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Research Paper

"Design and Characterization of Porous Floating Beads of Lafutidine"

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ABSTRACT: *The aim of present research work was to design and characterize porous floating beads of lafutidine a second-generation H_2–receptor antagonist. Using the emulsion gelation method, Lafutidine porous floating beads were meticulously crafted, incorporating hydrophilic polymers such as sodium alginate (serving as the gelling agent), along with hydroxypropyl methylcellulose K15M, hydroxypropyl methylcellulose K4M and Carbopol 934p as polymers. Calcium carbonate was introduced as the gas-generating agent, while calcium chloride played the crucial role of the cross-linking agent. The effect of different formulation variables was also studied. The beads were evaluated for particle size, surface morphology, percentage yield, drug entrapment efficiency, drug content, swelling index, buoyancy study and in-vitro drug release. Fourier-transform infrared spectroscopy and differential scanning calorimetry studies were carried out for compatibility studies. The micromeritic parameters of floating beads of lafutidine were within acceptable limits. The particle size was between 1210.53 ± 1.07 to 1249.46 ± 0.98 µm. When observed under scanning electron microscopy, the floating beads were spherical in shape with distinct pores inside. The percent yield was 76.04 ± 2.59 to 92.43±1.91%, entrapment efficiency was 70.91 ± 1.49 to 82.40 ± 2.41%, drug content was 71.85 ± 1.79 to 83.96 ± 1.83% and the swelling index was 67.34 ± 1.24 to 86.90 ± 1.51%. The buoyancy time was 43 ± 0.8 to 59 ± 0.5 s and the total buoyancy time was more than 12 h. The in-vitro dissolution studies showed 84.53 to 98.84% drug release in 12 h. F5 was selected as the optimized formulation as it released 98.84% of the drug in 12 h at a controlled rate, which is desired for diseases like peptic ulcer. All the formulations followed zero order kinetics indicating drug release by non-fickian release mechanism. Drug and excipient compatibility studies showed no interaction was observed.*

KEYWORDS: *Lafutidine, Porous Floating beads, Hydroxypropyl Methylcellulose K4M, Hydroxypropyl Methylcellulose K15M, Sodium Alginate, Peptic Ulcer, Emulsion Gelation Method.*

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I. INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to systematic circulation. In the pharmaceutical realm, there's been a notable surge in interest towards oral controlled-release drug delivery. This approach holds promise for enhancing therapeutic benefits, including simplified dosing administration, enhanced patient compliance and greater flexibility in formulation strategies. The problems related to oral drug delivery include aqueous solubility, membrane permeability, chemical and enzymatic stability of drugs.

For drugs with high gastrointestinal tract (GIT) absorption and short half-lives, rapid elimination from the systemic circulation is common. To maintain therapeutic efficacy, frequent dosing becomes necessary. In order to overcome this constraint, there is ongoing research into the creation of oral gastro-retentive formulations. These formulations aim to achieve a gradual release of the drug within the gastrointestinal tract (GIT), ensuring a sustained and effective drug concentration in the systemic circulation over an extended period [1]. Following oral administration, this type of drug delivery system aims to remain in the stomach, steadily releasing the drug to ensure continuous supply to the gastrointestinal absorption sites. However, these systems encounter two primary challenges: the brief gastric retention time (GRT) and the unpredictability of gastric emptying time (GET). These factors may lead to incomplete drug release within the absorption zone (stomach or upper small intestine), ultimately diminishing the efficacy of the administered dose. To formulate a site-specific

orally administered controlled-release dosage form, it is desirable to achieve prolonged gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, improves drug solubility and is less soluble in a high pH environment [2]. Rapid floating can be attained through a low-density system (density < 1 g/cm3), such as trapping air within the dosage form or integrating oil or waxes [3]. Single unit formulation (floating tablet) is associated with problem such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand, a floating system made of multiple unit form (floating beads) has relative merits compared to a single unit preparation [4]. Porous floating beads provide a constant and prolonged therapeutic effect which will reduce dosing frequency. Many methods have been developed for low-density floating systems like solvent evaporation, including a gas-forming agent or making the system porous [5]. Sodium alginate (gelling agent), Carbopol 934P, hydroxypropyl methyl cellulose (HPMC) K15M and hydroxypropyl methyl cellulose K4M are used as polymer, calcium carbonate as gas generating agent and calcium chloride as cross-linking agent in various floating approaches [6]. Lafutidine is a 2nd generation histamine H_2-receptor antagonist, belonging to BCS class-II drugs having poor water solubility and a short elimination half-life of up to 3.0 h. It is used in the treatment of ulcers and given orally at a dose of 10-20 mg, two or three times a day. It protects against gastric mucosal damage in both acute and chronic gastritis. Lafutidine also increases the blood flow to the gastric mucosa. It is exceedingly helpful in gastric and duodenal ulcers [7]. Lafutidine thus has all the requisite characteristics for developing as a gastroretentive drug delivery system which would increase its oral bioavailability. So, we intended to make the drug remain in the stomach for a prolonged time and used for the treatment of peptic ulcers.

II. MATERIALS AND METHODS

Materials

Lafutidine was obtained as a gift sample from Bajaj Health Care Ltd, Mumbai, India. Sodium alginate was purchased from Rolex Laboratory Pvt. Ltd., Mumbai; Carbopol 934P was procured from HiMedia Laboratory Pvt. Ltd., Mumbai, hydroxypropyl methyl cellulose K15M, hydroxypropyl methyl cellulose K4M and hydrochloric acid were purchased from SD Fine Chemicals Pvt. Ltd., Mumbai, Olive Oil from Sasso Pvt. Ltd., Italy and calcium chloride from finar chemical Pvt Ltd., Ahmedabad. All additional chemicals and reagents employed were of analytical grade, commercially available, and used without any additional processing.

Methods

Preparation of porous floating beads of lafutidine:

The porous floating beads of lafutidine were prepared by the emulsion gelation method. HPMC K15M, HPMC K4M and Carbopol 934P were used as rate-controlling polymers with sodium alginate as a thickening agent. Lafutidine, sodium alginate, Carbopol 934P and HPMC were passed through sieve no 80 separately. An accurately weighed quantity of sodium alginate (2% w/v) was dissolved in 100 ml of distilled water in a beaker and stirred well on a magnetic stirrer to obtain a clear solution. Lafutidine was added to the sodium alginate solution, followed by the addition of a weighed quantity of calcium carbonate, HPMC and Carbopol 934P (Table 1). The resulting mixture was sonicated for 30 min, to remove the air bubbles. To the above solution, olive oil (3 ml) was added and stirred to form a homogenous mixture on a magnetic stirrer. It was then kept aside for 30 min. The resultant mixture was dropped via 23-gauge needle into 100 ml (3% w/v) calcium chloride solution maintained under gentle agitation (800 rpm) using an overhead stirrer. The beads formed were allowed to remain in the same solution for 30 min to improve their mechanical strength. The beads were separated, washed with water and allowed to dry at room temperature overnight [8]. Formulation details are given in Table 1 and 2.

Table 1: Composition of Porous Floating Beads of Lafutidine F1-F12

Ingredients	Formulation Code*											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lafutidine (g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Sodium alginate (% w/v)	2	2	2	2	2	2	2	2	2	2	2	2
Carbopol 934P (g)	0.5	0.6	0.7	0.8	-	-	-	-	-	-	-	-
HPMC K15M (g)**	-	-	-	-	0.5	0.6	0.7	0.8	-	-	-	-
HPMC K4M (g)**	-	-	-	-	-	-	-	-	0.5	0.6	0.7	0.8

Calcium carbonate (g)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Olive oil (ml)	3	3	3	3	3	3	3	3	3	3	3	3
Calciumchloride (% w/v)	3	3	3	3	3	3	3	3	3	3	3	3

*****Note = 800 rpm was used for all formulations; **HPMC= Hydroxypropyl methyl cellulose

Table 2: **Composition of Porous Floating Beads of Lafutidine F13-F21 (Effect of Formulation Variables)**

Ingredients	**Formulation Code**								
	F13	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**
Lafutidine (g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Sodium alginate (% w/v)	2	2	2	2	2	2	2	2	2
Carbopol 934P (g)	-	-	-	-	-	-	-	-	-
HPMC K15M (g)*	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K4M (g)*	-	-	-	-	-	-	-	-	-
Calcium carbonate (g)	0.3	0.3	0.3	**0.4**	**0.5**	**0.6**	0.3	0.3	0.3
Olive oil (ml)	3	3	3	3	3	3	3	3	3
Calcium chloride (% w/v)	**4**	**5**	**6**	3	3	3	3	3	3
RPM**	800	800	800	800	800	800	**900**	**1000**	**1100**

*HPMC= Hydroxypropyl methyl cellulose **RPM= Rounds per min

Evaluation of porous floating beads of lafutidine:

The prepared floating beads of lafutidine were evaluated for the following parameters:

Particle size:

The particle size of the beads was evaluated by sieve analysis method. Accurately weighed quantity of beads were taken and sieved through a set of sieves No: 12, 16, 18, 22, and 25 on a vibratory sieve shaker for 20 min and the weight was determined. From the values particle size was calculated [9].

Determination of percentage yield:

The prepared beads were collected and weighed. The measured weight was divided by the total amount of all non-volatile components, which were used for the preparation of the beads [10]. The yield of prepared floating beads was calculated using the following equation:

$$\%\ \text{Yield} = \frac{(\text{Actual weight of product})}{\text{Weight of drug + mass of excipient}} \times 100 \ldots\ldots\ldots\ldots (1)$$

Drug entrapment efficiency:

Accurately weighed 100 mg of prepared beads from each batch were taken separately. Then beads were crushed using a mortar and pestle. The crushed beads were placed in 50 ml of 0.1 N hydrochloric acid pH 1.2. The polymer debris formed after the disintegration of the bead was removed by filtering through 0.22 μm pore size Whatman filter paper. The drug content in the filtrate was determined spectrophotometrically using a UV–visible spectrophotometer (Shimadzu, Japan) at 286 nm. The quantity of drug encapsulated within the beads was computed using the subsequent formula [11]:

$$\%\text{Drug Entrapment Efficiency} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100 \quad \ldots\ldots.(2)$$

Drug Content:

An accurately weighed sample of beads (100 mg) was crushed in a mortar and added to 100 ml of 0.1N hydrochloric acid buffer pH 1.2 and kept overnight under stirring to elute the complete drug from the polymer matrix. It was filtered and analysed at 286 nm against a blank bead mixture, which was treated similarly. The drug content of each formulation was recorded as mg/100 mg of beads [12]:

$$\%\ \text{Drug Content} = \frac{Actual\ amount\ of\ drug\ in\ floating\ beads}{Theoretical\ amount\ of\ drug\ in\ floating\ beads} \times 100 \ldots\ldots\ldots (3)$$

Buoyancy studies:
The period from introducing the porous floating beads into the medium until they reached the upper one-third of the dissolution vessel (floating lag time), along with the duration the formulation consistently remained afloat on the medium's surface (floating duration), was concurrently measured during dissolution studies through visual observation [13].

Swelling Index:
The beads were placed in a basket, which was then immersed in a beaker containing 100 ml of 0.1 N HCl, and maintained at 37 ± 0.5 °C. At specified intervals, the beads were taken out, weighed and the swelling ratio was determined using the following formula[14]:

$$\% \text{ Swelling index} = \frac{Weight\ of\ wet\ beads - Weight\ of\ dried\ beads}{Weight\ of\ dried\ beads} \times 100 \ldots\ldots\ldots (4)$$

In-vitro drug release study:
The drug release study from the porous floating beads (equivalent to 10 mg of drug) was performed using USP dissolution apparatus Type II in 900 ml of 0.1 N HCl pH- 1.2 dissolution media at 100 rpm and 37 °C. 5 ml of sample was withdrawn at every 1 h and study was continued up to 12 h. During sampling the same volume of fresh medium was replaced to maintain sink condition. Withdrawn samples were assayed spectrophotometrically at 286 nm [15].

Kinetic study:
The release mechanism was identified by fitting the release data to different kinetic equations, including zero-order, first-order, Higuchi and Korsmeyer-Peppas. The r^2 values corresponding to each model were then determined to analyze the release profile [16].

Fourier transformer infrared spectroscopy (FTIR) study:
The compatibility among the drug, polymer and other excipients was evaluated through FTIR spectra analysis. The pellets were prepared on KBr-press. The spectra were captured across the wavenumber range from 4000 to 500 cm-1. FT-IR spectra provide valuable support for identifying the functional groups present in the compound [17].

Differential Scanning Calorimetry (DSC):
A differential scanning calorimeter was used to obtain DSC peaks of the pure drug and the prepared beads. The DSC thermogram was obtained by sealing the drug or formulation hermetically in an aluminium pan and kept under nitrogen purging (atmosphere). The samples were subjected to scanning from room temperature up to 300°C, with a heating rate of 10°C per min [18].

Scanning electron microscopy (SEM):
The surfaces and cross-section morphologies of the beads were observed using a scanning electron microscope operated at an acceleration voltage of 25 kV. The beads were made conductive by sputtering a thin coat of platinum under vacuum using Jeol JFC-1600 auto fine coater and then the images were recorded at different magnifications [19].

Stability Studies:
The stability studies were carried out according to ICH guidelines for selected formulation. The formulation was wrapped in aluminium foil and kept at 25 ±2 ^{0}C /60±5% RH and 40±2 ^{0}C/75±5% RH for three months in a stability chamber [20].

III. RESULTS AND DISCUSSION

Porous floating beads of lafutidine were prepared and evaluated to increase the residence time of drug in the stomach. Lafutidine is an H_2 antagonistic agent acting on the H_2 receptor and shows site-specific absorption in the stomach and in the upper parts of GIT. The drug is very effective in the treatment of gastric ulcers, gastroesophageal reflux disease and pathological hypersecretory conditions. Lafutidine has a short elimination half-life of up to 3.0 h and belongs to BCS class-2 drugs. Thus, an attempt was made to design and characterize porous floating beads of lafutidine by Emulsion gelation method using hydrophilic polymers like sodium alginate, hydroxy propyl methylcellulose and Carbopol 934P and calcium carbonate as gas generating agent.

Alginate can form gel by emulsion gelation with divalent calcium ions. When an emulsion of olive oil containing alginate was dropped into calcium chloride solutions, spherical beads were then formed instantaneously in which intermolecular cross-links were formed between the divalent calcium ions and the

negatively charged alginate molecules. The formation of gel beads was achieved without the need for advanced equipment. It is essential to homogenize the emulsion; without proper homogenization, the oil tends to separate from the alginate solution even when stirred. Alginate might have helped to emulsify the mixture of water and oil phase during the homogenization process. However, the emulsifying property was limited when the oil concentration was increased to more than 3%. Above this concentration the oil started leaking from the beads. The oil-entrapped beads were spherical and translucent. It was found that a minimum of 3% w/w olive oil was necessary to impart satisfactory buoyancy to the beads [21].

Particle size:

The particle size of porous lafutidine floating beads was found in the range of 1210.53 ± 1.07 to 1215.31 ± 0.85 µm for F1 to F4, 1204.20 ± 1.25 to 1223.18 ± 1.78 µm for F5 to F8 and it was 1208.43 ± 0.92 to 1249.46 ± 0.98 µm for F9 to F12 formulations (Table 3). The size of beads proportionally increases with increase in polymer concentration. This might be attributed to increase in viscosity of polymer solution due to the higher concentration of polymer, which resulted in formation of large droplets, thus increasing the size of beads.

Percent yield:

The percentage yield of porous floating beads was in the range of 76.04 ± 1.09 to 92.43 ± 0.91%. The percentage yield was between 81.71 ± 1.25 to 88.75 ± 1.11% for formulation F1 to F4, it was from 76.04 ± 1.09 to 92.43 ± 0.91% for F5 to F8 and for F9 to F12 it was found to be 80.57 ± 0.83 to 86.75 ± 1.19% (Table 3). The percentage yield increased with an increase in the polymer concentration. This can be explained by the fact that as the concentration of co-polymers increases the quantity of polymer becomes adequate to cover drug particles completely. In addition, the beads become well distributed, discrete, and spherical and have no clumping, thus giving a good percentage yield [22]. The yield was higher for the formulations cross-linked with HPMC K15M as compared to other formulations as it has higher viscosity than other co-polymers.

Drug entrapment efficiency:

The drug entrapment efficiency of porous floating beads was in the range of 70.91 ± 0.91 to 82.40 ± 1.11% for all formulations. In case of formulation F1 to F4 it was between 70.91 ± 0.91 to 78.36 ± 0.75%, for F5 to F8 it was in the range of 75.72 ± 1.01 to 82.40 ± 1.11% and F9 to F12 between 71.48 ± 1.26 to 78.15 ± 1.04% respectively (Table 3). It was noticed that the drug entrapment efficiency of floating beads also increased with an increase in the concentration of polymer. The method used to develop beads resulted in satisfactory entrapment of the drug in the polymers. This happens due to increased viscosity and encapsulation, improved particle formation, enhanced drug-polymer interaction and polymer matrix formation. Beads prepared with HPMC K15M gave higher drug entrapment efficiency than other co-polymers; this was related to the enhanced viscosity as the concentration rose.

Drug content:

The percentage drug content of porous floating beads was in the range of 71.85 ± 0.79 to 83.96 ± 0.83%. The drug content for formulations F1 to F4 was found in the range of 71.85 ± 0.79 to 80.86 ± 0.98%, F5 to F8 was found in the range of 77.01 ± 1.15 to 83.96 ± 0.83% and F9 to F12 was found in the range of 73.01 ± 0.61 to 79.98 ± 1.02% respectively (Table 3). It was noticed that the drug content of floating beads also increased with an increase in the concentration of polymer. This may be due to improved drug solubility, increased encapsulation efficiency and polymer-drug interactions.

Swelling index:

The swelling index of porous floating beads was in the range of 67.34 ± 1.24 to 86.90 ± 0.91% for all formulations. The swelling index for formulation F1 to F4 was found to be 72.87 ± 0.79 to 81.20 ± 0.56%, for F5 to F8 it was 67.34 ± 1.24 to 82.98 ± 0.97% and for F9 to F12 it was from 74.98 ± 1.27 to 86.90 ±0.91% (Table 3).

Table 3: **Evaluation of Porous Floating Beads of Lafutidine F1 – F12**

Formulation Code	Particle size * (µm)	Percent yield* (%)	Entrapment efficiency (%)*	Drug content (%)*	Swelling index (%)*
F1	1210.53 ± 1.07	81.71 ± 1.25	70.91 ± 0.91	71.85 ± 0.79	72.87 ± 0.79
F2	1211.03 ± 1.23	84.26 ± 1.03	73.82 ± 1.10	75.15 ± 1.23	75.32 ± 1.04
F3	1214.69 ± 1.01	85.64 ± 1.08	75.51 ± 0.98	76.98 ± 0.84	79.56 ± 1.29
F4	1215.31 ± 0.85	88.75 ± 1.11	78.36 ± 0.75	80.86 ± 0.98	81.20 ± 0.56

F5	1204.20 ± 1.25	76.04 ± 1.09	75.72 ± 1.01	77.01 ± 1.15	67.34 ± 1.24
F6	1207.24 ± 0.95	80.92 ± 1.09	77.08 ± 0.95	78.16 ± 0.72	70.11 ± 0.63
F7	1221.77 ± 0.81	83.22 ± 0.72	79.60 ± 1.02	80.08 ± 1.30	71.23 ± 0.89
F8	1223.18 ± 1.78	92.43 ± 0.91	82.40 ± 1.11	83.96 ± 0.83	82.98 ± 0.97
F9	1208.43 ± 0.92	80.57 ± 0.83	71.48 ± 1.26	73.01 ± 0.61	74.98 ± 1.27
F10	1219.56 ±1.49	83.33 ± 1.13	73.36 ± 0.81	75.10 ± 0.76	77.37 ± 0.85
F11	1227.27 ± 1.11	85.64 ± 0.86	75.60 ± 1.39	77.28 ± 0.56	82.35 ± 0.98
F12	1249.46 ± 0.98	86.75 ± 1.19	78.15 ± 1.04	79.98 ± 1.02	86.90 ± 0.91

*****Average of 3 determinations (±SD).

This indicated that the swelling index of porous floating beads increases with increase in the concentration of polymer. The maximum swelling index was observed in formulations containing HPMC K4M with their increasing concentration in formulations. HPMC K4M had a larger swelling index than HPMC K15M and Carbopol 934P. This could be related to increased water absorbing capability of HPMC K4M, which induces swelling and as a result, an increase in size. In general for all formulations with different co-polymers it was observed that swelling increased with time because of gradual absorption of water by the polymers.

Buoyancy studies:

All the manufactured beads floated promptly with a floating lag time of 45-50 s and showed good integrity and floating endurance of more than 12 h. The buoyancy nature of beads showed that all formulations were able to float on the dissolution medium (0.1 N HCl, pH 1.2) for 12 h. The floating lag time of the beads was found to decrease with an increase in co-polymer concentration. This is because of the elevated viscosity of the polymer solution, which in turn is the reason for more dense microspheres and less formation of pores in addition to cavities during preparation [23]. The buoyancy decreases with time as the drug diffuses out from the beads, small pores are formed in the system which allows surrounding medium to enter and fill up the void spaces, thereby increasing weight [24]. The buoyancy lag time of formulations F1 to F4 was 43 ± 0.8 to 56 ± 0.5 s, F5 to F8 was 43 ± 0.3 to 55 ± 0.8 s and for F9 to F12 was 50 ± 0.5 to 59 ± 0.3 s and for F13 to F21 it was 35 ± 0.4 to 58 ± 0.6 s (Table 4). The floating ability was also found to be directly related to the amount of oil entrapped in the polymer matrix. It was found that varying the copolymer concentrations in the bead formulations affected the floating lag time and did not affect the floating duration of the beads. For the formulation F16, F17 and F18 the duration of buoyancy was more than 12 h and lag time was less about 35 to 40 s; the floating capacity increase in this formulation due to high concentration gas generating agent (calcium carbonate). The floating capacity increases due to the high concentration of gas-generating agent calcium carbonate. The gas generated is trapped within the beads thus decreasing the density of beads. It was observed that paddle speed also affected the floating property of beads.

Table 4: In-vitro Buoyancy of Porous Floating Beads of Lafutidine

Formulation code	Buoyancy studies		Formulation code	Buoyancy studies	
	Floating lag time (s)*	Floating duration (h)*		Floating lag time (s)*	Floating duration (h)*
F1	56 ± 0.5	≥12	F13	58 ± 0.9	≥12
F2	51 ± 0.6	≥12	F14	51 ± 0.8	≥12
F3	47 ± 0.4	≥12	F15	47 ± 0.6	≥12
F4	45 ± 0.6	≥12	F16	40 ± 0.4	≥14
F5	55 ± 0.3	≥12	F17	38 ± 0.7	≥15
F6	51 ± 0.5	≥12	F18	35 ± 0.5	≥17
F7	47 ± 0.7	≥12	F19	56 ± 0.8	≥12
F8	43 ± 0.8	≥12	F20	49 ± 0.3	≥12
F9	59 ± 0.5	≥12	F21	41 ± 0.6	≥12
F10	57 ± 0.7	≥12	--	--	--
F11	52 ± 0.6	≥12	--	--	--
F12	50 ± 0.3	≥12	--	--	--

*****Average of 3 determinations (±SD).

In-vitro drug release studies:

The cumulative percentage of drug released from all the prepared floating beads F1 to F12 was found to be 84.547 to 98.846. In the case of formulations F1 to F4, drug release was found in the range of 92.52 to 84.54%, F5 to F8 was found in the range of 98.84 to 89.29%, F9 to F12 was found in the range of 93.51 to 88.70% respectively. The in-vitro release profile showed an initial burst effect due to the entrapment of the drug over the surface of beads and later drug was released slowly over sustained period 8 to 12 h. The order of drug release was as follows F5>F6>F9>F1>F7>F10>F2>F11>F8>F3>F12>F4. The drug release decreased with an increase in the concentration of polymer. Among different grades of HPMC and Carbopol, HPMC K15M showed better drug release, than HPMC K4M and Carbopol 934P respectively. HPMC K15M generally has a higher molecular weight compared to HPMC K4M and Carbopol 934P, which means it can form a more viscous gel when hydrated. Higher viscosity can lead to a slower drug release, making HPMC K15M suitable for controlled-release formulations. F5 was selected as an optimized formulation based on the percentage release of a drug (98.846%). The results are shown in Figure 1.

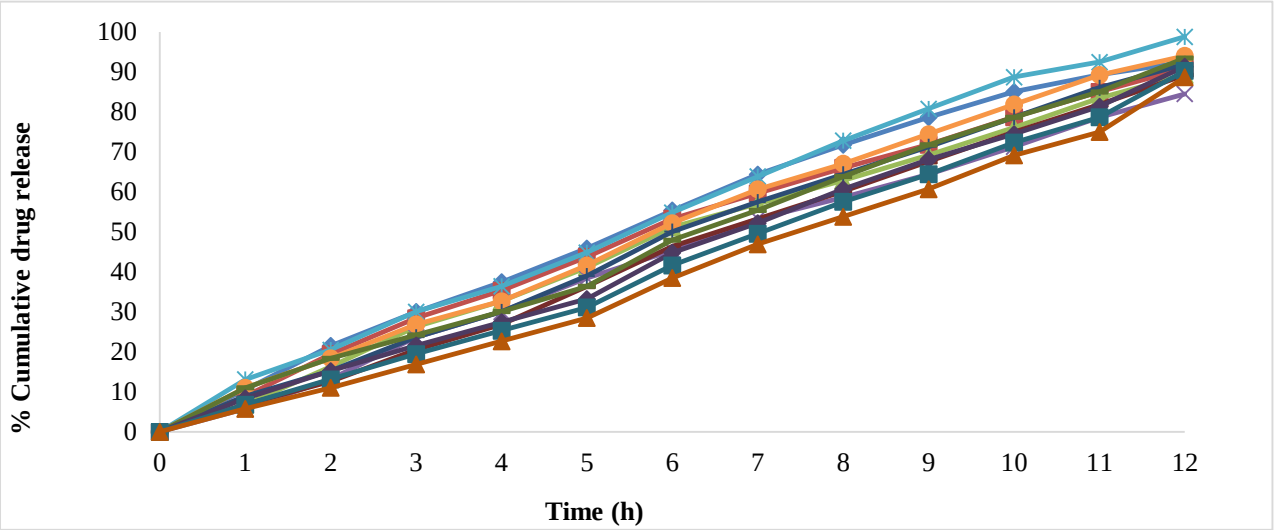


Figure 1: In-vitro release profile of porous floating beads of lafutidine F1 – F12

Effect of formulation variables:

Hardening agent:

The effect of the hardening agent (calcium chloride) was studied by formulating beads F13 (4%), F14 (5%) and F15 (6%) containing varying amounts of the agent. The concentration of calcium chloride had no significant effect on the drug content and drug entrapment efficiency of the beads. However, an increase in the concentration of calcium chloride resulted in bead size reduction. The size of the beads decreased from 1217.74 to 1208.12 µm as the concentration of hardening agent increased. As far as the swelling index is concerned the increase in calcium chloride concentration decreased the swelling index. This can be explained by the fact that as the concentration of calcium chloride solution is increased there is the formation of a more structured and rigid gel resulting in slow penetration of the medium into the matrix. It was observed that an increase in the hardening agent (calcium chloride) decreased the in-vitro drug release because the beads formed were very hard and it was difficult to release the drug from the beads. This may be because calcium (divalent ion) penetrates the inner space of droplets which causes the expulsion of water molecules and results in the formation of compact beads and results in increased cross-linking with sodium alginate. The results are shown in Table 5.

Gas generating agent:

The effect of gas generating agent (calcium carbonate) was studied by formulating beads F16 (0.4 g), F17 (0.5 g) and F18 (0.6 g) containing varying amounts of the agent. Gas-generating agents can lead to the formation of smaller particles. For instance, in effervescent formulations where gas bubbles are released, the gas escape can create voids or pores in the beads, potentially reducing the size of the particles. As the gas-generating agent is added in excess, it can lead to unwanted side reactions or complications in the process. This could potentially lead to a decrease in the yield of the desired product. In the case of drug content, it was observed that the drug content of beads decreased with an increase in gas generated agent. Increasing the amount of gas

generating can lead to a decrease in the overall drug content of the beads. This can happen if the increased gas generation causes the bead to disintegrate or degrade, leading to drug loss or instability from beads. Further in the case of drug entrapment efficiency, increasing the amount of gas-generating agent led to a decrease in drug entrapment efficiency. This may be due to damage to the carriers by increased effervescence, leading to drug leakage or lower entrapment efficiency. As far as the swelling index was concerned increasing the amount of a gas-generating agent led to an increase in its values. This was perhaps due to gas-generation within the bead can create internal pressure, which may lead to faster disintegration and subsequent swelling of the beads. This increased swelling could affect the rate and extent of drug release, as it may lead to a more porous structure or quicker exposure of the drug to the dissolution medium. Formulations F16, F17 and F18 showed drug release of 91.384, 94.567 and 97.750% respectively at the end of 12 h. A proportionate increase in drug release was observed with increasing concentrations of calcium carbonate in the beads. This could be due to a large amount of effervescence, which in turn resulted in pore formation and led to rapid hydration of the polymer matrix resulting in rapid drug release. The results are shown in Table 5 and Figure 2.

Effect of stirring speed:

The speed of the stirrer was changed from 900 rpm (F19), 1000 rpm (F20) and 1100 rpm (F21). The particle size of beads decreased from 1209.71 to 1194.59 µm with increasing agitation speed of the mechanical stirrer from 900 rpm to 1100 rpm. The anticipated outcome arose because elevated stirring rates supply the necessary shearing force to disperse the oil phase into smaller globules. High stirring speed produced an irregular shape of beads but a slightly increased entrapment efficacy and drug content was found. In-vitro drug release F19 (95.613%), F20 (94.427%) and F21 (90.826%) and swelling index F19 (83.49±1.04), F20 (83.01±1.39) and F21 (82.12±1.08) were decreased because of smaller particle size. The results are shown in Tables 5 and Fig 2.

Table 5: Evaluation of Porous Floating Beads of Lafutidine F13 – F21

Formulation Code	Particle size (µm)*	Percent yield (%)*	Entrapment efficiency (%)*	Drug content (%)*	Swelling index (%)*
F13	1217.74 ± 0.65	78.12 ± 1.28	72.08 ± 1.19	73.96 ± 1.18	84.60 ± 1.23
F14	1214.69 ± 0.78	81.70 ± 1.07	71.64 ± 1.29	74.28 ± 1.01	82.23 ± 1.07
F15	1208.12 ± 0.82	80.56 ± 1.12	72.84 ± 1.21	75.01 ± 1.13	80.07 ± 0.72
F16	1221.20 ± 0.81	84.88 ± 1.08	80.08 ± 1.01	82.01 ± 1.08	78.56 ± 1.02
F17	1220.98 ± 0.95	84.43 ± 1.21	77.84 ± 1.03	79.84 ± 1.02	83.79 ± 1.09
F18	1216.79 ± 0.93	82.76 ± 0.92	76.32 ± 1.11	77.36 ± 1.19	85.37 ± 1.19
F19	1209.71 ± 0.92	75.34 ± 1.09	80.91 ± 1.09	81.74 ± 1.23	83.49 ± 1.04
F20	1204.73 ± 1.08	78.15 ± 0.98	81.37 ± 1.02	82.98 ± 1.09	83.01 ± 1.39
F21	1194.59 ± 0.67	77.42 ± 1.01	82.59 ± 1.01	83.32 ± 1.05	82.12 ± 1.08

*****Average of 3 determinations (±SD).

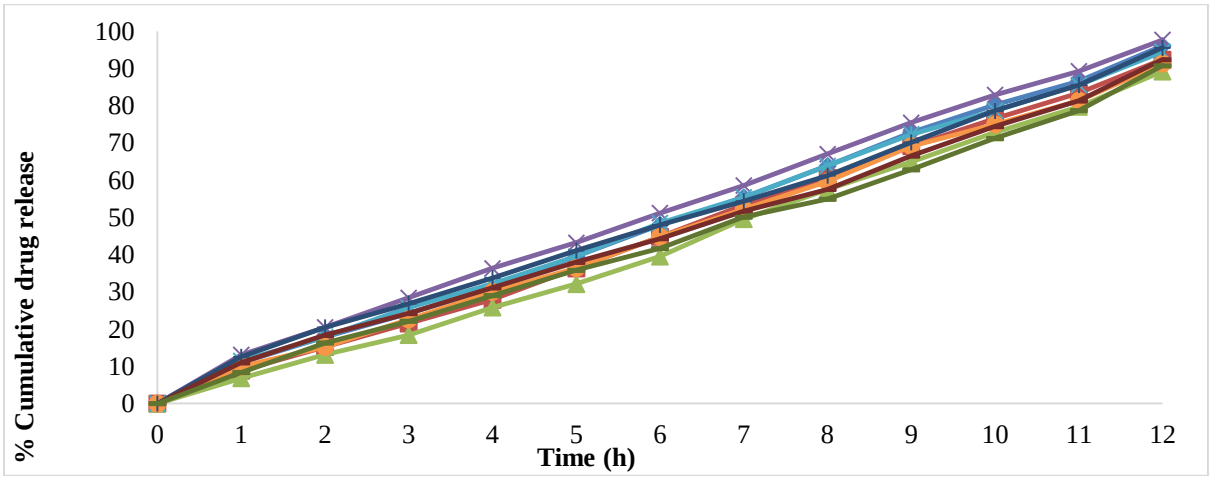


Figure 2: In-vitro release profile of porous floating beads of lafutidine F13 – F21

F13 F14 F15 F16 F17 F18 F19 F20 F21

Kinetic study:

To investigate the mechanism of drug release from the floating beads various kinetics models like zero order, first order, Higuchi's and Korsmeyer-Peppas equations were applied to the in-vitro release data. The results are given in Table 6. The values of correlation-coefficient (r^2) for all the formulations were high enough to evaluate the drug release behavior. The kinetic results revealed that formulations followed zero order, as correlation-coefficient (r^2) values (0.9876 - 0.9989) of zero order are higher than that of first-order values (0.8010 – 0.9552). When the data was plotted as per Higuchi kinetics, fairly linear plots were obtained with correlation coefficient values ranging from (0.8798 - 0.9427) for all the formulations. The drug release was proportional to the square root of time indicating that the drug release from porous floating beads of lafutidine was diffusion-controlled. In the Korsemayer-Peppas model the n values were found in the range of (1.2428 – 1.4006) indicating the mechanism of drug release was non-Fickian diffusion super case II type which is indicative of drug release mechanism involving a combination of diffusion and chain relaxation mechanism. The above observations led us to conclude that, all the porous floating beads of lafutidine followed diffusion-controlled zero-order kinetics.

Fourier transformer infrared spectroscopy study:

The IR spectra of pure drug and formulations F4, F8 & F12 were used to ascertain whether there is any interaction of the drug with excipients. In the case of IR of polymers, certain broad peaks were observed due to the presence of several functional groups & bonds present overlap in the same range. In the case of spectra of formulations certain peaks are poorly resolved and their positions can be easily identified.

The comparison of the IR spectrum of pure drug with that of formulation suggests that the important peaks of both drug and polymer have appeared with a negligible difference. Thus, all the peaks of the drug can be observed in the formulations in their expected positions. It is possible only when a drug has no interaction with the polymer and other excipients (Figure 3 – 6).

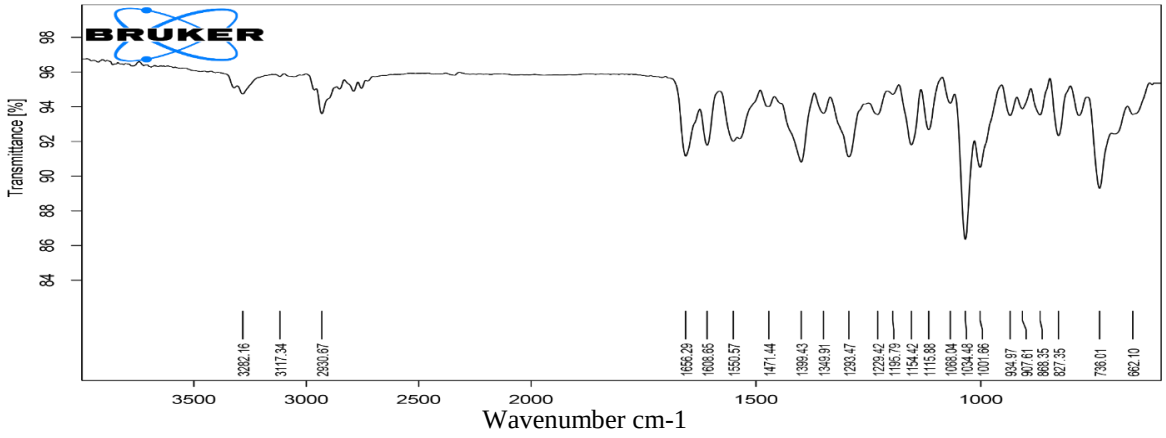


Figure 3: FTIR spectra of lafutidine pure drug

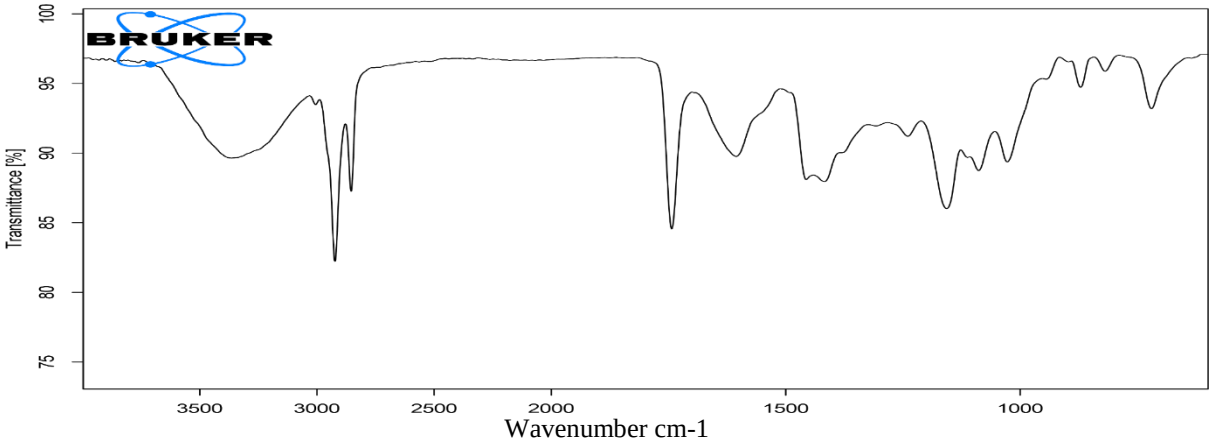


Figure 4: FTIR Spectra of porous floating beads of lafutidine (F4 - Carbopol 934P)

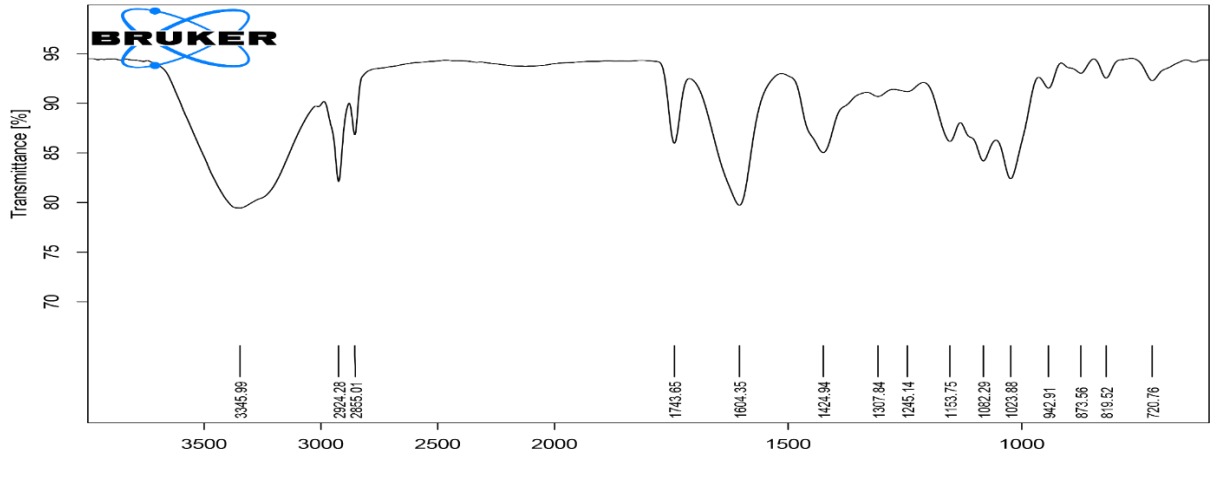


Figure 5: FTIR Spectra of porous floating beads of lafutidine (F8 - HPMC K15M)

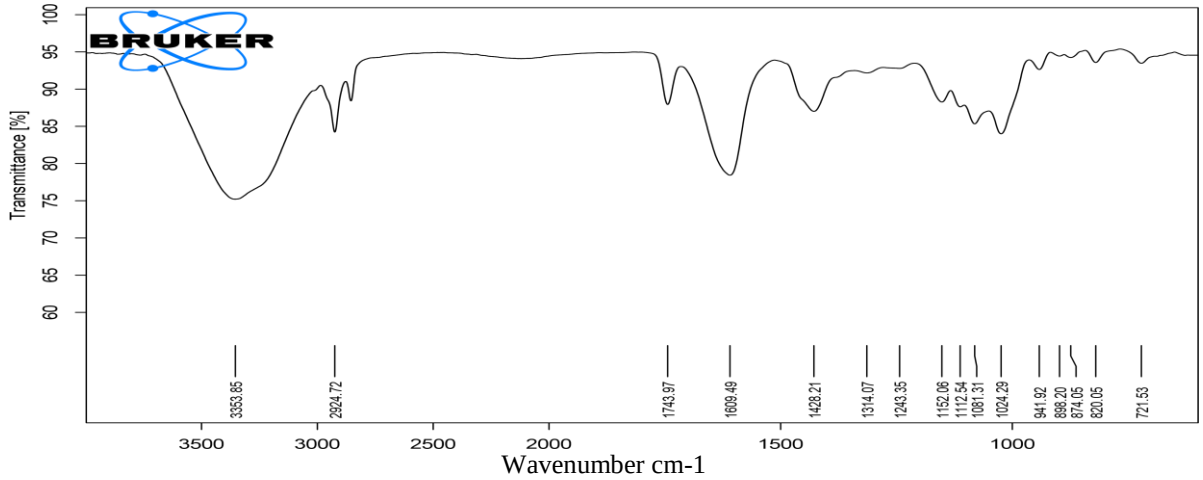


Figure 6: FTIR Spectra of porous floating beads of lafutidine (F12 - HPMC K4M)

Differential scanning calorimeter study:

Differential scanning calorimetry is used to study the thermal stability of the sample. It is mainly useful in the characterisation of drug substances and drug products. The thermogram of the pure drug lafutidine (Figure 7) is an endothermic curve which showed that the drug starts melting at 101.06 ºC. This endothermic peak absorbed at 101.06 ºC refers to an endothermic reaction by melting. The actual melting point of the pure drug Lafutidine is 98 – 101.57 ºC. Thus, the experimentally determined melting point of a pure drug by DSC thermogram matches with the theoretical melting point of the drug. The thermogram of the formulation F5 (Figure 8) containing a drug and excipients shows a broad endothermic peak where the melting of the mixture starts at 99.69 ºC which is approximately taken as 100 ºC and is within the range of theoretical melting point of the drug i.e., 98 – 101.57 ºC. Hence the drug in the formulation is thermally stable and does not undergo any decomposition.

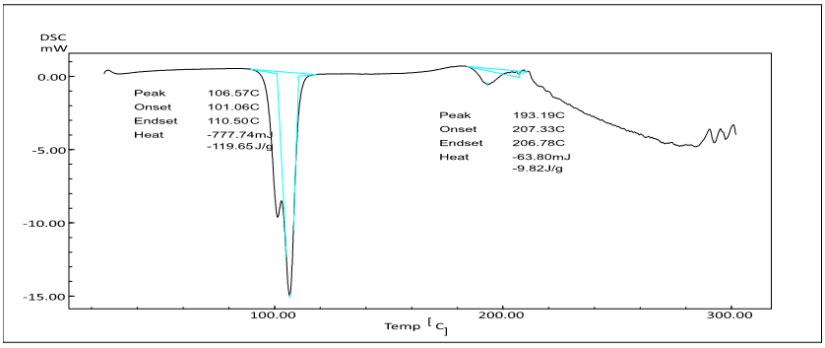


Figure 7: DSC thermogram of lafutidine pure drug

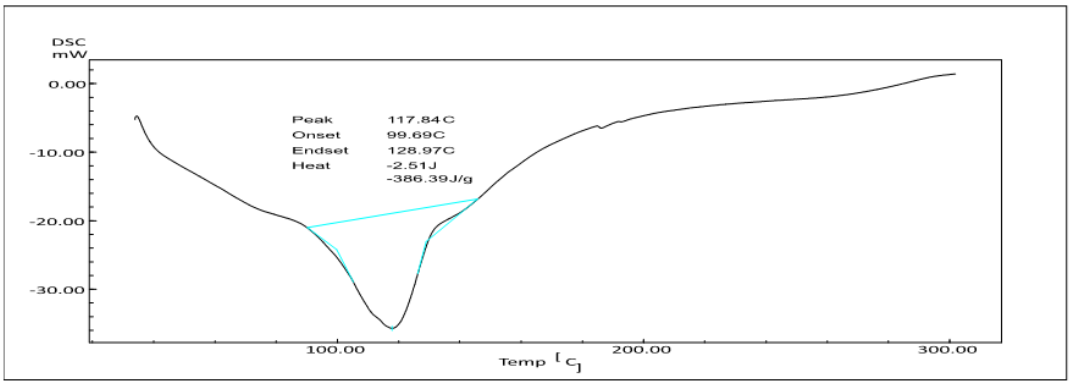
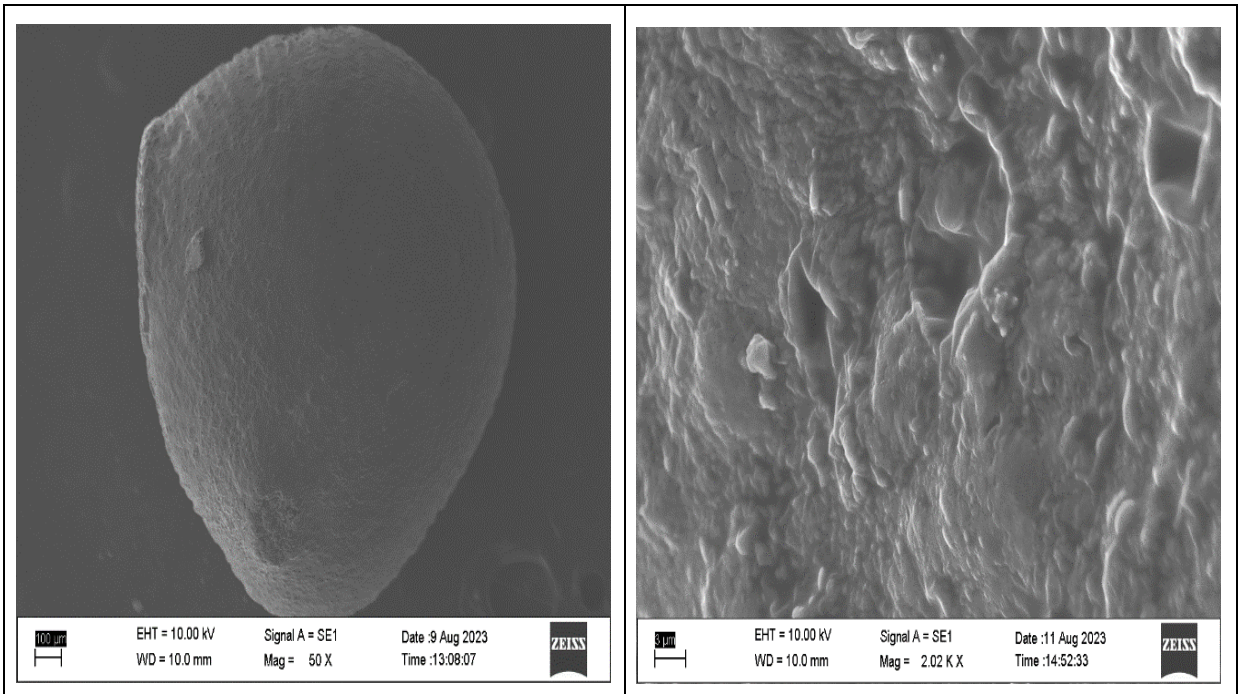


Figure 8: DSC thermogram of optimised porous floating beads of lafutidine (F5)

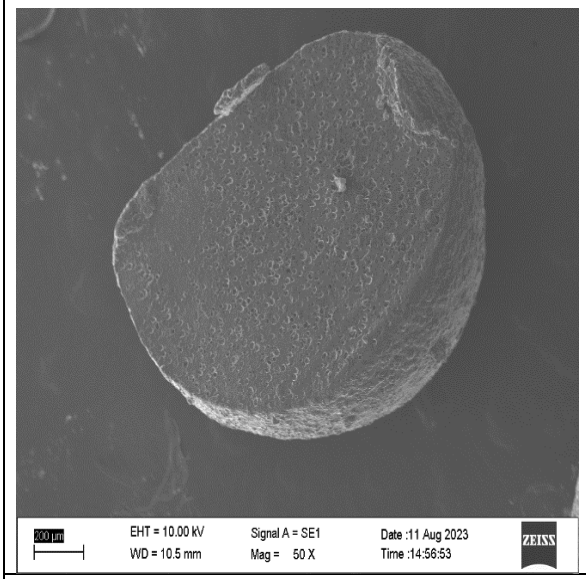
Scanning electron microscopy (SEM) study:

The surface and cross-sectional SEM pictures of the beads are shown in Figure 9 and 10. The surface of the beads of F5 was rough and porous (Figure 9). The cross-sectional morphologies of floating beads were also examined with SEM (Figure 10). Many large hollow pores or multiple small hollow pockets were observed in the alginate matrix. The number of observed pores appears to be directly related to the amount of incorporated gas-forming agent. The precipitated drug crystals can be seen embedded in the matrix.

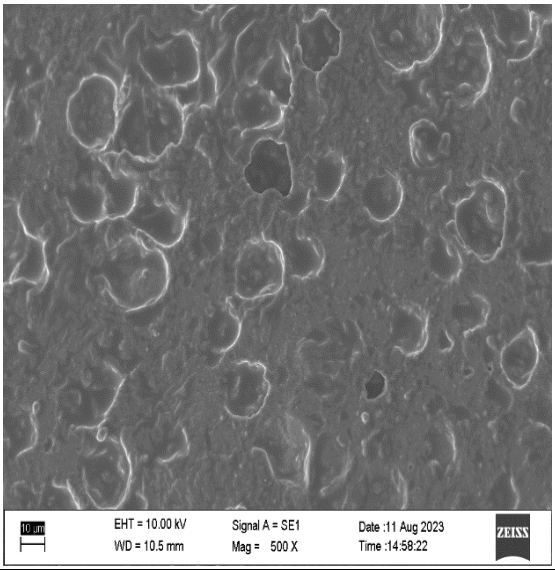


a) Magnification = 50 X **b) Magnification = 2.02 KX**

Figure 9: SEM Photograph of optimised porous floating beads of lafutidine (F5) at different magnification (Whole beads)



a) Magnification = 50 X



b) Magnification = 500 X

Figure 10: SEM Photograph of optimised porous floating beads of lafutidine (F5) at different magnification (Cross-section)

IV. CONCLUSION

Porous floating beads could be prepared by using sodium alginate, Carbopol, and different grade of HPMC polymer by Emulsion Gelation Method. The flow properties of all prepared beads were good as indicated by bulk density, tapped density, hausner's ratio, angle of repose and compressibility index. The buoyancy study was in the range of 43 ± 0.8 to 59 ± 0.5 sec. The nature of the polymer influenced the floating behaviour of the beads; the results indicated satisfactory performance of preparedd formulations. The buoyancy increased significantly as the amount of polymer was increased. The in-vitro release studies were in the range of 84.53 to 98.84% suggested that optimised parameters were used in the method of preparation. Optimised porous floating beads F5 released the drug in controlled manner for 12 h suitable for treatment of peptic ulcer. Porous floating beads containing lafutidine could be successfully developed and optimised. Hence, porous floating beads containing lafutidine showed promising results under in-vitro condition and thus there exist a scope for evaluation of the developed beads formulations for further pharmacokinetic studies, using appropriate test models.

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CONFLICT OF INTEREST

None declared.

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