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Design and Optimization of Low-Density Gastroretentive Polymeric Microballoons for the Supply of Lafutidine in the Management of Peptic Ulcer

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Abstract

Lafutidine is one of the newly developed powerful competitive second-generation H2 receptor antagonists. It is selectively absorbed from the upper part of the GIT, and it is stable in the gastric environment. The current study proposes developing an intragastric floating microballoon novel drug delivery system for the H2 receptor antagonist, lafutidine to release the drug into the stomach in a sustained manner for an extended period to treat peptic ulcer disease, gastroesophageal reflux disease, and Zollinger- Ellison syndrome. Hydroxypropyl methylcellulose and ethyl cellulose-based low- density floating microballoons were fabricated using the emulsion solvent diffusion method by varying the drug concentration and applying different variables like emulsifying agent concentration, polymer ratios, stirring speed and temperature, etc. The microballoon formulations were evaluated for percentage yield, particle size (μm), drug entrapment efficiency, and percentage buoyancy. According to the findings, the floating microballoons of lafutidine demonstrated good gastroretentive floating ability with expected drug bioavailability.

Keywords: Lafutidine; Microballoons; Peptic Ulcer; Floating Drug Delivery System; Gastroretentive Drug Delivery System

Abbreviations: FTIR: Fourier Transform Infrared Spectroscopy; GRDDS: Gastroretentive Drug Delivery System; H2: Histamine H2 Receptors; PUD: Peptic Ulcer Disease; EC: Ethyl Cellulose; HPMC: Hydroxy Propyl Methyl Cellulose; GIT: Gastrointestinal Tracts; NSAID: Non-Steroidal Anti-Inflammatory Drugs; CDH: Central Drug House; PVA: Polyvinyl Alcohol; SEM: Scanning Electron Microscope; DSC: Differential Scanning Calorimetry; TEM: Transmission Electron Microscopy.

Introduction

The term "peptic ulcer" refers to a digestive tract disease. Peptic ulcers are sores or lesions present in the gastric mucosa of the upper and lower gastrointestinal tracts (GIT) [1,2]. They are caused by a conflict between aggressive factors [acid and pepsin] and defensive factors (bicarbonate ions, mucus production, and prostaglandins) that protect the stomach and duodenal mucosa [3]. In addition, PUD has two

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important primary risk factors: the bacterium Helicobacter pylori (H-pylori) and long-term use of non-steroidal anti-inflammatory drugs (NSAID) [4]. The secondary risk factors

that may lead to peptic ulcers include stomach acid (gastric juice), alcohol, pepsin, and bile salts. These disputes have serious repercussions, such as bleeding or perforation, and a significant risk of death [5]. The most common technique for preventing PUD is lowering stomach acid production and increasing gastric mucosal protection [6].

Despite several acknowledged drawbacks, such as the fact that the oral route of drug administration cannot achieve optimal therapeutic effect due to first-pass metabolism, stomach emptying time, gastric retention, and drug half-life, among other factors, oral drug delivery seems to be the most common and suitable method of drug administration [7].

Many methods have been researched, including mucoadhesion, low-density floating systems, gas-producing, swelling, expandable, ultra-porous hydrogels, and raft-forming, for prolonged gastric residency durations of the system in the upper region of the gastrointestinal tract [8].

A floating GRDDS is a type of formulation in which the retention duration of the drug in the stomach can be prolonged, allowing the drug to float on the gastric juice for a prolonged period of time before being released from the system into the stomach [9].

Microballoons are a special type of gastro-retentive multiple-unit floating system based on the non-effervescent approach in which a higher amount of drug is entrapped and delivered at the site of action [10].

Microballoons are naturally free-flowing particles consisting of silica glass, polymers, surfactants, solvents, and proteins. The core of a microballoon is small, round sphere with a hollow space within it that provides buoyancy to float on stomach gastric juice with a specific density of less than 1 to the floating microballoons and increases the gastric residence time [11].

In the microballoons, the active pharmaceutical ingredients are incorporated between the layers of the formulation. Microballoons distribute the active pharmaceutical ingredients extensively all over the stomach, which provides the chance to attain a persistent and more constant release of drugs. The above property of microballoons results in delayed transit through the stomach [12]. This prolongs the gastrointestinal residence period and enhances the drug's absorption, thereby increasing its oral bioavailability [13,14].

Antiulcer drugs, especially H2-receptor antagonists such as lafutidine, are used in the treatment of Zollinger-Ellison syndrome, gastric ulcers, stress ulcers, peptic ulcers, duodenal ulcers, and gastroesophageal reflux disease (e.g. [15,16]). Lafutidine penetrates the stomach and small intestine walls, then directly and rapidly reaches the gastric parietal cells of the stomach with the help of blood circulation [17,18]. Then lafutidine directly inhibits the histamine H2 receptor of the gastric parietal cells, which results in gastric acid secretion and hydrogen ion concentration [19,20].

Lafutidine has a short biological half-life of 1.92 hrs and very low aqueous solubility therefore, it has low bioavailability and belongs to the BCS class II group [21]. Lafutidine is selectively absorbed from the upper part of the GIT and it is stable in the gastric environment [22]. Therefore, it was believed formulate a novel drug delivery system of newly developed H2 receptor antagonists (Lafutidine) in the form of floating microballoons to release the drug in a sustained manner into the gastric region for a prolonged period of time.

The anionic polymer ethyl cellulose, which was selected for the microballoon fabrication, is a linear polysaccharide made of cellulose in which some of the hydroxyl groups on the polysaccharide backbone have been swapped with ethyl ether groups. A hydrophobic polymer called ethyl cellulose delayed the release of both water-soluble and water-insoluble drugs from their matrices. It stabilizes the microballoons system in the upper part of GIT by requiring a higher pH medium and/or more time for solubilization [23,24].

For the fabrication of microballoons, hydroxypropyl methylcellulose (HPMC) is also employed. Methoxy and hydroxypropyl groups, which are often utilized in hydrophilic matrix drug delivery systems, are swapped for some of the hydroxyl groups in HPMC, a water-soluble non-ionic cellulose polymer [25]. In oral controlled delivery systems, HPMC is a common, low-density inert matrix material that is semi-synthetic. Although HPMC matrices exhibit prolonged release patterns, they float better than other hydrophilic polymers [26,27].

The main objective of the present study was to fabricate and characterize a floating microballoon system of lafutidine for the management of peptic ulcers (Figure 1). As a gastroretentive low-density polymer, the ideal ethyl cellulose (EC) and HPMC ratios were chosen to fabricate floating microballoons with higher formulation percentage yield, entrapment efficiency, and percentage floating buoyancy. Additionally, the different formulations and process variables were optimized. The morphology of the optimized formulations was investigated using SEM, TEM, and fluorescence microscopy, as well as particle size, in-vitro buoyancy, yield, entrapment efficiency, and drug release characteristics.

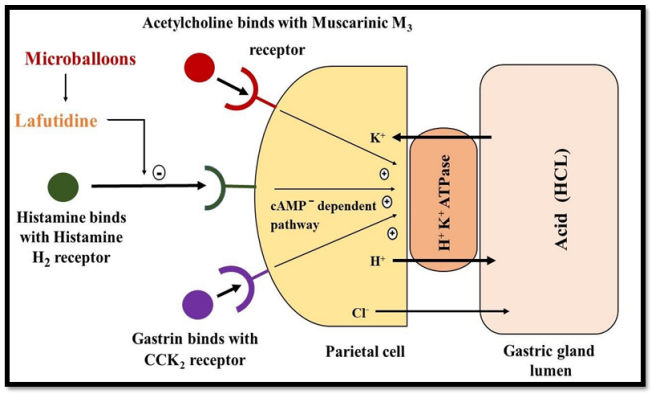

Figure 1: The Mechanism Involved in the Lafutidine-Loaded Microballoons through Receptors.

Determination of Λ Max of Lafutidine and Preparation of Calibration Curve

The λ max of lafutidine was determined by using UV-visible spectrophotometer and was observed to be 286 nm in SGF (pH 1.2), and 279.5 nm in PBS (pH 7.4), and then the standard curve of lafutidine was prepared using different aliquots of drug solution in SGF (pH 1.2) and PBS (pH 7.4) at 286 nm and 279.5 nm, respectively. The equation of a straight line from the calibration curve was obtained to be y = 0.0313x + 0.0072 with R2 value 0.9987 and y = 0.0188x + 0.0072 with R2 value 0.9904 in the concentration range 2-20 µg/ml in (SGF pH 1.2 and PBS 7.4) at 286 nm and 279.5 nm respectively.

Materials and Methods

Ethyl cellulose (EC) was obtained from Loba Chemie Pvt. Ltd., Mumbai, India, and hydroxypropyl methylcellulose (HPMC) was obtained from Central Drug House (CDH) Ltd., New Delhi. Methanol, polyvinyl alcohol (PVA), dichloromethane, and Tween 80 were obtained from the Drug Store, Department of Pharmaceutical Sciences, Sagar (India). Lafutidine was obtained as a gift sample from Zuventus Healthcare Limited, Mumbai, India. All of the other chemicals used were of analytical grade, and distilled water was used throughout the experiment.

Fabrication of Floating Microballoons of Lafutidine

Microballoons were made using the emulsion solvent diffusion method as described by Kawashima, et al. [28]. Ethyl cellulose and HPMC were dissolved in a 7:1 mixture of dichloromethane and methanol organic solvents at room temperature. The drug lafutidine was then evenly dispersed throughout this polymer solution at a dose of 25 mg. This drug-containing polymer solution was gradually added to a 200 ml aqueous solution of polyvinyl alcohol (0.75% w/v), an emulsifying agent, and comprising 0.2% w/v of tween 80, at a temperature of 40°C. The resulting emulsion was then continuously swirled for the required amount of time using a magnetic stirrer (Remi India) at 300 rpm to allow the volatile organic solvent to evaporate (Figure 2).

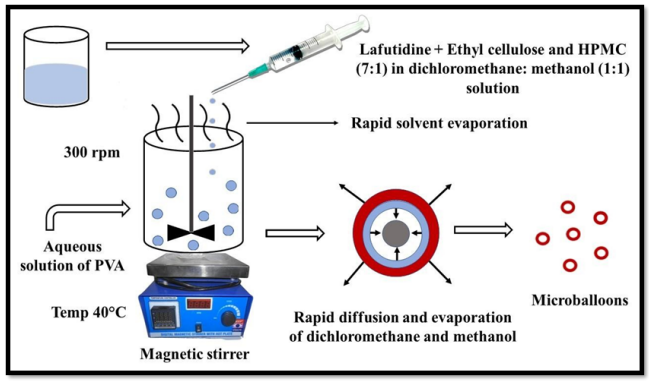

Figure 2: Schematic of Fabrication of Lafutidine-Loaded Floating Microballoons.

The resulting polymeric floating microballoons underwent filtering, collection, and washing with distilled water before being allowed to dry at room temperature for a whole night. The microballoons formulations of lafutidine were optimized for various formulation variables such as different polymer ratios, drug: polymer ratio, emulsifier concentration, and optimization of process variables stirring speed, and temperature (Table 1).

Formulation Code (F-MBL)	Polymer (EC: HPMC) Concentration Ratio (mg)	Drug Polymer Concentration Ratio (mg)	Emulsifier PVA Concentrat Ion (% w/v)	Stirring Speed (rpm)	Temperature (˚C)
F-MBL01	03:01	20.1	0.75	300	40˚C
F-MBL02	05:01	20.1	0.75	300	40˚C
F-MBL03	**07:01**	20.1	0.75	300	40˚C
F-MBL04	09:01	20.1	0.75	300	40˚C
F-MBL05	07:01	15.1	0.75	300	40˚C

F-MBL06	07:01	20.1	0.75	300	40˚C
F-MBL07	07:01	**25:100**	0.75	300	40˚C
F-MBL08	07:01	30:100	0.75	300	40˚C
F-MBL09	07:01	25:100	0.5	300	40˚C
F-MBL10	07:01	25:100	**0.75**	300	40˚C
F-MBL11	07:01	25:100	1	300	40˚C
F-MBL12	07:01	25:100	1.25	300	40˚C
F-MBL13	07:01	25:100	0.75	100	40˚C
F-MBL14	07:01	25:100	0.75	**300**	40˚C
F-MBL15	07:01	25:100	0.75	500	40˚C
F-MBL16	07:01	25:100	0.75	700	40˚C
F-MBL17	07:01	25:100	0.75	300	30˚C
F-MBL18	07:01	25:100	0.75	300	**40˚C**
F-MBL19	07:01	25:100	0.75	300	50˚C
F-MBL20	07:01	25:100	0.75	300	60˚C

Table 1: Optimization of Parameters for Preparation of Lafutidine Floating Microballoons.

The optimized conditions for the fabrication of microballoons were reported in Table 2 based on the various formulation and process parameters, and in accordance with the optimized method, microballoons containing lafutidine were fabricated and evaluated. The drug-polymer ratios used to prepare the microballoons varied from 15/20/25/30:100. On the basis of particle size, yield, buoyancy, and drug entrapment efficiency, the prepared microballoons were evaluated.

Formulation Code (F-MBL)	Polymer (EC: HPMC) Concentration Ratio (mg)	Response 1 (% Yield)	Response 2 Entrapment Efficiency (%EE of LFD)	Response 3 (% Buoyancy)
F-MBL01	3:1	59.5±2.97	43.68±1.74	87.5±3.5
F-MBL02	5:1	61.9±3.09	54.8±2.74	84.2±4.21
F-MBL03	**7:1**	**70.4±3.52**	**68.8±2.06**	**81.4±3.25**
F-MBL04	9:1	69.3±2.77	64.64±2.58	77.4±3.87
F-MBL05	7:1	58.0±2.32	54.01±2.16	80.0±3.2
F-MBL06	7:1	60.2±3.01	65.33±2.61	81.6±3.26
F-MBL07	**7:1**	**68.7±2.74**	**72.53±2.90**	**83.64±3.34**
F-MBL08	7:1	69.5±2.78	67.77±2.71	74.8±2.99
F-MBL09	7:1	53.6±2.14	62.3±2.49	76.7±3.06
F-MBL10	**7:1**	**57.3±2.29**	**74.8±2.99**	**84.3±3.37**
F-MBL11	7:1	49.1±1.96	67.7±2.70	81.2±3.24
F-MBL12	7:1	42.8±1.71	51.06±2.04	71.8±2.87
F-MBL13	7:1	57.9±2.89	68.8±3.44	80.4±4.02
F-MBL14	**7:1**	**63.5±3.17**	**74.74±3.73**	**83.64±4.18**
F-MBL15	7:1	60.8±3.04	70.85±3.54	74.8±3.74
F-MBL16	7:1	54.7±2.73	66.00±3.30	72.8±3.64
F-MBL17	7: 1	61.7±2.46	63.5±3.17	79±3.16
F-MBL18	**7:1**	**63.2±2.52**	**73.9±2.95**	**81.3±3.25**
F-MBL19	7:1	57.3±2.86	69.4±2.77	76.4±3.82
F-MBL20	7:1	53.8±2.15	65.1±3.25	74.3±2.97

Table 2: The Formulation Variables Response for Lafutidine Floating Microballoons Formulation.

Physicochemical Characterization

Physical Interaction and Integrity Study (Drug Excipient Compatibility)

Compatibility between drug and polymer was determined by fourier transform infrared spectroscopy (FTIR).

FTIR spectroscopy: FTIR spectroscopy is an analytical technique used to determine various functional groups present in test samples, an infrared spectrum of light was used to evaluate the samples (400 and 4000 cm-1). This analytical technique is used to check the drug purity and is also used to study the compatibility between pure drug & polymer i.e., (lafutidine and ethyl cellulose and HPMC), which is used in the formulation of floating microballoons. The test sample was gradually comminuted with anhydrous KBr and compressed to obtain a pellet before recording the FTIR spectra (Shimadzu, Jasco, Japan, Model 8400S) and interpreting the obtained peaks.

Melting Point Determination

Melting point instruments were used to ascertain lafutidine's melting point (Super fit, India). The drug (lafutidine) was inserted into the capillary tube from one side, which had been fused, and it was then placed in the melting point apparatus. Visual observation was used to record the temperature at which the liquid form of the solid drug was transitioned, and the same process was carried out three times.

Solubility

Knowing the solubility criteria of the drug is important to check whether it is soluble in a particular solvent. Solubility of lafutidine was determined in SGF (pH 1.2), glacial acetic acid, ethanol, 0.1 N HCL, methanol, dichloromethane, PBS (pH 7.4), and distilled water by taking each solvent in a separate beaker and added 100 mg of drug in each beaker and checked the solubility by stirring it.

Particle Size and Polydispersity Index

Particle size and polydispersity index of floating microballoons were analysed by laser diffraction particle size analyzer master sizer 2000 (Malvern Instrument, UK). In brief, Floating microballoons were scattered in double-distilled water, and the dispersion was then examined for mean particle size (diameter) and polydispersity index in triplicate. The results were then expressed as mean SD.

Morphology Study

Fluorescence Microscopy

The floating microballoons' shape, external morphology, and superficial structure were investigated by fluorescence microscope. The sample was prepared by placing a drop of the formulation on a microscopic slide, covered by a cover slip, and investigated under a fluorescence microscope (Magnus MIPS) at a magnification in the range of 10x – 40x, and photomicrographs of the microballoons were captured at suitable magnification. The same procedure was used to determine the shape and structure of the powdered microballoons.

Surface Morphology Study (SEM): Particle size and surface morphology (external and internal), and surface topography of the floating microballoons was investigated by scanning electron microscope (SEM). The powdered microballoons were gently sprinkled over the double-sided adhesive tape that was stuck to an aluminum brass stub to form the sample for SEM, which was then allowed to air dry at room temperature. The stubs were then coated with gold to a thickness of about 300Å by using a sputter coater. The sample was investigated under SEM (NOVA NANOSEM 450, FEI Company) at an accelerated voltage of 10 kV and magnified in the ×100-2000 kx.

Transmission Electron Microscopy: Microballoons were observed under the transmission electron microscope (FEI Tecnai G2 F-20 S-Twin, transmission electron microscope, Netherlands). A drop of the microballoons formulation was placed onto a carbon-coated copper grid to form a thin film over the grid, and it was negatively tarnished with 2% w/v phosphotungstic acid (PTA) before drying. The grid was then allowed to be air-dried at room temperature. The sample was examined at an acceleration voltage of 100 kV, and photomicrographs of microballoons were captured at suitable magnification.

Percent Yield of Microballoons

The percent (%) yield of microballoons was calculated by using the weight of the obtained microballoons' (final product) after drying and the initial weight of the drug and polymers used for the preparation of microballoons. The % yield of obtained microballoons was calculated using the following formula:

Weight of microballoons collected

$$\%Yield = \frac{Weight\ of\ microballoons\ collected}{Weight\ of\ drug + polymer\ used\ for\ preparation\ of\ microballoons} \times 100$$

Entrapment Efficiency of Microballoons

100 milligrams of microballoons containing lafutidine were precisely weighed, finely crushed in a mortar pestle, and sonicated for 30 minutes, after being dissolved in 8 ml of a 1:1 v/v mixture of methanol and dichloromethane. Then the solution was centrifuged for 10 minutes at 3000 rpm

using centrifugation apparatus (Remi, India), then 1 ml of supernatant was removed, the sample was appropriately diluted, filtered, and then spectrophotometric analysis was performed to determine the quantity of lafutidine. The proportion of drug entrapment was estimated using the calculation below:

$$\%Entrapped\ Efficiency = \frac{Amount\ of\ drug\ in\ microballons\ formulation}{Total\ amount\ of\ drug\ used\ in\ the\ preparation} \times 100$$

In-Vitro Buoyancy Percentage

The buoyancy behavior of lafutidine-loaded microballoons was studied using USP dissolution test apparatus II (USP XXII) by individually scattering 100 mg microballoons in a dissolution assembly containing 900 ml of simulated gastric fluid (pH 1.2, Temp. 37 ± 1˚C) and Tween 20 (0.02 w/v %). Using dissolution paddle equipment, the medium was agitated at 100 rpm. After some time, the layer of buoyant microballoons was pipetted out, and the floating microballoons were separated. Then, the particles that had settled in the medium were separated by filtration, and both the separated microballoon portions were dried in a vacuum desiccator. The weight ratio of floating particles to the total of floating and sinking particles was used to calculate buoyancy for both microballoon fractions as follows:

$$\%Buoyancy = \frac{Mf}{Mf + Ms} \times 100$$

Where Mf and Ms are the mass of the floating and sinking microballoons, respectively.

X-Ray Diffraction Studies

X-ray diffraction of pure lafutidine and optimized floating microballoons formulation was studied to investigate the effect of polymerization on the crystallinity of the drug. Both samples were investigated using an X-ray powder diffractometer (D8 Advance Bruker). Samples were scanned for 2θ from 5 to 80°. Diffraction patterns of lafutidine and microballoons were obtained.

Estimation of *In-Vitro* Drug Release Studies of Optimized Microballoons Formulation and Lafutidine-Marketed Tablet

In-vitro release of lafutidine from microballoons was carried out using the dialysis membrane diffusion technique. 100 milligrams of the prepared microballoons formulations were placed in the dialysis membrane (MWCO 10–14 kDa, Hi-Media, India), sealed at both ends and suspended in separate beakers (receptor compartment) containing 100 ml of simulated gastric fluid of (pH 1.2). A magnetic stirrer (Remi, Mumbai, India) was used to continually agitate the receptor compartment at 50 rpm, and the temperature was kept constant at 37 ± 1°C during the experiment. The samples were taken from the receptor compartment at appropriate time intervals, and after each sampling, an equal volume of SGF (pH 1.2) was introduced to the receptor medium to maintain a constant volume throughout the experiment. The receptor compartment was continuously agitated by a magnetic stirrer (Remi, Mumbai, India) at 50 rpm, and the 37±1°C temperature was maintained throughout the experiment. The samples were withdrawn at a suitable time interval from the receptor compartment, and after each sampling, an equal volume of SGF (pH 1.2) was added to the receptor medium so as to uphold a constant volume throughout the study. The samples were analysed by UV-visible spectrophotometer (UV mini 1240 Shimadzu, Kyoto, Japan) [29-31]. Also, the in-vitro release of the marketed tablet of lafutidine was also performed simultaneously in simulated gastric fluid (pH 1.2) using USP dissolution testing apparatus II (USP XXII), in which 1 tablet was placed in 900 ml of simulated gastric fluid (pH 1.2) at a temperature 37±5 °C at a 100 rpm for half an hour and samples were taken at a time interval of 5 min, and their absorbance was taken using UV visible spectrophotometer [32].

Results and Discussion

Fabrication of Lafutidine Microballoons

The values of percentage entrapment efficiency (EE), percentage buoyancy, and percentage yield determine how well-floating microballoons are prepared. Higher value of % EE shows that a lot of the active pharmaceutical ingredient is incorporated into the microballoon, which means that a lot of the drug will release into the body and could have the intended therapeutic effect. The buoyancy values represent the buoyancy capacity of the digestive tract of the drug-loaded microballoons. While "% yield" is a characteristic of drug-loaded microballoons that describes how well the preparation procedure is employed to generate the highest number of drug-loaded microballoons, it also assists in the precise determination of drug-loaded microballoon production techniques.

Following the process outlined in Kawashima, et al. [28] with a simple modification in methodology, the microballoons of lafutidine were developed by using the emulsion solvent diffusion methodology [28].

According to the study's findings, the formula with a higher ratio of EC to HPMC was able to elevate the % (EE, buoyancy, and yield). EC is a water-insoluble polymer that may readily capture lafutidine, it can behave as a floating

enhancer. Additionally, compared to HPMC, the EC was more dominating given the influence of floating. To rigidify lipid particles, the process includes intensive methanol diffusion into the surrounding aqueous phase, transverse to the solvent polymer phase. This is followed by quick evaporation of the methanol and dichloromethane.

To control how rapidly drugs are released from microballoons, a polymeric phase consisting of ethyl cellulose and HPMC polymer was added to the aqueous (PVA) solution. When the polymer solution in dichloromethane: methanol (1:1) was introduced dropwise to the aqueous solution of 0.75% w/v polyvinyl alcohol (PVA) at 40 °C, the methanol partitioned quickly into the aqueous phase (PVA solution) and formed a stiff polymer shell around the dichloromethane droplet. Therefore, the evaporation of dichloromethane creates a gas phase in the dispersed polymer droplet, which creates an interior cavity in the microballoons. These microballoons get their floating characteristic from their hollow nature.

The polymers used to make microballoons were initially optimized by changing the ratio of ethyl cellulose to HPMC while maintaining the amount of HPMC constant. The formulation of prepared microballoons was further assessed for % yield, % buoyancy, particle size, and entrapment efficiency.

Effect of Concentration of Polymer

Formulation with 7:1 ethyl cellulose to HPMC ratio was preferred for additional process variable optimization because it demonstrated an ideal size of 4.703±0.23 µm and 81.4±3.25 percentage buoyancy (Figure 3A). The size of the microballoons increased when the ethyl cellulose ratio was raised, as seen in Figure 3A. This may be caused by the medium becoming more viscous at greater polymer concentrations, which would increase interfacial tension. At greater viscosities, shearing efficiency is reduced, and as a result, larger particles are created. The microballoons with the maximum buoyancy (Figure 3A) and highest yield were obtained using ethyl cellulose to HPMC ratio of 7:1. The size of the microballoons expanded with an increase in the HPMC ratio, but the percentage yield was diminished.

Effect of the Drug: Polymer Ratio

It was found that the % entrapment efficacy increased up to a drug: polymer ratio of 25:100 when the amount of lafutidine was increased while keeping the amount of polymer (ethyl cellulose and HPMC) constant in each formulation. However, as the drug concentration was increased further (30:100), the entrapment efficacy slowly decreased (Figure 3B). This may be due to the drug-polymer saturation. The microballoons prepared by 25:100 (drug-polymer solution) has shown 83.64±3.34 % buoyancy.

Effect of Emulsifier PVA Concentration

The preparation of a stable emulsion was achieved by the use of a polyvinyl alcohol aqueous solution. PVA aqueous solution was used in 0.5 - 1.25 % w/v concentration to optimize the microballoons. At 0.75 % emulsifier (PVA) concentration, the microballoon % entrapment efficiency was found to be the highest, i.e. (74.8±2.99%) Figure 3C. At lower PVA concentrations (0.5 % w/v), a stable emulsion was not obtained, which led to reduced % entrapment efficiency, and the % yield value was decreased if the PVA emulsifier concentration was increased to 1.25 % w/v.

Effect of Stirring Speed

The magnetic stirrer speed greatly influences particle size, % buoyancy, % entrapment efficacy, and % yield. The average particle size of the microballoons reduced as the magnetic stirrer speed increased from 100 to 700 rpm, and the buoyancy of the microballoons also reduced as a result of a reduction in the proportion of the cavity present inside the microballoon formulation. Smaller particles with greater buoyancy, yield, and entrapment efficiency were produced at 300 rpm (Figure 3D). Shear force was insufficient to create a stable emulsion at speeds below 300 rpm. To avoid foam forming on the emulsion's surface, which might affect the pace at which dichloromethane and methanol evaporate and, in turn, affect how quickly microballoons develop, a minimum speed of 300 rpm was employed to prepare microballoons.

Effect of Temperature

The temperature of the dispersion medium affects how quickly the solvents evaporate; therefore, it must be properly considered (Figure 3E). Due to the low temperature (30°C) and the slugging rate at which dichloromethane and methanol vaporized, the microballoons had rough surfaces. Contrary to expectations, microballoons made at 60°C lacked hollowness and floated poorly. Dichloromethane and methanol evaporated quickly, leaving a single, sizable hollow at the surface of the microballoons. Thus, the progressive evaporation of methanol and dichloromethane at 40°C led to the development of microballoons with high buoyancy (81.3±3.25%), yield (63.2±2.52%), and entrapment efficiency (73.9±2.95%).

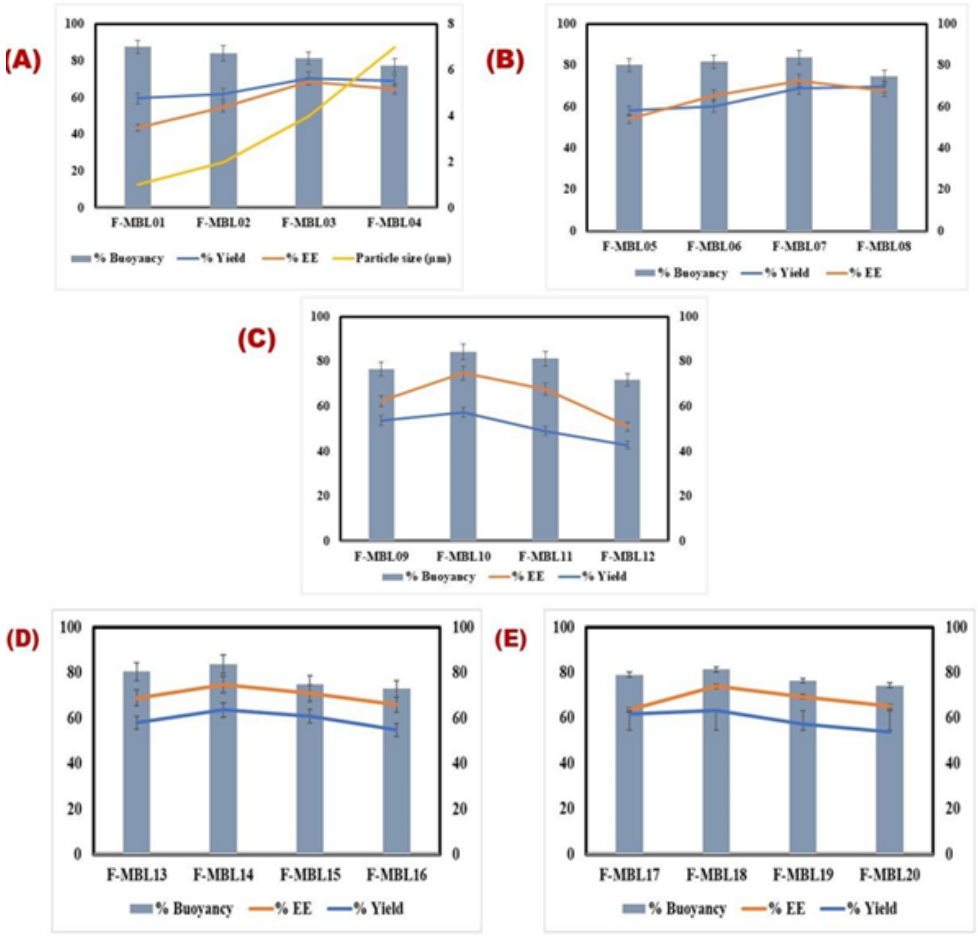

Figure 3: Optimization of (A) different polymer ratio with respect to particle size, (B) drug: polymer ratio, (C) emulsifier, (PVA) concentration, (D) stirring speed and (E) temperature with respect to particle size, % yield, % buoyancy, and % drug entrapment efficiency.

Solubility

The solubility of lafutidine was checked in different solvents, and the results suggested that the lafutidine was freely soluble in organic solvents ex., (methanol, and glacial acetic acid) and it is sparingly soluble in ethanol, and lafutidine was found to be practically insoluble in water.

Melting Point

The melting point testing apparatus (Super fit, India) indicated that the overall melting point temperature of lafutidine was found between 97 - 100°C. Differential Scanning Calorimetry (DSC) was also used to estimate it, as illustrated in (Figure 4).

To assess the purity of the drug sample lafutidine, differential scanning calorimetry was used. DSC thermal analysis confirmed that the drug was lafutidine, and there was a prominent sharp endothermic peak at 99.6°C, which also revealed a noticeable to its melting point temperature (Figure 4).

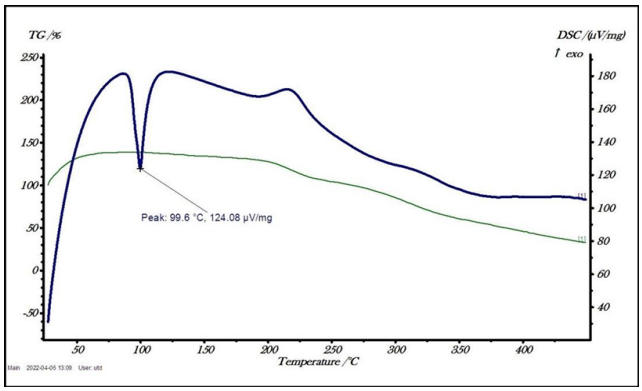

Figure 4: DSC Curve of Pure Lafutidine Drug.

Particle Size and Polydispersity Index Determination

The average and normal size of the microballoons formulation was found to be between 1 – 7 µm, with a PDI of less than 1 (Figure 5). The PVA concentration and polymer (Ethyl cellulose and HPMC) ratio changes, i.e., variation in particle size, also exhibited an influence on the % buoyancy, % yield, and entrapment efficiency of the optimized (F-MBL18) microballoons formulation (Figure 3C). The microballoons formulation with an average and normal particle size of 4 µm has the highest entrapment efficiency (73.9±2.95%) and was considered an optimized formulation as compared with different microballoons formulations.

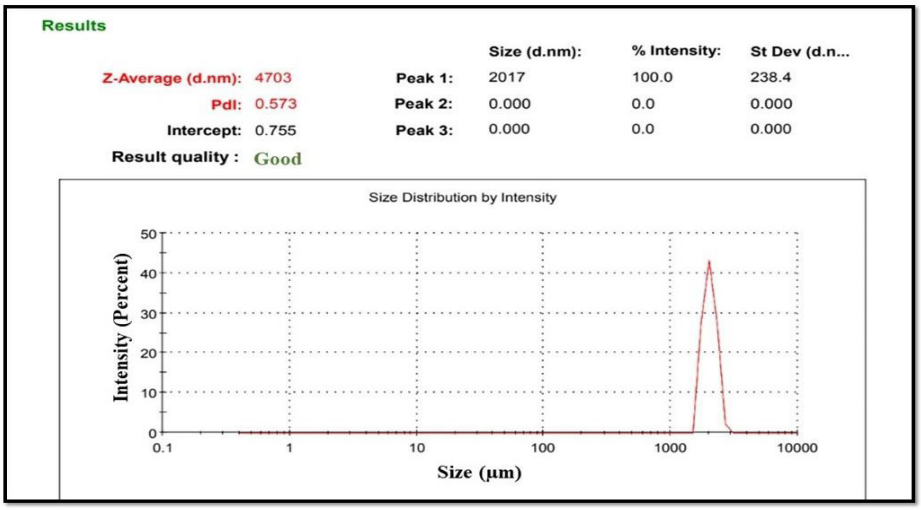

Figure 5: Particle Size and PDI of Floating Microballoons.

Morphology

The morphology, size, and shape of microballoons were studied using a fluorescence microscope, scanning electron microscope, and transmission electron microscope. The formation of microballoons at different polymeric ratios (3:1–9:1) was analysed by a fluorescence microscope. Studies revealed that the microballoons were to be spherical in form with a smooth surface under magnification in the range of 10x–40x (Figure 6). SEM images confirmed the formation of microballoons; the microballoons were spherical and smooth on the surface. However, the particle size and shape were maintained, demonstrating successful linking between the polymers (Figure 7). Furthermore, the wall's stability and rigidity were established, and subsequently, microballoons showed a sustained release of drugs from the core material.

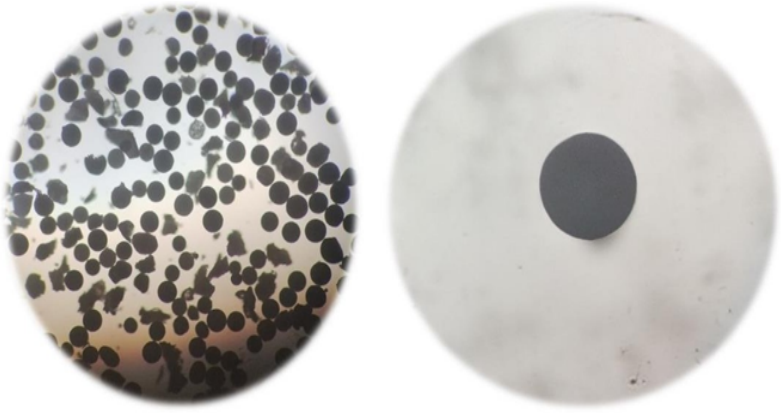

Figure 6: Image of Prepared Microballoons in Fluorescence Microscope under Magnification in the Range of 10x-40x.

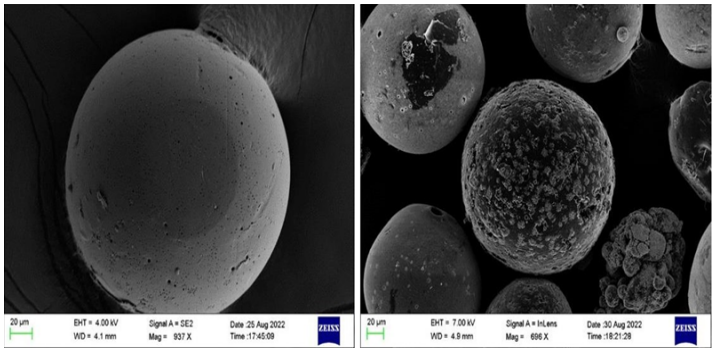

Figure 7: SEM Images of Microballoons under Magnification in the Range of 696 x-8.98 kx.

Lafutidine-loaded microballoons had a smooth, approximately spherical form, as shown in the transmission electron microscopy (TEM) images (Figure 8). Samples can be negatively stained as a helpful method for enhancing the micro balloon's high resolution.

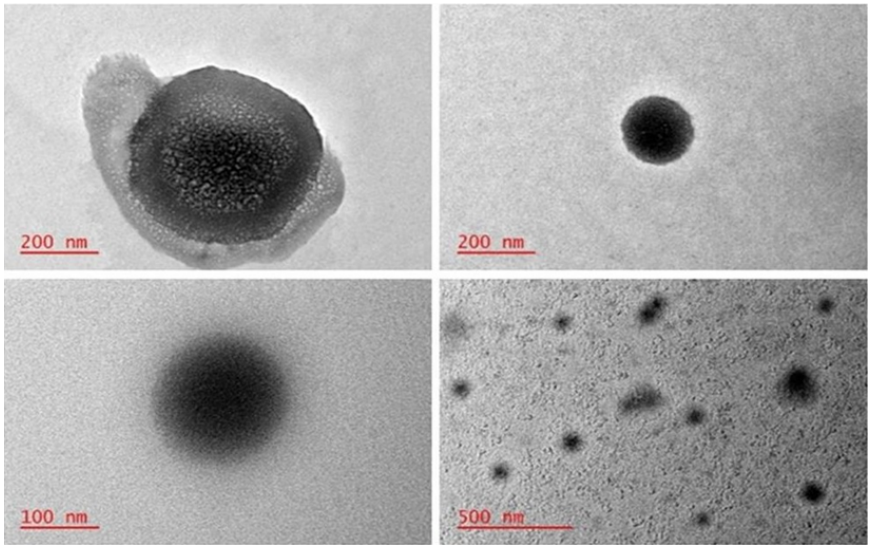

Figure 8: TEM Photomicrograph of Lafutidine-Loaded Microballoons.

Percentage Yield of Microballoons

Microballoons were weighed after drying, and the % yield was calculated. The highest % yield of optimized microballoons formulation was (63.2±2.52 %). It was found that a greater % yield of microballoons was obtained at the polymer concentration [7:1 (Ethyl cellulose and HPMC)] and the % emulsifier concentration 0.75% w/v PVA (Table 3). The stable emulsion was not developed at lower PVA concentrations, which led to reduced % yield and entrapment efficiency.

Drug Content Determination

Drug content also depends on the % yield of microballoons and formulation F-MBL18 shows the highest drug content. It was found that the greater entrapment efficiency of lafutidine microballoons (73.9 ± 2.95 %) in their particular microballoons formulation was found with 7:1 Ethyl cellulose and HPMC, 0.75 % w/v emulsifier concentration and (25:100) drug: polymer ratio (Table 3).

In-Vitro Buoyancy Percentage

The range of % buoyancy varied from 87.5±3.5% to 74.3± 2.97%. Over the course of 10 hours, it was revealed that all of the formulations were able to continuously float on the dissolution medium. Lafutidine microballoons in-vitro buoyancy was caused by the occurrence of pores and low bulk density. Consequently, it may be inferred that these microballoons have the ability to float in gastric fluid,

delaying their entry into the gastrointestinal tract and extending their duration within. Due to swelling properties with a density less than gastric fluid, it was shown that the in-vitro % buoyancy increased with increasing concentrations of polymer (ethyl cellulose) and decreased concentrations of emulsifiers (PVA), such as F-MBL18 (83.1±3.25%) (Table 3).

Formulation Code	Particle Size (µm)	(%) Yield	Entrapment Efficiency (%)	(%) Buoyancy
F- MBL1 8	4.703±0.23 µm	63.2±2.52 %	73.9±2.95 %	83.1±3.25 %

Table 3: Particle Size (µm), % Yield, % Entrapment Efficiency and % Buoyancy of the Optimized Microballoons Formulation.

X-Ray Diffraction Study

The physical characterization of the lafutidine drug and the optimized microballoons formulation are both studied using XRD. Diffractograms of the pure drug and drug- loaded MBs are shown in Figure 9. XRD of lafutidine showed various sharp characteristic peaks at 5.57, 6.22, 7.20, 8.16, 9.12, 10.01, 20.56, 21.17, 22.99, 23.117, 24.70, 25.01, 26.19, 27.64 and 28.95 at 2θ and various characteristic peak intensities of lafutidine were observed at 3962, 3320, 3494, 3277, 26.96, 2430, 4392, 2394, 2458, 2640, 2829, 2364, 2404, 2643 and 2705. Lafutidine's XRD spectra show that the powder was crystalline in form; the diffractograms of the pure drug are shown in Figure 9. The spectra of the optimized microballoons formulation showed the disappearance of the drug's distinctive peaks in the formulation because the drug was accurately disseminated at a molecular level in the polymer matrices, the drug was accurately disseminated at the molecular level, which resulted in a complete amorphous lafutidine microballoons powder (conversion of crystalline lafutidine into an amorphous form). The diffractograms of drug-loaded microballoons are shown in Figure 9.

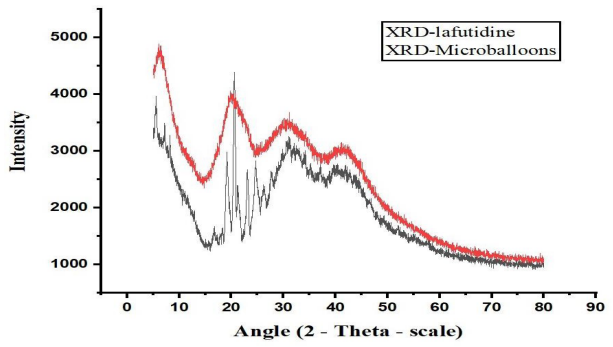

Figure 9: XRD Spectra of Lafutidine and Drug-Loaded Microballoons.

Fourier-Transform Infrared Spectroscopy (FTIR)

The infrared spectrum obtained for lafutidine, EC, HPMC, and physical mixtures of (EC, HPMC, and LAF) and lafutidine-loaded floating microballoons (F-MBL18) are shown in Figure 10. IR spectra of pure lafutidine show distinguishing sharp peaks at 3325.42 cm-1 (R-NH of 2° amide), 1004.96 cm-1 (C–O in furan ring), 1659.82 cm-1 (C=O stretch) and–C–NH exhibited a peak at 1350.23 cm-1. Also, some functional groups like S=O stretching of sulfoxide and – C– S stretching of thiols showed vibrations at 1067.65 cm-1 and 735.87 cm-1 respectively. In the IR spectra of lafutidine, the ring breathing is present between 2932.89 to 2688.88 cm-1 and multiple peaks under 1500 cm-1 (simultaneously =C–H, C–H stretching & bending of the heteroaromatic and cyclic ring), alkane stretching (-CH2 aliphatic and cyclic) vibration at 2850.91 cm^{-1}. C=C stretching at 1638.60 cm^{-1} Figure 10 (S1).

For EC, the IR spectrum shows sharp peaks at 3648.51 cm^{-1} of free O-H alcoholic stretching and alkane (C– H) and C– C stretching between 2965.68 cm^{-1} to 2877.92 cm^{-1}. Also, the spectra show some multiple peaks between 1365.66 cm^{-1} to 1006.89 cm^{-1} for (–C–O of –C–OH) of the compound Figure 10 (S2).

The IR spectrum of HPMC shows various sharp peaks between 3564.60 cm^{-1} to 3459.48 cm^{-1} of the free -OH alcoholic group, 2929.03 cm^{-1} to 2836.45 cm^{-1} for C– C and C– H in the compound and the spectra show some multiple peaks between 947.09.66 cm^{-1} to 1458.25 cm^{-1} for (–C–O of–C–OH) of the compound Figure 10 (S3).

The physical mixture of ethyl cellulose, HPMC, and lafutidine contained all of the identified peaks in Figure 10 (S4). Additionally, most of the peaks were found within the IR spectra of lafutidine-loaded microballoons Figure 10 (S5), indicating drug- polymer compatibility and the lack of any chemical interactions.

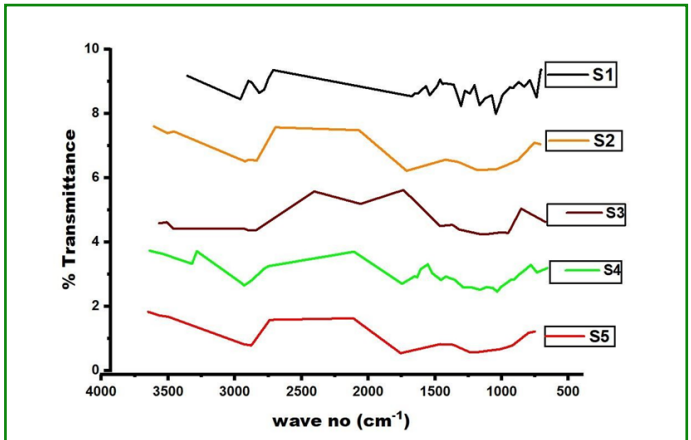

Figure 10: FTIR Spectra of Pure Lafutidine, EC, HPMC, Physical Mixture, and Optimized Microballoons.

In-Vitro Drug Release Study

Studies on in-vitro drug release were conducted for 20 hours in simulated gastric fluid with a pH of 1.2. The surface-associated drug may have contributed to the first burst release up to (15.87 ± 0.79%) in 0.5 hours of the in-vitro release profile, which was biphasic. This was followed by a slower release phase as the drug that was entrapped gradually diffused into the release medium. Up to (83.54 ± 4.1%) of the drug was released, according to Figure 11. Drugs were continuously released at a constant rate.

Initial release of the drug from floating microballoons was higher and later after some time interval it was sustained release as the polymer matrix becomes denser, thus the diffusion path length increases that favouring the prolonged drug release characteristics. The interlocalization of the drugs inside the polymeric network may be the cause of the prolonged drug release from microballoons.

Also, the in-vitro drug release studies of marketed lafutidine tablets were performed similarly to in microballoons in-vitro drug release studies. The in-vitro release profile was found to be (4.7 ± 0.23 %) initially in 5 min and after 50 minutes the in-vitro drug release profile was found (86.94 ± 4.34 %) as reported in Figure 11.

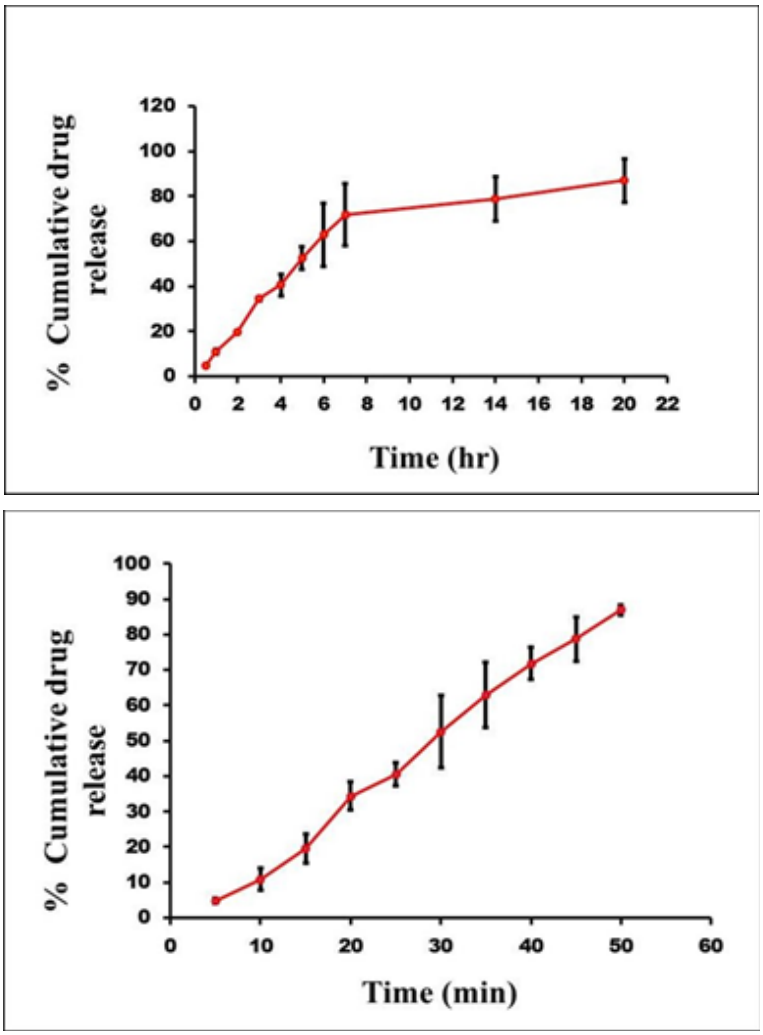

Figure 11: In-vitro drug release of (a) optimized microballoons and (b) marketed lafutidine tablet.

Conclusion

According to the data obtained, the solubility of BCS class II drugs can be improved if they are administered in the form of floating microballoons. The microballoons buoyancy helps the drugs to be absorbed from the upper GIT more effectively. Also, it is concluded that EC and HPMC can be used to create lafutidine-loaded floating microballoons that

were successfully created utilizing the emulsion solvent diffusion approach. The majority of the factors (emulsifying agent concentration (PVA), polymer ratio, drug: polymer, stirring speed, and temperature) appear to have had a substantial impact on the physical properties and drug release profile of the prepared microballoons, according to the overall results. As a result, it was determined that the microballoons demonstrated sustained release of lafutidine for gastroretentive purposes, which may be contributing to an improvement in lafutidine's bioavailability given that they displayed a prolonged drug release pattern for about 20 hours when compared with the lafutidine marketed tablet dosage form. Due to the presence of a floating polymer matrix system made up of HPMC and ethyl cellulose in which HPMC provides porous nature to the matrix system and ethyl cellulose provides low bulk density to microballoons and due to its hydrophobic nature, it increases the floating ability of the microballoons. The study also concludes that lafutidine microballoons may offer a more effective method of treating peptic ulcers.

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