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Formulation and Evaluation of Floating in Situ Gel of Lafutidine

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Abstract— *Gastroesophageal reflux disease (GERD) and peptic ulcers are prevalent gastrointestinal disorders that significantly impact the quality of life of affected individuals. Lafutidine, a histamine H2-receptor antagonist, has demonstrated effectiveness in managing these conditions. However, its short gastric residence time limits its therapeutic efficacy. To address this limitation, we aimed to formulate and evaluate a floating in situ gel of Lafutidine for prolonged gastric retention and enhanced therapeutic outcomes. In vivo studies were conducted on albino Wistar rats to assess the pharmacokinetic parameters and gastric residence time. The pharmacokinetic evaluation demonstrated that the floating in situ gel exhibited improved Lafutidine bioavailability compared to the conventional dosage form. Gastric residence time was significantly extended, enhancing Lafutidine's therapeutic efficacy. Overall, the formulation and evaluation of the floating in situ gel of Lafutidine demonstrated its potential as an effective drug delivery system for the management of GERD and peptic ulcers. The extended gastric retention and enhanced bioavailability of Lafutidine make this formulation a promising option for improving patient compliance and therapeutic outcomes in the treatment of these gastrointestinal disorders. Further clinical studies are warranted to establish its clinical efficacy and safety profile.*

Keywords— ***In situ gel, Gastroesophageal reflux disease, omeprazole magnesium, In vitro floating duration, In vitro gelling capacity bioavailability, Gastric resident time.***

I. INTRODUCTION

Controlled medication distribution inside the stomach with improved gastroretention may be achieved with the use of a gastroretentive in situ gelling device. In situ gelling systems are thermodynamically liquid at ambient temperature but gel when exposed to bodily fluids or when the pH changes. The gel produced by the in-situ gelling system is lighter than gastric fluids, so it either floats on top of the stomach contents or sticks to the gastric mucosa due to the bioadhesive nature of the polymer, resulting in gastric retention of the dosage form and an increase in gastric residence time, both of which contribute to a more sustained release of the drug. The system uses polymers that go through a sol-gel phase transition when exposed to certain variations in physical and chemical conditions. In situ gel may be formed using a variety of polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, polycaprolactone, polylactic acid, and poly(lactic-co-glycolide). pH-induced ionic gelation is the underlying mechanism that allows gels to form on-site. The addition of trisodium citrate keeps the formulation liquid-like until it enters the stomach. In the stomach, the presence of an acidic environment causes Ca++ to be released, causing the formulation to gel. The carbon dioxide produced by the stomach's pH assists the in-situ gel to stay buoyant for a long time.

The histamine H2 -receptor antagonist lafutidine is cutting-edge medicine. It is absorbed in the small intestine, circulates to the stomach, and binds quickly

and directly to histamine H2 receptors on gastric cells, blocking acid production in the stomach. Lafutidine is used for patients with acute gastritis, gastric ulcers, duodenal ulcers, or gastric mucosal lesions. If you compare lafutidine to other typical H2 -receptor antagonists, you'll find that its receptor binding affinity is two to eight times greater. Lafutidine has a limited bioavailability and short biological half-life, hence it must be dosed often. Thus, oral in situ gel for gastroretentive drug administration of lafutidine may decrease dose frequency and improve bioavailability due to the medication's longer residence duration and sustained release.

II. LITERATURE REVIEW

Sindhoor S M (2018) The current investigation sought to develop and assess a new in situ gel of lafutidine for gastroretentive drug administration. Using the pH-triggered ionic gelation approach and varying amounts of gelling polymer such sodium alginate, gellan gum, and xanthum gum, a gastroretentive in situ gel of lafutidine was developed. The medication concentration, as well as the formulation's viscosity and density, were measured. All formulations were also subjected to in vitro drug release tests. We examined the improved formulation using in vivo fluorescence imaging and compared it to the control group. The formulations' viscosity, floating behavior, and in vitro drug release were all strongly impacted by the gelling agent and release retardant polymer concentrations. Results showed a pH range of 6.72-7.20 and a medication concentration of 88.74%-95.33%. Floating caused a delay of around two minutes, and it lasted for more than twelve hours. After 12 hours, formulation F9 showed the lowest drug release (51.74%) while F1 showed the highest drug release (82.76%) in vitro. All of the formulations showed a steady rate of drug release. The formulation was shown to be retained in the stomachs of mice for 8 hours in in vivo testing. Results from stability tests showed no discernible change in form, buoyancy, or active ingredient. Longer gastric residence duration was achieved because to the gastroretentive in situ gel technology, which enabled site-specific medication release in the stomach.

Asmaa H. Esmaeil (2020) The purpose of this study was to create and assess the efficacy of a liquid gastroretentive drug delivery system, in this case a floating in situ gel of leflunomide (LEF), for the treatment of juvenile rheumatoid arthritis (JRA). This would increase patient compliance, increase the amount of time the drug spent in the stomach, and decrease the variability in plasma drug concentration. LEF is a DMARD that helps alleviate symptoms of active juvenile idiopathic arthritis (JIA) in kids and rheumatoid arthritis (RA) in adults. Different amounts of sodium alginate and calcium carbonate were used to create formulations for floating in situ gelling. The produced gels were tested for a variety of properties, including their gelling strength, in-vitro release study, in-vitro gelling capacity, floating lag time, and floating duration. The best formula was C4, which had the lowest floating lag time (40 seconds), highest viscosity (295.4 cps), and strongest gel strength (45 seconds) and provided the longest drug release duration (98% for over 6 hours). Due to the high likelihood of gel formation in the stomach, this formulation was selected for further ex-vivo research in rats. The ex vivo research of Formula C4 found that it formed a gel effectively. Therefore, the LEF floating in situ gelling device is a revolutionary method to improve patient compliance and lengthen the amount of time the medicine spends in the stomach, where it can keep its plasma concentration steady.

B. PADMASRI (2022) For the treatment of rheumatoid arthritis, creating in-situ gel formulations of Lornoxicam for prolonged release to cut down on dose frequency. The formulations demonstrated the optimal viscosity for simple dosing and swallowing. All formulations floated for 12 hours with a lag time of 2-3 seconds at a pH of 6.7-7.3. Optimised formulation F11 released 99.52 percent of the medicine during a 12-hour period, whereas the commercial sustained release formulation of lornoxicam released 99.92 percent of the drug in 8 hours. No drug-excipient interactions were found in FTIR analyses. In vivo kinetic experiments have confirmed the improved efficacy of the revised formulation. The AUC, t1/2, Cmax, and Tmax all point to the same conclusion. Improved patient compliance and therapeutic response to lornoxicam therapy for rheumatoid arthritis may be achieved by

the use of an oral in situ gel containing chitosan as a drug release regulating polymer.

SINDHOOR S M (2018) The current investigation sought to develop and assess a new in situ gel of lafutidine for gastroretentive drug administration. The formulations' viscosity, floating behavior, and in vitro drug release were all strongly impacted by the gelling agent and release retardant polymer concentrations. Results showed a pH range of 6.72-7.20 and a medication concentration of 88.14%-95.33%. Floating caused a delay of around two minutes, and it lasted for more than twelve hours. After 12 hours, formulation F9 showed the lowest drug release (51.74%) while F1 showed the highest drug release (82.76%) in vitro. All of the formulations showed a steady rate of drug release. The formulation was shown to be retained in the stomachs of mice for 8 hours in in vivo testing. Results from stability tests showed no discernible change in form, buoyancy, or active ingredient. Targeting site-specific medication release in the stomach and esophagus was made possible by the gastroretentive in situ gel technology.

III. METHODOLOGY

Liquid paraffin, concentrated HCl, and sodium fluorescein were obtained from Loba Chemie in Mumbai, India; xanthum gum, trisodium citrate, calcium carbonate, Tween 80, and sodium fluorescein were provided as gifts by Zuventus Healthcare Ltd. Sodium alginate and gellan gum were purchased from companies in Mumbai, India: Himedia laboratories and Yarrow chem Products. Mangalore, India's BN laboratories supplied the deionized water. Accurate amounts of Tween 80 and liquid paraffin were weighed, as were the necessary amounts of sodium alginate, gellan gum, xanthum gum, trisodium citrate, calcium carbonate, propylparaben, and methylparaben. Sodium alginate and gellan gum, two types of gelling polymer, were dissolved in deionized water with a measured quantity of trisodium citrate using a magnetic stirrer heated to 70 degrees Celsius. Calcium carbonate and the release-retarding polymer xanthum gum were added to the aforesaid solution after it cooled to 40 degrees Celsius. The necessary amount of Tween 80 and liquid paraffin were added to a separate beaker and stirred with a magnetic stirrer. A weighed quantity of the medicine was added while stirring continuously, and then water was added drop by drop to make an emulsion. This drug solution was then preserved with methyl and propylparaben before the polymeric solution was added. The volume was then corrected with the deionized water, and the final product was kept in amber-colored bottles for later use after being well mixed.

IV. DATA ANALYSIS

The melting point of Lafutidine matched with the value found in literature.

Table 1. Melting point of Lafutidine.

Drug	**Melting Point range**	
	Literature	**Practical**
Lafutidine	98-101°C	98-100°C

Fourier transform infrared spectroscopic (FTIR) studies

The FTIR spectrum of Lafutidine is shown in Figure below and interpretation of FTIR spectra is given in Table. FTIR spectrum of Lafutidine showed all the peaks corresponding to the functional groups present in the structure of Lafutidine.

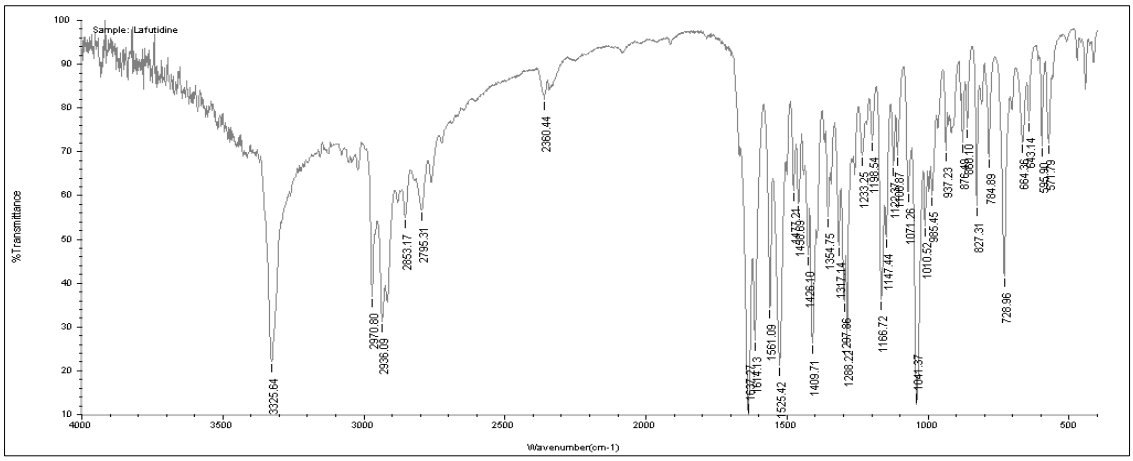

Fig.1. FTIR spectrum of Lafutidine.

The major peaks for pure Lafutidine were seen as below, 3325.64 for–NH stretching, 2360.44 for–CH (alkyl) stretching, 1632.24 for-C=O stretching, 937.23 for SO stretching which confirms the important functional group Lafutidine.

Differential Scanning Calorimetric (DSC) studies

Differential Scanning Calorimetry studies indicated a sharp endothermic peak at 99.21°C corresponding to melting of pure Lafutidine is as shown in Figure.

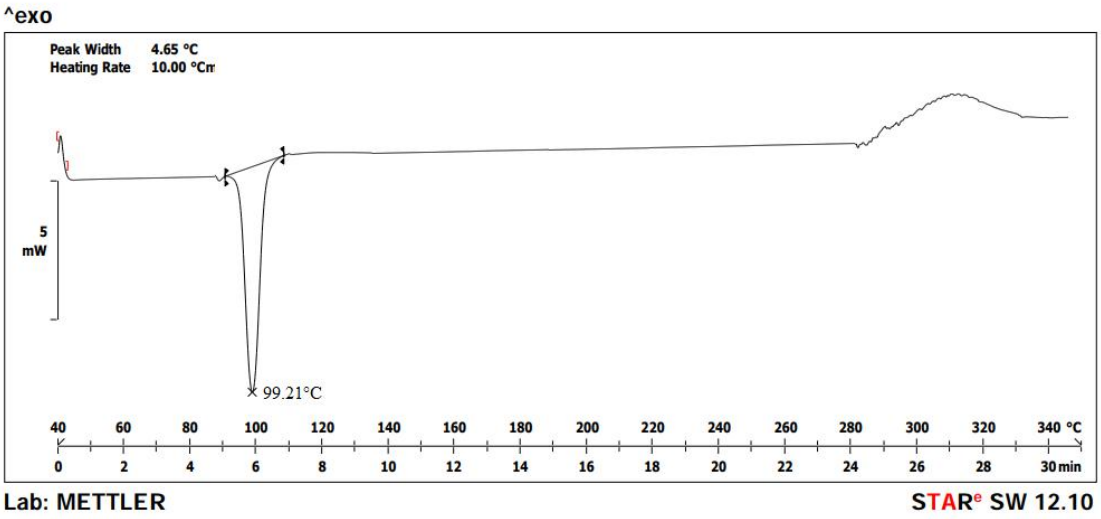

Fig.2. DSC thermogram of Lafutidine.

Physical compatibility test using Infrared Spectroscopy

For physical compatibility test FTIR of drug and excipients were mixed and kept strictly for 30 days. The spectrum was scanned over a frequency range 4000-400 cm^{-1}. FTIR spectra of drug-excipient mixtures retained the characteristic functional peaks of the drug as shown in Figures below. Thus, the polymer and the drug show no interaction.

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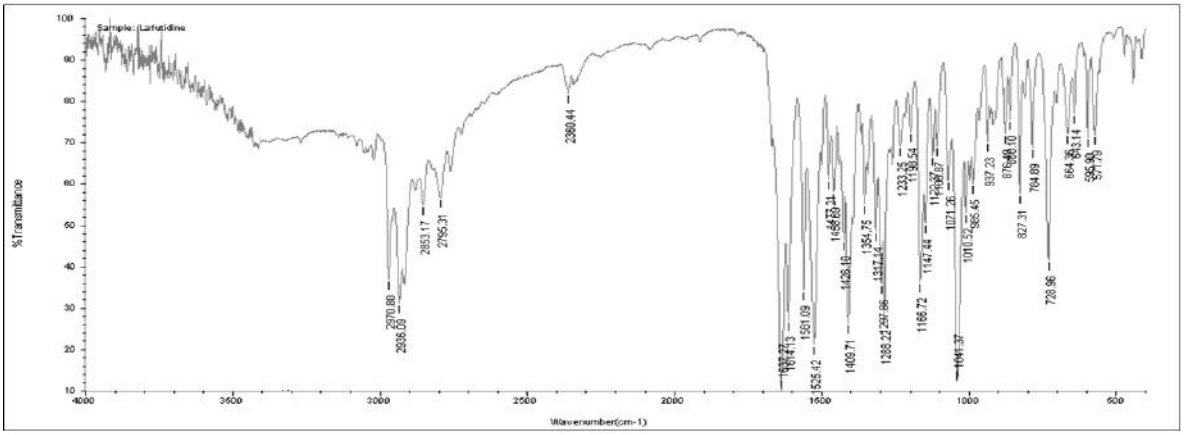

Fig.3. IR spectrum of Lafutidine + Xyloglucan + HPMC K750PH physical Mixture.

The major peaks for pure Lafutidine were seen as below, 2360.44 for–CH (alkyl) stretching, 1632.24 for-C=O stretching, 937.23 for SO stretching which confirms the important functional group Lafutidine.

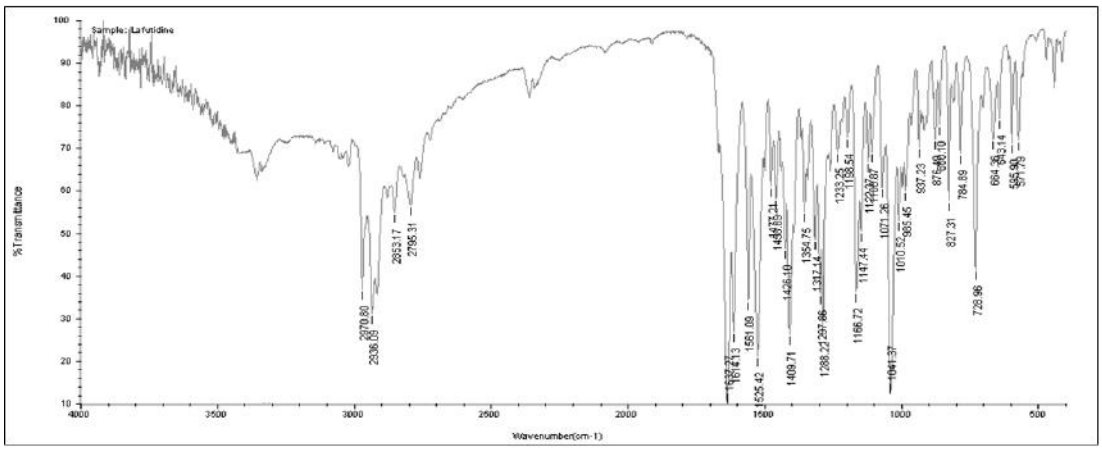

Fig.4. IR spectrum of Lafutidine + gellan gum + HPMC K100 M physical mixture.

The three main peaks for pure Lafutidine were seen as follows: 2360.44 for-CH (alkyl) stretching, 1632.24 for-C=O stretching, and 937.23 for SO stretching, confirming Lafutidine as an essential functional group. There is no interaction between the drug and excipients, according to the FTIR spectra of pure Lafutidine and physical mixtures, which demonstrate the vibration of functional groups found in the drug's structure.

The solubility of Lafutidine as observed in 0.1 N HCl (pH 1.2) and buffers of pH values 4.6 (acetate buffer) and 6.8 (phosphate buffer) are presented in Table. Lafutidine exhibited a pH dependent solubility in these aqueous buffers. Higher solubility of Lafutidine was observed at acidic pH values, while the solubility dropped rapidly as the pH increased (Figure).

Table 2. Solubility analysis of Lafutidine.

Solvent	Solubility (mg/ml)
pH 1.2 (0.1N HCl)	52.22
pH 4.5	40.12
pH 6.8	11.44

Calibration curve for Lafutidine

The calibration curve for Lafutidine in 0.1 N HCl is shown in Figure 3. The graph of absorbance vs. concentration for Lafutidine was found to be linear in the concentration range of 5-30 µg/ml at 290 nm. The r^2 of the calibration curve was found to be 0.9996. The standard calibration curve detail for Lafutidine is shown in Table 3.

Table 3. Concentration and absorbance values for Lafutidine in 0.1 N HCl.

Concentration (µg/ml)	Absorbance
05	0.0124
10	0.024
15	0.0367
20	0.0485
25	0.062
30	0.0745

Robustness of method was measured by multiple injections of a homogenous sample containing Lafutidine by changing flow rate 1.2 mL/min and 1.6 mL/min, mobile phase composition Methanol: water ratio 79:21 and 81:19, wavelength i.e. 289nm and 291nm. The method was found to be robust in the range of deliberate changes made.

Table-4: Robustness study with change in flow rate of Lafutidine

Flow rate mL/min	Conc. µg/mL	Area	AVG	%RSD
1.2	20	120451	120496	0.04909
1.2		120563		
1.2		120474		
1.6	20	120458	120452.7	0.0084
1.6		120459		
1.6		120441		

Conc, Concentration; AVG, average; RSD, Relative standard deviation

Table-5: Robustness study with change in concentration of mobile phase of Lafutidine

Mobile phase	Conc µg/mL	Area	AVG	%RSD
79:21	20	120236	120379.7	0.13029
79:21		120547		
79:21		120356		
81:19	20	120454	120422.7	0.06312
81:19		120478		
81:19		120336		

Conc,Concentration; AVG, average; RSD, Relative standard deviation

Table-6: Robustness study with change in Wavelength of Lafutidine.

Wavelength nm	Conc. µg/mL	Area	AVG	%RSD
289	20	120568	120527.3	0.05489

289		120451		
289		120563		
291	20	125044	122061.3	2.11819
291		120458		
291		120682		

V. CONCLUSION

The formulation and evaluation of a floating in situ gel of Lafutidine represent a promising approach to improve the therapeutic efficacy of this drug for the treatment of gastrointestinal disorders, such as gastroesophageal reflux disease (GERD) and peptic ulcers. In conclusion, the formulation and evaluation of a floating in situ gel of Lafutidine represent a significant advancement in drug delivery technology for gastrointestinal disorders. This innovative approach has the potential to enhance patient outcomes by ensuring optimal drug delivery and improved therapeutic efficacy. Continued research and clinical validation are essential steps in bringing this formulation closer to clinical application, offering hope for more effective management of GERD and peptic ulcers in the near future.

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