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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING ALGINATE BEADS OF LAFUTIDINE BY IONOTROPIC GELATION METHOD

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ABSTRACT

The present investigation aim to formulate gastroretentive floating drug delivery system of lafutidine to prolong gasric residence time, target stomach mucosa and increase the bioavailability. Lafutidine a newly developed histamine H_2-receptor antagonist, 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. The calcium alginate beads prepared by ionotropic gelation method using sodium alginate, hydroxyl propyl methyl cellulose and sodium bicarbonate. The developed beads were evaluated for physical appearance, micromeritic studies, particle size analysis, drug entrapment efficiency, swelling index, buoyancy studies, percentage yield, Fourier transform infrared spectroscopy (FTIR) studies, DSC Study, *In vitro* drug release study. The optimized formulation (F3) at the end of 12 hr shows % CDR 89.66%. The drug release data fitted in kinetic data. The optimized formulation follows zero order release kinetic and accelerated stability studies were performed for optimized batch.

KEYWORDS: Alginate beads, Lafutidine, Gastroretentive floating drug delivery system.

INTRODUCTION

The main goal of any drug delivery system is to achieve the desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period.

Conventional oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug level. Oral controlled release (CR) formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in

the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation.[1, 2]

Lafutidine a newly developed histamine H_2-receptor antagonist, 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. It is absorbed in the small intestine, reaches gastric cells via the systemic circulation and rapidly binds to gastric cell histamine H_2 receptors, resulting in immediate inhibition of gastric acid Lafutidine having biological half life 1.92±0.94 hr, Moreover, the site of absorption of Lafutidine is in the stomach.[3]

The recommended adult oral dosage of is Lafutidine 10 mg, two times in Day, due to its selective absorption from upper part of GIT. Hence, the focus of present work is to prepared and evaluate gastro-retentive floating beads of the Lafutidine were developed to increase the gastric residence time of the drug, which could be retained in the stomach for a longer time, improving the buoyancy and drug release characteristics also help in controlled released of drug upto 12 hr. Once in day Lafutidine gastro-retentive beads offer better patient compliance through less frequent administration and lower the cost of total therapy. A Gastro-retentive beads of Lafutidine was prepared to give sustained effect for 12 hrs. The Floating Gastroretentive beads were made using the gel-forming polymers such as HPMC K4M and sodium alginate.[4]

Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process and thus, they may cause high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT. While the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and lead to development of Gastro retentive floating multiple unit particulate dosage form (microsphere and gel microbead).

Multi particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles thus multiparticulate dosage forms are

pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. The system is based on the expansion of the core (non effervescent FDDS or low density approach), which lead to floating due to low density. Also the air entrapped by the swollen polymer confers buoyancy to this dosage forms.

Microbeads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of active agents without major side effects. The beads also maintain functionality under physiological conditions and can incorporate drug to deliver locally at high concentration ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low.

MATERIALS AND METHOD

Materials

Lafutidine purchased from Pure Chem. Pvt. Ltd, Ankaleshwar, Gujarat HPMC and Sodium bicarbonate were purchased from Research-Lab Fine Chem. Industries, Mumbai Sodium Alginate was purchased from Modern Industries, sinner. Other chemicals and reagents used in the study were of analytical grade.

Preparation of floating Lafutidine beads

Four different formulations (as shown in Table 1) of Lafutidine alginate beads were tried lafutidine dispersed in 15 ml water The resulting dispersion was added to 20 ml of sodium alginate solution (3 and 4%) containing hydroxypropyl methylcellulose, in the ratio of (sodium alginate: HPMC) 9:1 w/w. The gas-forming agent $NaHCO_3$ was added to the dispersion, with levels starting from ratios (gas-forming agent: alginate w/w) 0.25:1 and 0.5:1 and mixed in a mechanical stirrer. The prepared mixture was then sonicated and the resulting dispersion was dropped through a 24G syringe needle into 5%w/v of calcium chloride solution. The solution containing beads was stirred slowly using magnetic stirrer for 10 min. The beads were further allowed to remain in the same solution for 20 min to improve beads mechanical strength The formed beads were filtered, washed, air dried at room temperature.

Table 1: Formulation of Lafutidine Floating Beads

Batch no.	Drug (mg)	Polymer (%) Sodium alginate: HPMC (9:1 w/w)	Polymer: gas forming agent (%)
A	10	3	1:0.25
B	10	3	1:0.5
C	10	4	1:0.25
D	10	4	1:0.5

EVALUATION[5]

The prepared beads were evaluated for Micromeritic Studies, % yield, encapsulation efficiency, particle size, swelling, DSC, FTIR, short term stability and *in vitro* drug release study.

Physical Appearance

All the batches of lafutidine beads were studied for colour and physical appearance.

Micromeritic Studies of Floating Microbeads

Floating microbeads are characterized by their micromeritic properties such as particle size, bulk and tapped density, compressibility index, true density and flow properties.

Bulk and tapped density

Bulk and tapped densities were measured by using 5 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

Bulk density = Mass of Formulation / Bulk Volume.

Tapped density = Mass of Formulation / Tapped Volume.

Carr's Compressibility Index

Compressibility index (C.I.) or Carr's index value of microbeads was computed according to the following equation:

$C.I. = \rho t - \rho o / \rho t \times 100$

Where, ρt = tapped density, ρo = bulk density

The value given below 15% indicates a powder with usually give rise to good flow Characteristics, whereas above 25% indicate poor flow ability.

Hausner's ratio

Hausner's ratio of microbeads was determined by comparing the tapped density to the bulk density using the equation:

Hausner's ratio = ρt /ρo

Where, ρt = tapped density, ρo = bulk density.

The Angle of repose (θ)

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. Angle of repose of different formulations was measured according to fixed funnel standing method. The beads were allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of beads on the paper. The angle of repose was calculated by substituting the values of base radius 'r' and pile height 'h' in the following equation,

$\tan \theta = h / r$

Where, θ is the angle of repose, *h* is the height and *r* is the radius.

Size Analysis

Size distribution analysis of microbeads was done by optical microscopy using motic microscope. A small quantity of microbeads randomly selected from each batch, was dispersed on the slide with the help of capillary tube. The diameters were sized using a suitable objective (10X and 40X).

Drug Entrapment Efficiency

Accurately weighed quantities of approximately 50 mg of Beads were crushed using mortar and pestle; were dissolved in 50 ml of 0.1N HCl (pH 1.2) and the drug content was analyzed at 281 nm using a UV/visible spectrophotometer. Encapsulation efficiency was calculated as the percentage (w/w) of the theoretical drug content.

Drug Entrapment efficiency = (Practical drug content/Theoretical drug content) x 100

Swelling Index

Swelling studies for beads was performed in dissolution media (0.1 N HCl). The beads were removed at time t by filtration and blotted carefully to remove excess surface water. The swollen beads were weighed. The swelling ratio was calculated using the following formula

Swelling Index = (final weight-initial weight) / initial weight

Buoyancy studies

Prepared beads were evaluated for buoyancy and floating time by USP type I dissolution apparatus. Twenty beads of each batch were placed in 900 ml of 0.1N hydrochloric acid, agitated at 100 rpm; during study temperature was maintained at 37°C ± 2°C for 12 hr. The time required for beads to rise to the surface and float (floating lag time). The floating ability of the beads was observed visually for 12 hr.

% Yield

% Yield for the different formulations was calculated by the formula given below.

% Yield =Total weight of floating beads produced ×100 / Total weight of drug and polymer

FT-IR Study

IR spectrums of drug and beads formulation were performed on FTIR Spectrophotometer (shimadzu, 8400S). The sample (1 mg) mixed with the (10 mg) of dry powdered potassium bromide. The powdered 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. An FTIR spectra is used to see the presence of interactions and identification of the changes in functional groups.

DSC Study

DSC analysis was performed using DSC-1 ($STAR^e$ System). Samples (2-5 mg) were heated in an open aluminum pan at a rate of 10^0C/min conducted over a temperature range of 30 to 320^0C under a nitrogen flow of 2-bar pressure. The DSC studies to characterize the phase equilibrium, polymorphic changes, melting and crystallization and decomposition behavior of alginate beads. Thus the DSC was used for the characterization of the complex.

***In vitro drug* release study**

In vitro drug release study was carried out in acidic solution 0.1 N HCl using USP type II (Basket type) dissolution rate test apparatus (TDT-08L, Electro lab, Mumbai, India). Accurately weighed, 20 mg of dried beads were placed in 900 mL of dissolution medium and maintained at 37 ± 0.5^0C. The basket was rotated at 50 rpm. Aliquots were withdrawn at different time intervals and replenished the medium immediately with the same volume of fresh solution. Suitably diluted samples were analyzed spectrophotometrically at 281 nm. Each sample was tested and analyzed in triplicate.

Calibration Curve of Lafutidine in 0.1 N HCL[6]

The calibration curve of Lafutidine was performed in 0.1 N HCL. The calibration curve was found to be linear in the concentration range of 10-50µg/ml having a coefficient of regression value R^2 =0.997 and line equation, y =0.010x.

Table 2: Concentration and Absorbance values for Lafutidine in Methanol (λ_{max} 281 nm)

Sr.No.	Concentration	Absorbance (λ_{max}281nm)
1	10	0.139±0.011
2	20	0.231±0.013
3	30	0.339±0.012
4	40	0.428±0.013
5	50	0.530±0.011

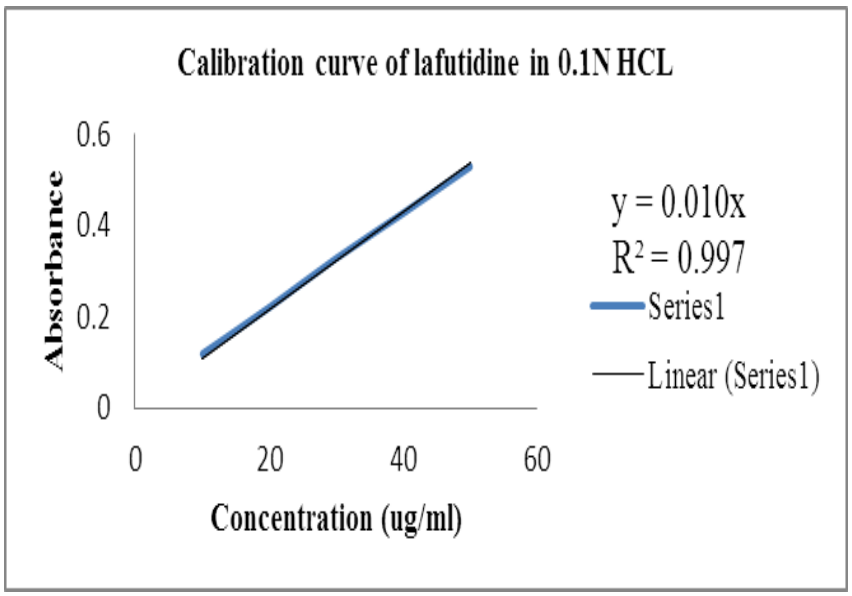

Figure 1: Calibration Curve of Lafutidine in 0.1 N HCL

RESULT AND DISCUSSION

Drug-Excipient Compatibility[6]

The drug and combination of drug with excipients were taken in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400 cm-1 using FTIR spectrophotometer. The recorded spectrums is shown in Figure 2.

The characteristics absorption peaks of Lafutidine were obtained at 3283.82cm^{-1}, 2932.86 cm^{-1}, 3068.85 cm^{-1}, 1546.96 cm^{-1}, 1290.42 cm^{-1}, 1657.87 cm^{-1}, 1032.92 cm^{-1}. IR spectra of combination of drug with excipients compared with IR spectra of pure drug. The principle

peaks for the combinations of excipients were almost similar to that of drug. The possibility of interaction ruled out as there was no shift in the absorption bands of drug with excipients. So we conclude that the drug found to be compatible with all the excipients in the formulation. Hence all these ingredients were selected and used in the present work.

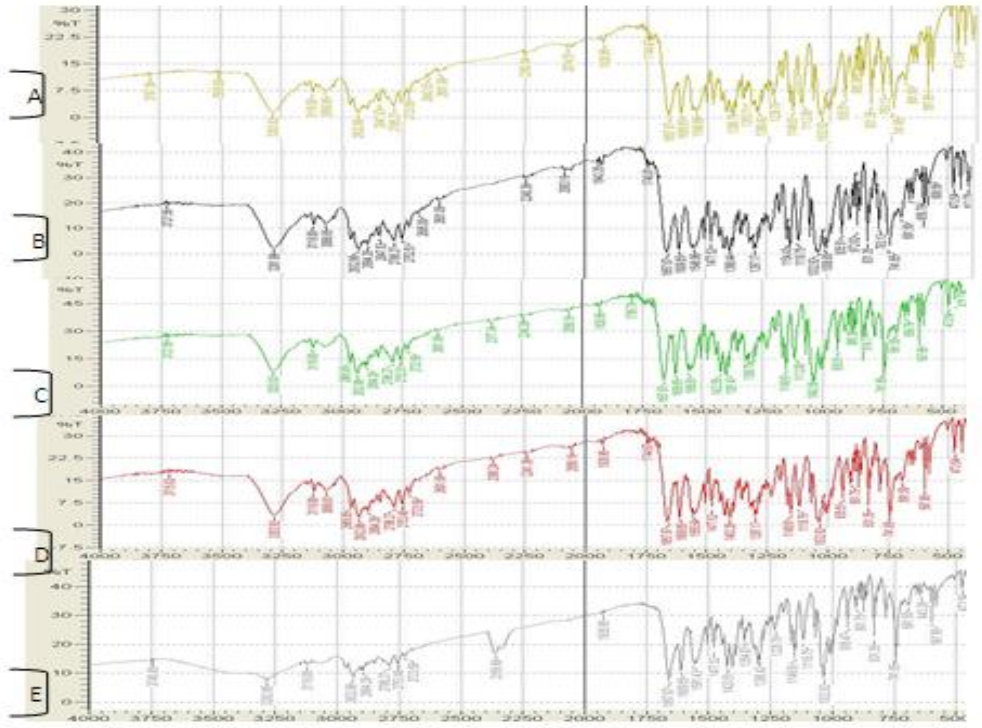

Figure 2: FTIR Spectrum of A] Lafutidine, B] Mixture of Lafutidine with Sodium alginate, C] Mixture of Lafutidine with HPMC K4M, D] Mixture of Lafutidine with $NaHCO_3$, E] Mixture of Lafutidine with all excipients in formulation.

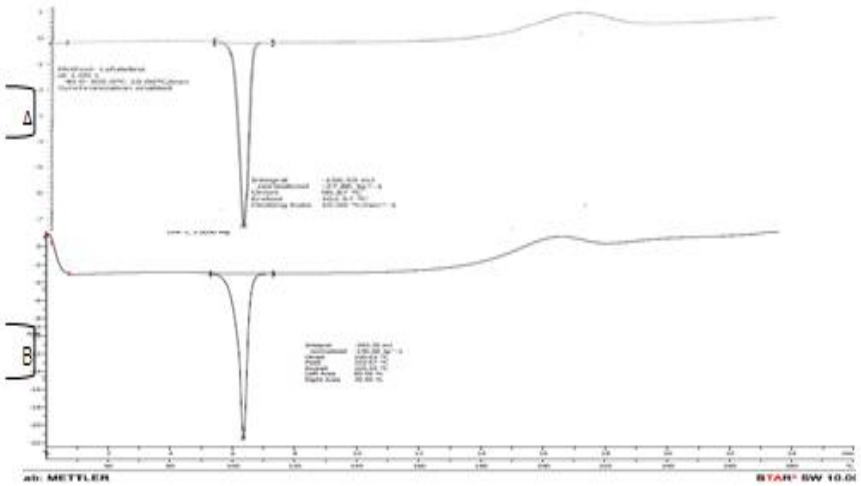

Figure 3: DSC thermogram of A] Lafutidine, B] Lafutidine with all excipients in formulation (Physical mixture)

The DSC spectra of drug and drug-excipients physical mixture (HPMC K4M, Sodium alginate, $NaHCO_{3,}$ $CaCl_2$ mixture) studies reveal that there was no significant change in position of peak in thermogram of drug and drug-excipients was recorded. The differential scanning colorimeter thermogram of Lafutidine exhibited a single sharp endothermic peak at 96.87°C related to its melting transition temperature showed in Figure 3 A] and drug excipients physical mixture shows melting endothermic peak of Lafutidine at 102.67°C shown in Figure 3 B]

From drug excipients compatibility study, it was concluded that the given drug was compatible after 1 month treatment of 40^0C temperature and 75 ± 5% RH with all the excipients and it was confirmed by differential scanning colorimeter study. Therefore, this study revealed that there was no interaction between the drug, polymers and other excipients.

EVALUATION OF BEADS[7]

Physical appearance of lafutidine beads

The prepared beads of all four batches evaluated for its physical appearance and colour. The concentration of polymer: $NaHCO_3$ affect the appearance of the beads and the results are shown in table 3. Outer surface of some beads is rough along with pores to the bead that helps the passage of drug from the inner part of the beads.

Micromeritics Study

From the micromeritics study result it is concluded that the all the formulations showed good flow property.

Size analysis of lafutidine beads

Average particle size calculated for each batch. Increase in mean particle size with increase in polymer concentration may occurred due to fact that increase in polymer concentration it produces a significant increase in the viscosity, leading to an increase of the emulsion droplet size and finally increase the bead size.

Percentage Yield

The yield was found to be less due to small batch size and thus can be improved by making bigger batches and improving the cross linking methods.

Floating study

The increased polymer and $NaHCO_3$ concentration decreases the floating lag time of beads in 0.1 N HCl. When the beads come into contact with acidic medium, $NaHCO_3$ effervesces, releasing $C0_2$ which make the beads remain float over the surface. The released CO_2 lowers the beads density and makes them float for a prolonged time. The floating time was found to be increased as the concentration of $NaHCO_3$ increases.

Swelling Index

The release of a drug from a polymeric matrix is controlled by the swelling behavior of the polymer. It was further observed that increase in polymer concentration decreased the swelling of beads. At low polymer: $NaHCO_3$ concentration, the polymeric network is loose with a greater hydrodynamic free volume which allows more of the liquid to be absorbed leading to greater swelling of beads.

Drug Entrapment Efficiency (DEE)

Increase in concentration of polymer resulted in higher drug entrapment efficiency. As concentration of $NaHCO_3$ increases, drug encapsulation efficiency was found to be decreased. High $NaHCO_3$ concentration form many pores in hydrogel matrix and make the internal structure of hydrogel become less dense, with the result that drugs cannot be retained in hydrogel network for long time.

Table 3: Evaluation of formulation batches

Sr. No.	Evaluation Parameters		F1	F2	F3	F4
1	**Angle of repose(θ)**		$42^0 64'$	$41^0 67$	$40^0 25'$	$40^0 32'$
2	**Bulk density(g/ml)**		0.5263	0.556	0.5605	0.5102
3	**Tapped density(g/ml)**		0.5938	0.6097	0.6410	0.5296
4	**Carr's index (%)**		11.36	8.80	12.55	14.46
5	**Hausner's ratio**		1.128	1.096	1.143	1.038
6	**Physical Appearance**	**Colour**	Yellow	Yellow	Yellow	Yellow
		Appearance	Some are Oval and Round	Some are Oval and Round	Round	Round
7	**Average size (um)± SD**		653.1 ±6.46	761.8 ±4.59	765.1 ±6.35	656.1 ±2.58
8	**% Yield**		72.36	66.50	74.92	69.47
9	**Swelling Index (%)**		10	11.86	8.37	8.61
10	**% DEE**		83.72	80.72	92.79	87.56
11	**Floating lag time**		8 Sec	6 Sec	10 Sec	5
12	**Floating time(hr)**		>20	>20	>20	>20
13	**% CDR**		93.63	95.36	89.66	92.28

FTIR Study

The FTIR spectra of formulation are shown in figure 4. The carboxylate anion peak of sodium alginate observed at 1398 cm-1. The formation of beads could have resulted due to ionic linking between Ca^{++} ion and carboxylate groups of sodium alginate. In case FTIR spectrum of bead the frequency of IR absorption for carboxylate anion was shifted to a higher absorption frequency 1404 cm-1, indicating ionic interaction between $–COO^{–}$ and Ca^{++} ions.

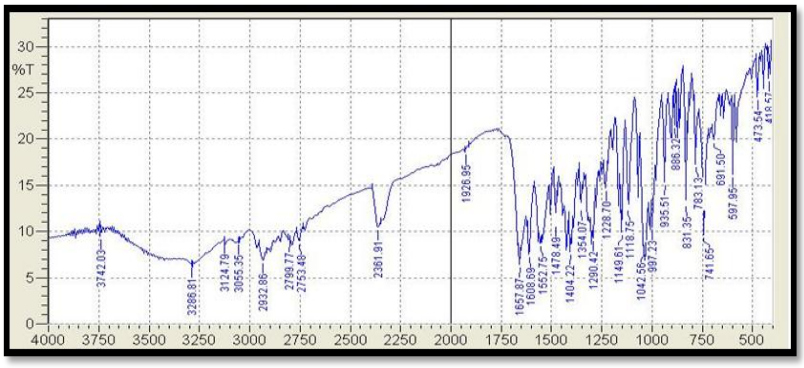

Figure 4: FTIR Spectrum of Lafutidine Beads

Differential Scanning Calorimetry (DSC) Study

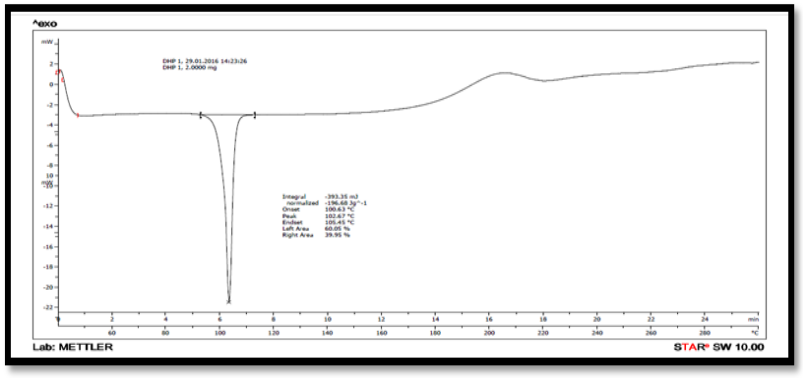

Figure 5: DSC thermogram of Lafutidine and all Excipients in formulation.

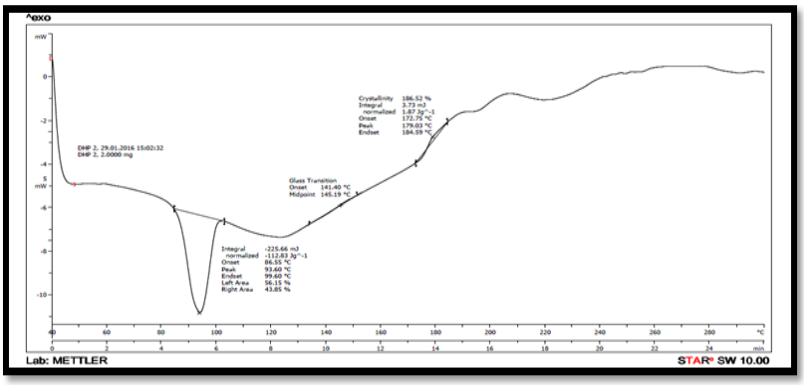

Figure 6: DSC thermogram of floating lafutidine bead.

DSC thermogram of lafutidine physical mixture and drug loaded bead are shown in figure 5 and 6 respectively. The DSC thermogram for lafutidine physical mixture has an endothermic peak at 102.67°C, which corresponds to melting point of lafutidine. The endothermic peaks were also observed in the bead at 93.60°C. The sodium alginate –polymer drug loaded beads showed a lower endothermic peak than that of pure lafutidine. The changes in transition temperature results from the formation of a polyelectrolyte complex (or formation of a bead) between drug and polymer.

***In vitro* drug release profile**

The F1 formulation batch containing polymer concentration 3% (Sodium alginate: HPMC) (9:1 w/w) and Polymer: gas forming agent (%) in 1:0.25 proportion. These batch shows drug release 93.63% at 12 hr, in these batch the polymer and gas former concentration both in a low concentration, The F2 formulation batch also contains 3% (Sodium alginate: HPMC) (9:1 w/w) but different Polymer: gas forming agent (%) concentration, that is 1:0.5 in these batch the concentration of gas former is doubled than the F1 batch these batch shows drug release 95.36% at 12 hr.

The result of F1 and F2 indicate that as the concentration of the gas former increases the pores formation in beads increases due to these drug release of F2 is more than F1 batch at the same polymer concentration.

The F3 and F4 formulation batch contains 4% polymer concentration (Sodium alginate: HPMC) (9:1 w/w) and 1:0.25 and 1:0.5 (Polymer: gas forming agent (%) respectively. F3 and F4 batch shows drug release 89.66% and 92.28% at 12 hr respectively. In these both batches the concentration of polymer is increased from 3% to 4% which lead to formation of more thick gel and the drug release is low than the F1 and F2 which contains low polymer concentration (3%). The F3 formulation batch shows low drug release than other formulation batches that is it shows sustained drug release for longer period of time, from these it is the optimized formulation from all the formulation batches.

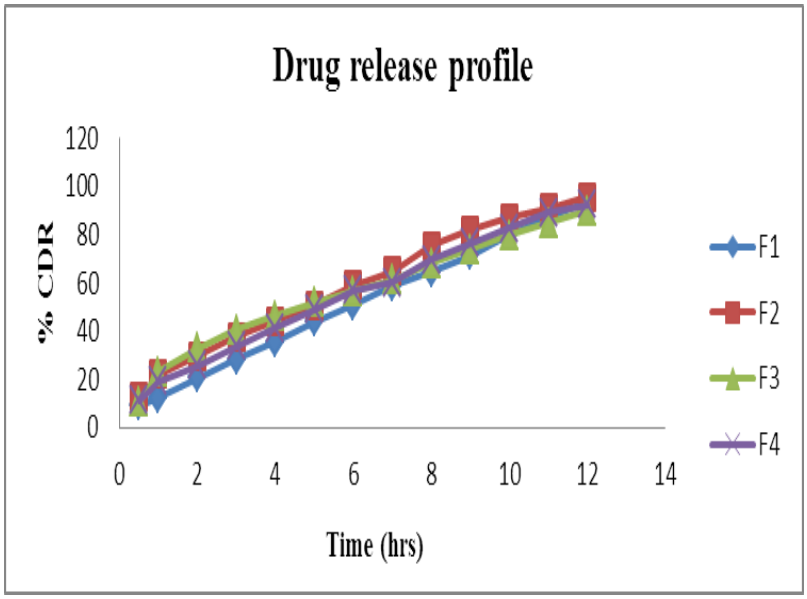

Figure 7: Drug release profile of all Formulations.

Drug Release kinetics of formulation

Various release kinetic models were applied to the data obtained from *in vitro* release studies to elucidate the mechanism of drug release from the floating gel beads, such as Zero order, First order and Higuchi and Korsmeyer peppas models.

Table 4: Curve fitting data of drug release rate profile of formulation F1-F4.

Model		Formulation code			
		F1	F2	F3	F4
Zero order	R^2	0.999	0.990	0.999	0.994
First order	R^2	0.998	0.988	0.975	0.994
Higuchi matrix	R^2	0.974	0.987	0.983	0.985
Hixon Crowell	R^2	0.976	0.989	0.988	0.970
Korsmeyer-peppas	R^2	0.992	0.961	0.921	0.990

The R^2 value for zero order is greater than Korsmeyer-Peppas model indicating the formulations followed zero order release kinetics. The optimized F3 formulation follows zero order release kinetics.

Stability study of optimized formulation

The stability studies of optimum formulation revealed that no significant changes in the physical parameters when stored at temperature humidity conditions of 40^0C / 75% RH and at room temperature. No significant changes in physical characteristics and % CDR at 12 hrs was observed over a 2 month as shown in table 5.

Table 5: Stability study of optimized formulation

Stability ($40^0C \pm 2^0C$ and 75% RH ± 5%)	Physical changes	%CDR	Floating Study
Initial	No	89.660	Floating
15 days	No	88.79	Floating
30 days	No	90.59	Floating
45 days	No	89.94	Floating
60 days	No	90.15	Floating

CONCLUSION

Lafutidine a newly developed histamine H_2-receptor antagonist, it is used in the treatment of gastric ulcers, duodenal ulcers and gastric mucosal lesions. The site of absorption of Lafutidine is in the stomach it has biological half life 1.92 ± 0.94 hr, Therefore, an attempt is made to retain the dosage form in the stomach for longer period of time. The floating drug delivery was a promising approach to achieve in-vitro buoyancy. Floating alginate beads prepared for increasing the gastric residence time and sustained drug release up to 12 hrs thereby increasing the bioavailability of the drug leading to reduced frequency of dosing.

The optimized F3 formulation batch shows drug release 89.66%. The drug release F3 batch is low than other formulation batches that is it shows sustained drug release for longer period of time.

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