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Preparation and *In-Vitro* Evaluation of Lafutidine Floating Microspheres

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ABSTRACT

The present research was aimed to prepare Lafutidine floating microspheres for sustained release using polymers such as sodium alginate and Hydroxy propyl methyl cellulose (HPMC K4M) by ionotropic gelation method. The prepared microspheres were evaluated for the Percent drug content, entrapment efficiency and In-vitro dissolution studies. Among all the formulations F12 was selected as optimized formulation based on the micromeretic and physico chemical parameters including drug release studies. I*n vitro* release study of formulation F12 showed 96.11% drug release after 12 h in a controlled manner, which is desired for disease like peptic ulcer. The marketed product shows the drug release of 94.11% within 12 h. Drug and excipient compatibility studies were carried out by FT-IR and DSC and no interactions were observed. The optimized formulation was best fit with the highest correlation coefficient was observed in Korsmeyer – Peppas, zero order and Higuchi model, indicating non fickian diffusion.

Keywords: Lafutidine, buoyancy, HPMC, Floating microspheres, Peptic ulcer.

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INTRODUCTION

Since the past three decades, the population of the GERD patients has recently been increasing. These situatuions are demanding to take drug for prolonged period of in multiple doses which causes non-compliance. To overcome this problem is to develop sustained or controlled release dosage forms which will deliver the drug for upto 24 hrs and many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications. The bioavailability of drugs with an absorption window in the upper small intestine is generally limited with conventional pharmaceutical dosage forms. The residence time of such systems and thus, of their drug release into the stomach and upper intestine is often short. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used [1].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms [2]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices [3].

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach [4]. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms [5].

Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach [6]. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs the increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism [7].

Peptic ulcer disease, also known as a peptic ulcer or stomach ulcer, is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus [8].

Lafutidine, a newly developed histamine H_2 receptor antagonist, inhibits daytime as well as night time gastric acid secretion, it has also exhibited gastroprotective activity. Which is used to treat gastric ulcers, Zollinger–Ellison syndrome, erosive esophagitis, gastro-oesophageal reflux disease and gastritis. Lafutidine has less bioavailability (80%) and lesser half life of 1.92 ± 0.94 hours [9]. The aim of present work is to design and in vitro evaluation of Lafutidine floating microspheres to enhance its bioavailability and prolonged residence time in stomach.

MATERIALS AND METHODS

Floating microspheres

Formulation of Lafutidine Floating microspheres:

Lafutidine floating microspheres were prepared by ionic gelation technique using polymers Sodium alginate and HPMC K4M. Sodium bicarbonate was used as a floating agent and calcium chloride was used as crosslinking agent.

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Table 1: Formulation trials of lafutidine Floating microspheres

Formulation code	Lafutidine (mg)	Sodium alginate	HPMC K 4M (mg)	Sodium bicarbonate (mg)	Calcium chloride
F1	100	1%	50	25	1%
F2	100	1. 2%	75	50	1%
F3	100	1.4 %	100	75	1%
F4	100	1.6%	150	100	1%
F5	100	1.8 %	175	125	1%
F6	100	2.%	200	150	1%
F7	100	2.1%	200	175	1%
F8	100	1%	150	25	1%
F9	100	1. 2%	200	50	1%
F10	100	1.4%	250	75	1%
F11	100	1.6%	300	100	1%
F12	100	1.8%	350	125	1%
F13	100	2.0%	400	150	1%
F14	100	2.2%	450	150	1%

Procedure for the preparation of floating microspheres:

Floating alginate microspheres of Lafutidine were prepared by ionic gelation technique using different proportion of polymers as shown in table .A solution of sodium alginate solution is prepared weighed quantity of drug and HPMC K4M was triturated to form fine powder, and then added to above solution. Sodium bicarbonate, a gas forming agent was added to this mixture.

Resultant solution was extruded drop wise with the help of syringe and needle into 100ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained microspheres were washed with water and dried at 60 degrees -2 hours in an hot air oven and stored in dessicator [10].

Evaluation of Lafutidine floating microspheres:

Micromeretic properties like particle size, angle of repose, bulk density, Tapped density, Compressibility index, Hausner's ratio and evaluation parameters like Swelling index, Drug entrapment efficiency and % yield, In vitro dissolution studies and percentage buoyancy studies were performed.

In vitro drug release studies:

In vitro drug release studies for developed lafutidine microspheres were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900 ml of 0.1 N HCl at 37± 0.5^{0}C temperature at 100 rpm. The amount of drug release was determined at different time intervals of 0, 1, 2, 3, 4, 6, 8, 10 & 12 hours by UV visible spectrophotometer (Shimadzu UV 1800) at 220nm.

Percentage buoyancy of Lafutidine floating microspheres:

In vitro floating ability can be determined by calculating percentage buoyancy and performed in USP type II dissolution test apparatus by spreading the floating microspheres in 0.1N HCL buffer containing the surfactant at 100 revolutions per minute (rpm) at 37± 0.5° C. After specific intervals of time, both the fraction of microspheres (floating and settled microspheres) is collected and buoyancy of the floating microspheres is determined by using formula [11].

$$\% \text{ Floating Microspheres} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100$$

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Kinetic modeling of drug release:

In order to understand the kinetics and mechanism of drug release, the result of the in vitro dissolution study of floating microspheres were fitted with various kinetic equations like Zero order as cumulative percentage released Vs. time, First order as log percentage of drug remaining to be released Vs. time, Higuchi's model cumulative percentage drug released Vs. square root of time.r^2 and K values were calculated for the linear curves obtained by regression analysis of the above plots. To analyze the mechanism of drug release from the tablets the in vitro dissolution data was fitted to zero order, first order, Higuchi's release model and Korsmeyer – Peppas model.

Drug excipient compatibility studies

The drug excipient compatibility studies like Fourier Transmission Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) method and SEM were performed.

Stability studies

The stability study of the optimized formulation was carried out under different conditions according to ICH guidelines. The optimized microspheres were stored in a stability chamber for stability studies (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency and cumulative % drug released during the stability study period.

RESULTS AND DISCUSSION

Floating microspheres:

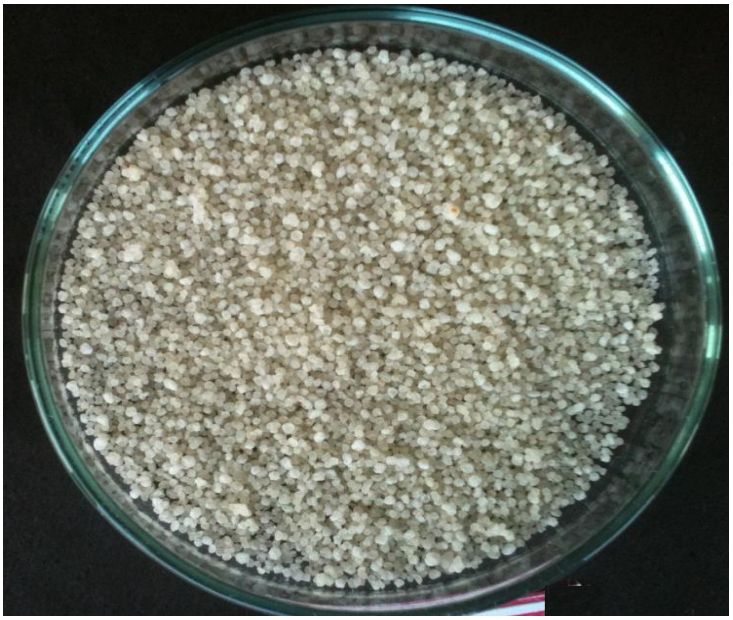

Figure 1: Lafutidine floating microspheres

All the formulations were evaluated for their various physical parameters like particle size, bulk density, tapped density, angle of repose, Carr's index and % buoyancy and found to be within the results. The formulation F12 shows best results like particle size 65.45±0.09µm, bulk density of 0.74g/cc^3, angle of repose 25˚.60, compressibility index 9.90% and % buoyancy of 94.5%.

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Table 2: Micromeretic properties of Lafutidine floating microspheres

Formulation code	Particle size (µm)	Bulk density g/cc³	Tapped density g/cc³	Angle of repose	Carr's index	% Buoyancy
F1	64.45±0.04	0.59	0.55	25˚.93	13.56%	90.2%
F2	60.12±0.08	0.66	0.59	27˚.74	12.34%	84.5%
F3	65.29±0.13	0.74	0.62	29˚.67	11.34%	83.3%
F4	73.43±0.04	0.76	0.73	26˚.03	14.36%	92.1%
F5	67.35±0.04	0.59	0.63	29˚.74	12.12%	81.64%
F6	79.67±0.09	0.89	0.83	31˚.15	11.23%	89.4%
F7	45.45±0.09	0.77	0.62	26˚.54	13.95%	87.1%
F8	55.23±0.14	0.75	0.63	28˚.91	10.32%	72.5%
F9	81.22±0.11	0.79	0.75	26˚.70	11.03%	75.8%
F10	83.34±0.10	0.68	0.84	30˚.24	12.34%	76.4%
F11	78.45±0.21	0.67	0.72	26˚.91	11.90%	85.3%
F12	65.45±0.09	0.74	0.85	25˚.60	9.90%	94.5%
F13	77.23±0.19	0.85	0.73	27˚.54	10.34%	89.4%
F14	81.67±0.13	0.79	0.74	28˚.91	13.94%	92.2%

The results of Percentage yield, entrapment efficiency and swelling index floating microspheres of all formulations were within the limits shown in **Table 3.**

The Percentage yield, entrapment efficiency and swelling index of F12 was found to be 95.5%, 95.2% and 96% respectively.

Table 3: Percentage yield, entrapment efficiency and swelling index of Lafutidine microspheres

Formulation code	Percentage Yield	Entrapment efficiency	Swelling index
F1	90%	90%	90%
F2	82%	82%	88%
F3	84%	80%	86%
F4	92.87%	92.3%	93%
F5	89.3%	86.2%	88%
F6	86.3%	84.1%	83%
F7	85.3%	83.3%	87%
F8	86%	84.3%	82%
F9	81%	72%	79%
F10	76%	83%	81%
F11	89%	85%	84%
F12	95.5%	95.2%	96%
F13	85.3%	81.3%	83%
F14	85.3%	80.88%	87%

Table 4: In vitro cumulative % drug release of Lafutidine floating microspheres

Time in hours	F1	F2	F3	F4	F5	F6	F7
0	0%	0%	0%	0%	0%	0%	0%
1	10.45%	22.67%	15.89%	12.10%	22.34%	16.10%	14.31%
2	19.5.7%	25.23%	23.41%	20.50%	25.12%	24.30%	21.15%
3	27.06%	30.10%	30.56%	28.03%	30.78%	30.20%	28.19%
4	35.08%	38.20%	38.95%	36.50%	38.28%	39.40%	37.23%
6	50.92%	51.34%	49.95%	51.60%	51.36%	53.80%	51.73%
8	66.25%	63.33%	61.26%	67.49%	63.38%	68.60%	66.46%
10	80.90%	69.99%	71.21%	82.80%	73.39%	73.90%	78.45%
12	92.03%	89.52%	86.15%	93.22%	89.54%	84.07%	89.23%

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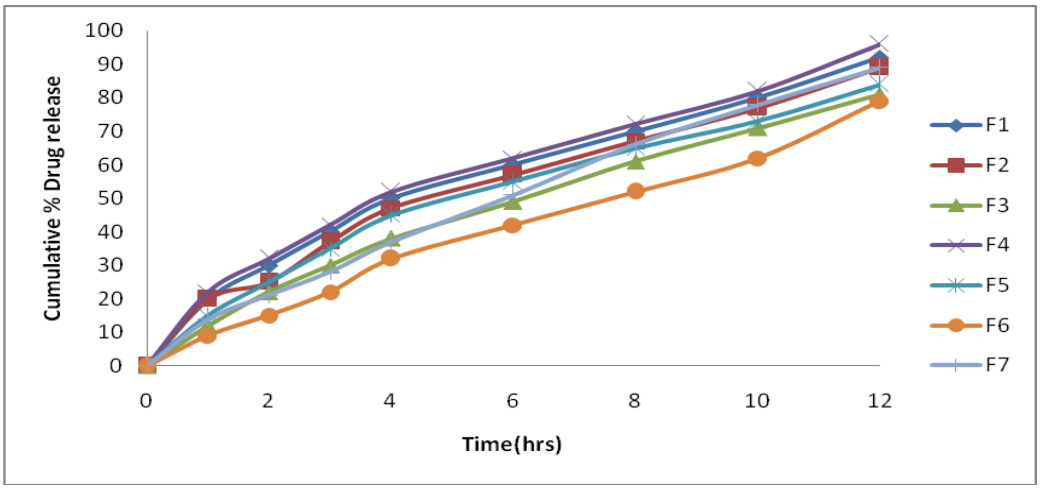

Figure 2: In vitro cumulative % drug release of Lafutidine floating microspheres

Table 5: In vitro cumulative % drug release of Lafutidine floating microspheres

Time in hours	F8	F9	F10	F11	F12	F13	F14	Marketed product
0	0%	0%	0%	0%	0%	0%	0%	0
1	22.32%	16.43%	20.55%	22.09%	13 .40%	15.62%	21.63%	15.11
2	25.45%	23.55%	24.85%	25.48%	21.05%	23.01%	32.01%	22.32
3	31.01%	33.65%	31.03%	30.33%	28.02%	29.11%	37.11%	29.34
4	37.25%	38.89%	44.43%	38.26%	36.66%	38.24%	44.83%	38.64
6	50.33%	49.69%	51.6%	51.13%	51.18%	52.83%	57.47%	53.77
8	61.35%	62.24%	60.35%	63.03%	67.58%	67.03%	64.46%	68.09
10	67.09%	70.18%	70.06%	69.69%	82.79%	72.22%	75.56%	83.66
12	86.56%	83.56%	85.45%	89.42%	96.11%	85.36%	87.17%	94.11

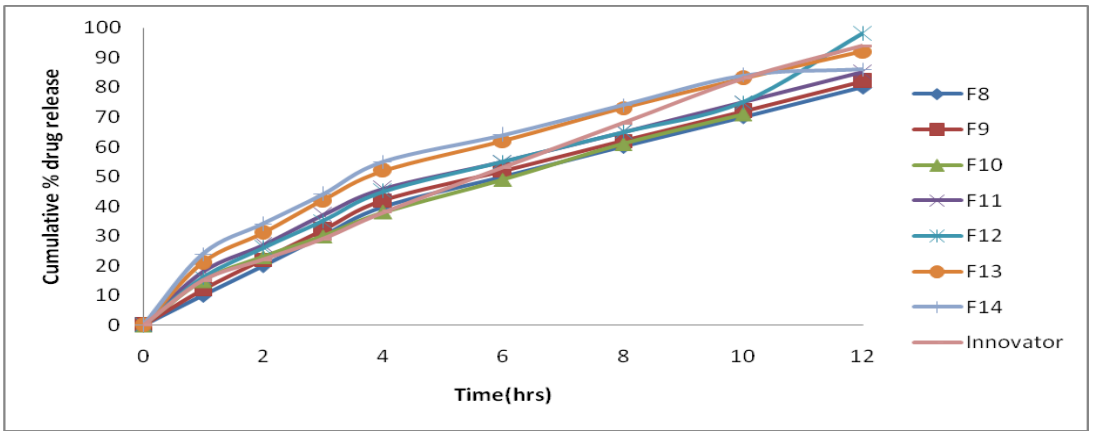

Figure 3: In vitro cumulative % drug release of Lafutidine floating microspheres Release order kinetics of Lafutidine optimized floating microspheres (F12)

Table 6: Release order kinetics of optimized formulation of floating microspheres

Formula Code	Zero Order		First Order		Higuchi		Korsemeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F12	0.962	7.832	0.866	0.101	0.9580	34.43	0.989	2.123

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.962 indicates that the drug release follows a zero order mechanism (Table no 6). This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

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Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsemeyer-Peppas plots.

The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.958 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsemeyer-Peppas plots i.e. 0.989 suggest that the drug release from floating tablet was anomalous Non fickian diffusion.

Drug excipient compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR)

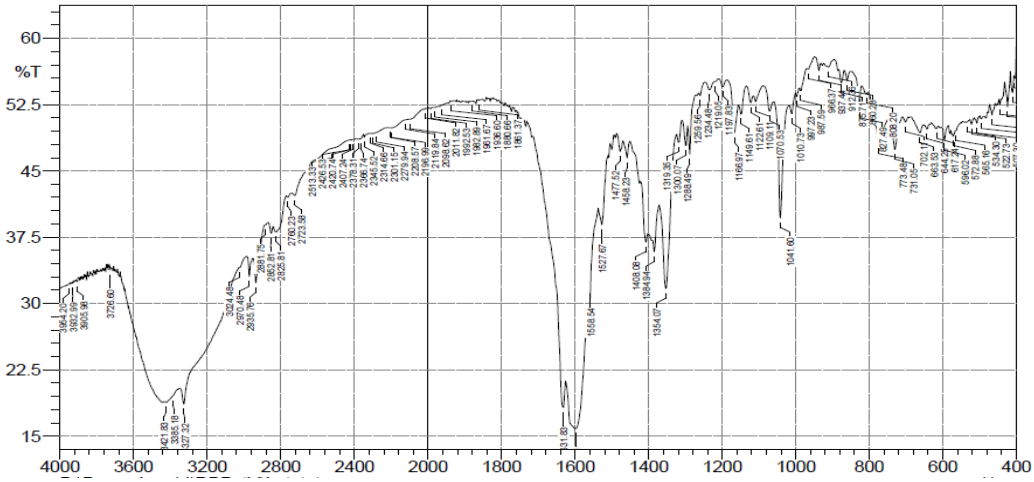

Figure 4: FT-IR spectrum of pure drug Lafutidine

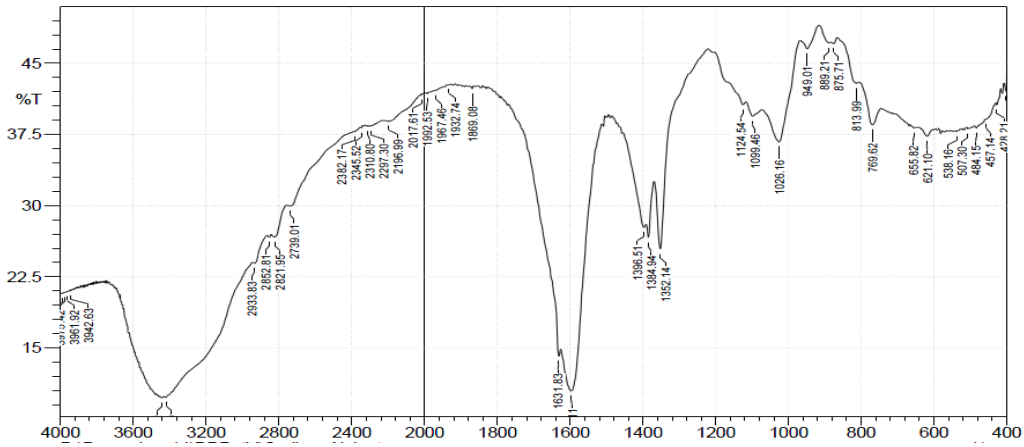

Figure 5: FT-IR spectrum of physical mixture

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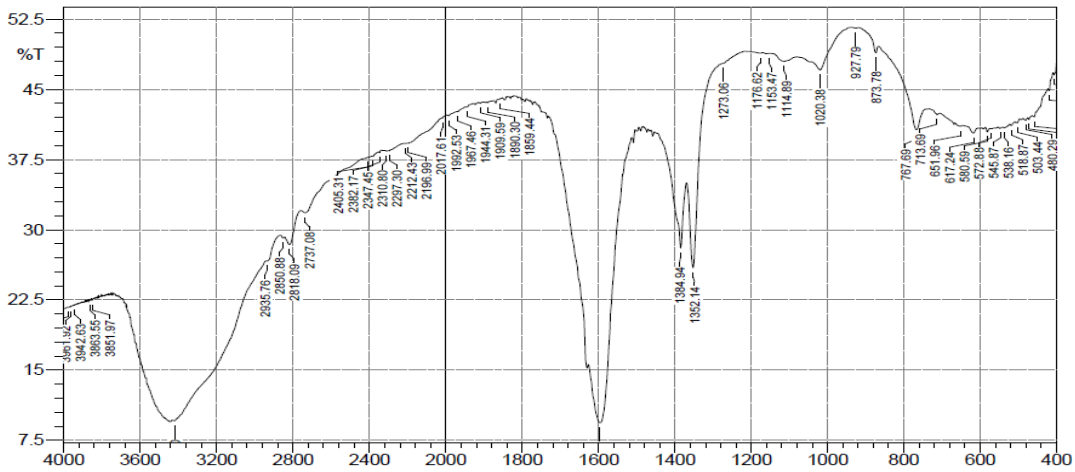

Figure 6: FT-IR spectrum of Lafutidine optimized formulation F12

Possible interactions between drug and polymer were investigated by FT-IR. FT-IR of pure LAFT characteristic sharp peaks of alkene stretching (=C–H and CH_2) vibration at 3324.32–3016.48 cm^{-1} and alkane stretching (–CH_3, –CH_2 and –CH) vibration at 2853.73 cm^{-1}. Also exhibited C=O stretch at 1738.2 cm^{-1} due to saturated ketone and C=O–NH stretching at 1635.90 cm^{-1}. A selective stretching vibration at 1561.57 cm^{-1} and 1525.80 cm^{-1} for primary and secondary amine was also observed. For functional groups like S=O stretch and –C–S stretch showed vibrations at 1041.78 cm^{-1} and 729.57 cm^{-1} respectively. Overall there was no alteration in peaks of Lafutidine pure drug and optimized formulation, suggesting that there was no interaction between drug & excipients. There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug , indicating absence of any interaction.

DSC Studies:

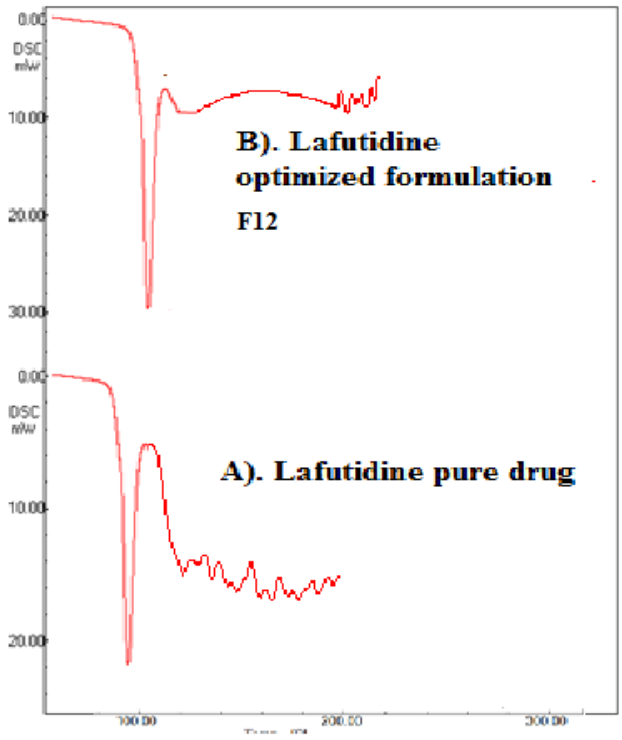

Figure 8: DSC thermogram of Lafutidine pure drug (A) and optimized formulation F12 (B)

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DSC was used to detect interaction between Lafutidine and excipients. The thermogram of pure Lafutidine exhibited a sharp endotherm melting point at 96 ^{0}C. The thermogram of optimized microspheres loaded with Lafutidine exhibited a sharp endotherm melting point at 99 ^{0}C **(Figure 8)**. The DSC thermogram of microsphere loaded with Lafutidine retained properties of pure Lafutidine. There is no considerable change observed in melting endotherm of drug in optimized formulation. It indicates that there is no interaction between drug & excipients used in the formulation.

Scanning electron microscopy studies:

SEM of Lafutidine Floating microspheres

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy.

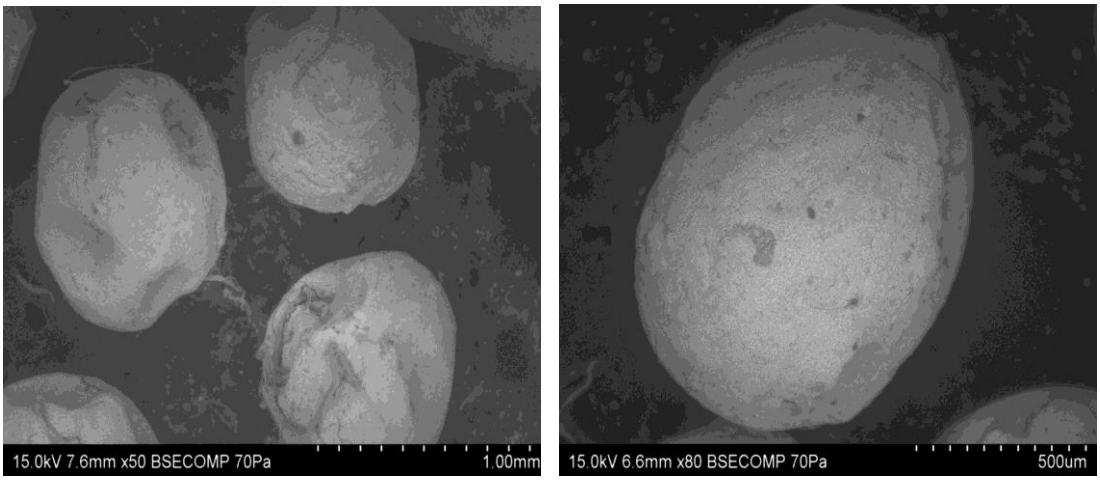

Figure 9: Scanning electron micrograph of Lafutidine floating microspheres

The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. Some of microsphere showed dented surface structure but they showed good floating ability on medium indicated intact surface (Fig 9). The shell of microspheres also showed some porous structure it may be due to release of carbon dioxide.

Stability studies:

Optimized formulation was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in Table 6.

Table 6: Stability studies of optimized floating microspheres

Retest Time For Optimized formulation	Percentage yield (%)	Entrapment efficiency (%)	*In-vitro* drug release profile (%)
0 days	95.50	95.20	96.11
30 days	94.66	94.18	95.46
60 days	93.53	94.43	94.73
120 days	92.12	92.17	93.42
180 days	91.34	91.45	92.78

CONCLUSION

In the present study, an attempt was made to prepare different types of Lafutidine floating microspheres, which were characterized for particle size, scanning electron microscopy, FT-IR study, DSC,

percentage yield, %drug entrapment, stability studies and found to be within the limits. Among all the formulations F12 was selected as optimized formulation. *In vitro* release study of formulation F12 showed 96.11% release after 12 h in a controlled manner. The *in vitro* release profiles from optimized formulations were applied on various kinetic models. The best fit with the highest correlation coefficient was observed in Higuchi model, indicating diffusion controlled principle. The innovator Laciloc 10 mg sustained release tablet shows the drug release of 94.11% up to12 h. FT-IR and DSC analyses confirmed the absence of drug-polymer interaction. From the results it can be concluded that the drug release from the floating microspheres was controlled by the polymer proportion. Prepared Lafutidine floating formulation showed best appropriate balance between buoyancy and drug release rate.

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