardness (kg/cm^2)	Weight Variation (mg)	Friability (%)	Floating Lag Time (Sec.)	Total Floating Time (Hr.)	Time to release more than 90% drug (Hrs.)	Best fit model
F1	4.1 ±0.02	300.12±0.24	0.016±0.01	64	12	86.209	Zero Order
F2	4.2± 0.00	300.10±0.80	0.34±0.088	76	12	86.48	Zero Order
F3	5.0 ± 0.02	300.55±0.11	0.36±0.084	60	12	82.234	Zero Order
F4	4.3±0.092	300.58±0.41	0.28±0.011	68	12	72.832	Zero Order
F5	4.4±0.025	300.33±0.24	0.65±0.64	72	12	85.701	Zero Order
F6	5.3±0.023	300.01±0.33	0.75±0.098	58	12	77.431	Zero Order
F7	4.6±0.32	300.50±0.11	0.34±0.008	63	12	97.809	Zero Order
F8	4.8±0.00	301.10±0.23	0.62±0.04	72	12	86.506	Zero Order
F9	6.0±0.00	300.45±0.53	0.51±0.02	65	12	69.653	Zero Order

***In Vitro* Buoyancy Studies**

Floating lag time of prepared tablets was found between 58 to 76 seconds and all tablets were floated for more than 12 hours.

All the tablets were floated by effervescent and low density swelled matrix approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in existence of dissolution medium (0.1 M hydrochloric acid). It was observed that the gas generated is trapped and protected within the swelled matrix, formed by hydration of low density polymer Bees wax and Carnuba wax, thus reducing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro*

buoyancy studies. In this study, penetration of water into tablets prepared with Bees wax, Carnuba wax was rather slow, causing delayed matrix formation and subsequent increase in the floating lag time compared to the tablets prepared with Cetyl alcohol.

***In-vitro* dissolution studies**

In vitro dissolution studies of all the formulations of floating tablets of lafutidine were carried out in 0.1N HCl. The study was performed for 12hr and cumulative drug release was at every one hour. Prepared floating tablets contain 30% HPMC K15M as sustain release polymer.

It was observed that the F1 formulation batch contain polymer concentration 20% Bees wax showed drug release 90.2% at 12 hr. The F2 formulation batch contain 20% Carnuba wax showed drug release 86.48% at 12 hr. The F3 formulation batch contain 20% Cetyl alcohol showed drug release 82.234% at 12 hr. The F4 formulation batch contain 3.3%, 6.6% and 10% Bees wax, Carnuba wax and Cetyl alcohol respectively showed drug release 72.832% at 12 hr. The F5 formulation batch contains 6.6%, 10% and 3.3% Bees wax, Carnuba wax and Cetyl alcohol respectively showed drug release 85.701% at 12 hr. The F6 formulation batch contain 10%, 3.3% and 6.6% Bees wax, Carnuba wax and Cetyl alcohol respectively concentration showed drug release 77.431% at 12 hr. The F7 formulation batch contain 10% Bees wax and 10% Carnuba wax showed drug release 97.809% at 12 hr. The F8 formulation batch contain 10% Carnuba wax and 10% Cetyl alcohol showed drug release 86.506% at 12 hr. The F9 formulation batch contain 10% Bees wax and 10% Cetyl alcohol showed drug release 69.153% at 12 hr. The F7 formulation batch shows more drug release than other formulation batches that is it shows sustained drug release for 12 hrs, from these it the optimized formulation from all the formulation batches.

Analysis of release mechanism

The drug release statistics of optimized formulation F7 were fitted to models representing Higuchi's, zero order, first order and Korsmeyer's equation kinetics to be acquainted with the release mechanisms. In the present study, *in-vitro* release profiles could be best articulated by Higuchi's equation as optimized formulation F7 showed good linearity (R^2: 0.9988) indicates that diffusion is dominant mechanism of drug release with these formulations. The values of slope for the korsemeyer's - Peppas model indicates that drug release from the tablets were non fickian diffusion.

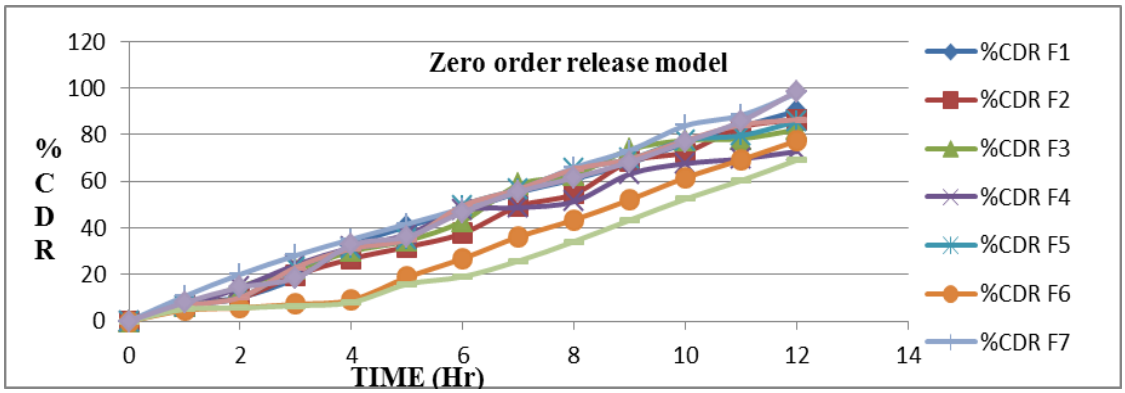

Figure 3: Zero Order release model of formulation F1 – F9.

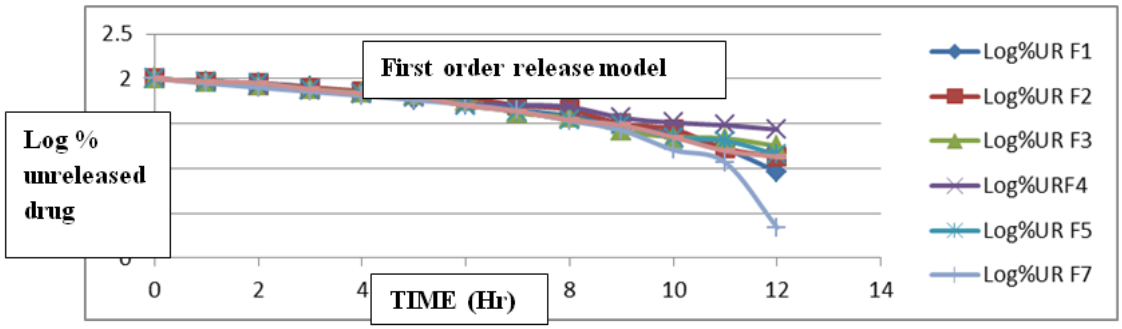

Figure 4: First Order release model of formulation F1 – F9.

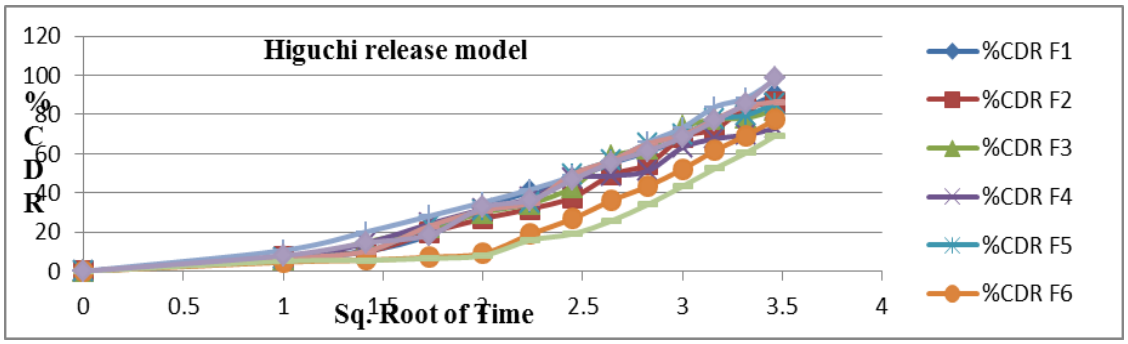

Figure 5: Higuchi model of formulation F1 – F9 and Marketed.

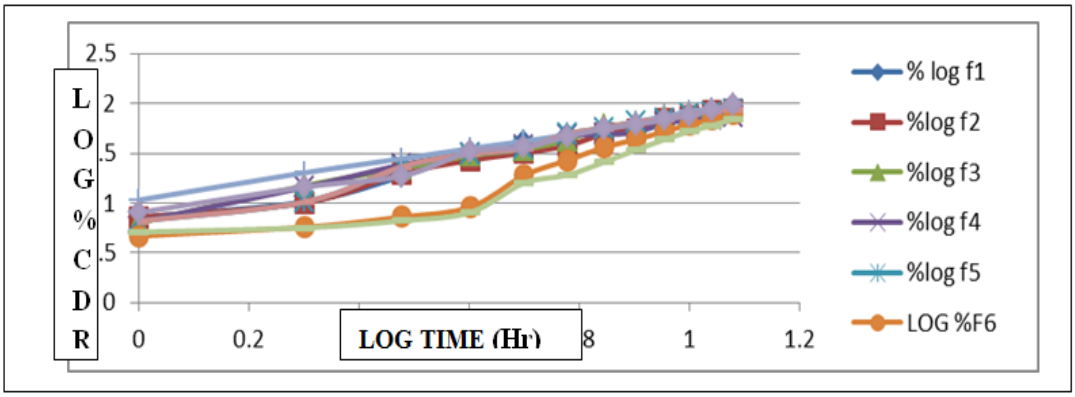

Figure 6: Korsmeyer-Peppas Release Model of formulation F1- F9 and Marketed.

Stability study of optimized formulation

The optimized floating tablets F7 were preferred for stability study on the source of *in vitro* buoyancy and *in-vitro* drug dissolution studies. The tablets were investigated at 40°C/75% RH for 2 months. From the data, the formulation is found to be stable under the conditions mentioned before since there was no noteworthy change in the percentage amount of drug content (Table 4). Thus, it was found that the floating tablets of Lafutidine (F7) were unwavering under these storage conditions for at least 2 months.

Table 4: Stability studies of stomach specific floating tablets of Lafutidine.

Stability (40^0C ± 2^0C and 75% RH ± 5%)	Physical changes	%CDR	Floating Study
Initial	No	89.660	Floating
15 days	No	88.79	Floating
30 days	No	95.59	Floating
45 days	No	89.00	Floating
60 days	No	96.15	Floating

CONCLUSION

Buoyant delivery systems are promising dosage forms which could be a better alternative to the conventional oral dosage forms in order to improve bioavailability by increasing the gastric retention time of the drug.

From the compatibility studies, it is concluded that, HPMC K15M, Bees wax, Carnuba wax and Cetyl alcohol were compatible with drug Lafutidine and thus suitable for the formulation of Lafutidine floating tablets. Lafutidine tablets were fabricated by melt granulation method. *In-vitro* buoyancy studies were performed for all the formulations, F1 to F9 by using 0.1 N HCL solutions at 37^0C. Tablet containing Bees wax and Carnuba wax(F7) showed good buoyancy with very short lag time and long floatation time of more than 12 hrs in 0.1 N HCL. *In-Vitro* release study is performed for 12 hrs. Optimized formula containing (F7) showed better release compare to other formulations and it followed zero order kinetics. The non-Fickian diffusion was confirmed as the drug release mechanism from this formulation. From this study, it was concluded that Bees wax and Carnuba wax can be used in formulation of Lafutidine sustained release gastro retentive floating drug delivery system. Overall, this study concludes that viscosity of the polymer is a major factor affecting the drug release and floating properties of FDDS.

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