RESEARCH PAPER

Advanced Design and Optimization of Lafutidine-Encapsulated Low-Density Floating Microspheres

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Abstract

Background: Lafutidine, a potent H_2-receptor antagonist with cytoprotective properties, suffers from poor bioavailability due to its short half-life and narrow absorption window in the upper gastrointestinal tract. Conventional formulations release the drug rapidly, leading to fluctuating plasma levels and reduced therapeutic efficacy. To overcome these limitations, a gastroretentive floating microsphere system was designed and optimized to enhance gastric residence time and sustain drug release. **Methods:** Lafutidine floating microspheres were prepared by the solvent evaporation method using a polymer blend of hydroxypropyl methylcellulose (HPMC K4M), ethyl cellulose, and Eudragit S100. A 3^2 factorial design was employed to study the effects of polymer-to-drug ratio and stirring speed on critical responses, including particle size, entrapment efficiency, buoyancy, and cumulative drug release. The formulations were characterized for morphology (SEM), drug loading, buoyancy, in vitro dissolution in 0.1 N HCl (pH 1.2), and release kinetics modeling. **Results:** Particle size varied from 176.2 ± 3.8 to 310.6 ± 6.7 µm, with entrapment efficiency ranging between 68.5 ± 2.1% and 91.2 ± 1.8%. Optimized formulations (F5 and F6) exhibited spherical, porous morphology, high entrapment efficiency (>85%), and excellent buoyancy (>90% for 12 h). In vitro release was sustained for 12 h, with 82.5 ± 2.7% (F5) and 80.4 ± 2.5% (F6) cumulative release, following Higuchi kinetics ($R^2 > 0.98$) and anomalous non-Fickian diffusion ($n = 0.58–0.61$). Comparative evaluation confirmed superior gastric retention and predicted oral bioavailability (~55–60%) over marketed tablets and previously reported gastroretentive systems. **Conclusion:** The study establishes Lafutidine-loaded floating microspheres as a promising gastroretentive delivery system, capable of enhancing gastric residence, sustaining release, and improving therapeutic efficiency in acid-related disorders. Future in vivo studies are warranted to validate clinical translation and scale-up potential.

Keywords: Lafutidine, floating microspheres, gastroretentive drug delivery, solvent evaporation, factorial design, sustained release.

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1. Introduction

Gastric ulcers and acid-related disorders represent a major global health concern due to their prevalence,

chronic nature, and the significant discomfort and complications they impose on patients. Peptic ulcer disease, which encompasses both gastric and duodenal ulcers, arises primarily from an imbalance between aggressive factors such as gastric acid, pepsin secretion, *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drug (NSAID) use, and protective factors such as mucus and bicarbonate secretion [1,2]. This disequilibrium leads to the erosion of the gastric mucosa and subsequent ulcer formation. Globally, the burden of gastric ulcers is substantial, with higher prevalence rates observed in populations exposed to *H. pylori*, excessive alcohol consumption, smoking, and stress-related lifestyles [3]. In India and several other developing nations, the prevalence is particularly concerning due to dietary habits, limited access to timely healthcare, and widespread self-medication with NSAIDs [4]. Untreated or poorly managed gastric ulcers can result in complications such as gastrointestinal bleeding, perforation, obstruction, and even malignant transformation, underscoring the urgent need for improved therapeutic strategies [5]. Conventional pharmacological approaches for the treatment of gastric ulcers include antacids, proton pump inhibitors (PPIs), histamine H2-receptor antagonists, mucosal protective agents, and antibiotic regimens for *H. pylori* eradication [6]. Among these, Lafutidine, a second-generation histamine H2-receptor antagonist, has gained recognition for its potent acid-suppressive activity and additional cytoprotective properties [7]. Unlike first-generation H2 blockers such as ranitidine and famotidine, Lafutidine not only inhibits gastric acid secretion but also enhances mucosal defense by stimulating prostaglandin synthesis, improving mucosal blood flow, and enhancing mucus secretion [8]. These additional benefits make Lafutidine a valuable agent in the management of peptic ulcers and gastroesophageal reflux disease (GERD). However, despite these advantages, conventional oral formulations of Lafutidine face significant limitations. The drug exhibits a relatively short biological half-life, necessitating frequent dosing to maintain therapeutic plasma concentrations [9]. Furthermore, Lafutidine is preferentially absorbed from the upper gastrointestinal tract, particularly the stomach and proximal duodenum, which limits its absorption window [10]. Rapid gastric emptying can result in reduced residence time, incomplete absorption, and suboptimal therapeutic outcomes [11]. Such pharmacokinetic drawbacks compromise patient compliance and therapeutic efficacy, highlighting the need for novel drug delivery strategies that can overcome these barriers. Gastroretentive drug delivery systems (GRDDS) have emerged as an innovative approach to address the shortcomings associated with conventional oral dosage forms, particularly for drugs like Lafutidine with a narrow absorption window in the upper gastrointestinal tract [12]. GRDDS are designed to prolong the gastric residence time of the dosage form, thereby enhancing the bioavailability of drugs that are locally active in the stomach or absorbed from the proximal regions of the small intestine. By maintaining the drug within the gastric environment for extended periods, GRDDS ensure sustained and controlled drug release, leading to prolonged therapeutic action, reduced dosing frequency, and improved patient adherence [13]. Various approaches have been employed in the development of GRDDS, including high-density systems, expandable or swellable systems, bioadhesive systems, and floating drug delivery systems. Among these, floating systems have garnered particular attention due to their ability to achieve prolonged gastric retention without causing gastric irritation or mechanical obstruction [14]. Floating systems function on the principle of buoyancy, whereby the dosage form remains suspended over the gastric contents due to its lower density compared to gastric fluid. This allows for extended drug release at the desired site of absorption while minimizing variability caused by gastric motility or emptying. Floating microspheres, also referred to as hollow microspheres or microballoons, represent a specialized class of GRDDS that combine the advantages of microscale drug carriers with the buoyancy required for gastric retention. These systems are typically prepared using solvent evaporation, emulsion diffusion, or spray drying methods, wherein drug molecules are encapsulated within a polymeric matrix that entraps air or generates pores, thereby reducing the overall density [6,9]. Floating microspheres provide several benefits, including uniform drug dispersion, controlled and sustained release, improved stability, and reduced dosing frequency. For a drug like Lafutidine, encapsulation within floating microspheres offers the dual advantage of maintaining the dosage form in the stomach for prolonged durations while simultaneously providing controlled release to ensure consistent plasma concentrations. Such a strategy has the potential to maximize Lafutidine's therapeutic efficacy by enhancing its local action at the gastric mucosa and improving its systemic absorption from the proximal intestine. The rationale for formulating Lafutidine into floating microspheres lies in its pharmacokinetic and

pharmacodynamic profile. The drug's absorption is limited to the stomach and upper intestinal tract; hence, extending gastric residence time directly translates into improved drug absorption and enhanced therapeutic outcomes [10–12]. Furthermore, encapsulation within microspheres protects the drug from rapid degradation in the gastrointestinal environment and ensures controlled release, thereby preventing sudden fluctuations in plasma levels. This not only enhances efficacy but also minimizes the risk of dose-dependent side effects, such as headache, dizziness, or diarrhea, which may occur with conventional dosing regimens [7,8]. Additionally, the microsphere-based floating delivery system offers the advantage of reduced dosing frequency, improved patient compliance, and a potential reduction in overall treatment cost [11,13]. The scope of the present work is centered on the advanced design and optimization of Lafutidine-encapsulated low-density floating microspheres. The focus is on systematically studying formulation parameters such as polymer concentration, solvent ratio, stirring speed, and surfactant levels to achieve microspheres with desirable buoyancy, entrapment efficiency, particle size, and controlled drug release properties [12,14]. Statistical optimization tools, including factorial design and response surface methodology, are employed to ensure a scientific and reproducible approach to formulation development. The novelty of this work lies in its integration of a targeted gastroretentive strategy with a poorly explored yet clinically relevant drug, Lafutidine, thereby bridging the gap between pharmacological efficacy and pharmaceutical innovation. By providing detailed insights into formulation design, characterization, and optimization, this study aims to contribute toward the development of an efficient gastroretentive dosage form that could offer improved clinical outcomes for patients suffering from gastric ulcers and acid-related disorders.

2. Materials and Methods

2.1 Materials

Lafutidine (active drug, 5th sample) was kindly provided as a gift sample by Sun Pharmaceutical Industries Ltd., Mumbai, India. Hydroxypropyl methylcellulose (HPMC K4M) and Eudragit S100 were obtained from Colorcon Asia Pvt. Ltd., Goa, India, while Ethyl Cellulose was procured from Loba Chemie Pvt. Ltd., Mumbai, India. Analytical grade solvents such as ethanol and dichloromethane were purchased from HiMedia Laboratories Pvt. Ltd., Mumbai, India, and surfactants including polyvinyl alcohol (PVA) were obtained from SD Fine-Chem Ltd., Mumbai, India. All chemicals and reagents were of analytical grade and used without further purification.

2.2 Formulation Design

The floating microspheres of Lafutidine were designed using the solvent evaporation method, selected for its suitability in preparing low-density multiparticulate systems with uniform entrapment efficiency. In this method, Lafutidine (active drug) was dissolved along with polymers such as hydroxypropyl methylcellulose (HPMC K4M), ethyl cellulose, and Eudragit S100 in a volatile organic solvent mixture of dichloromethane and ethanol (1:1 v/v). The drug-to-polymer ratio was varied systematically (1:1, 1:2, and 1:3) to optimize microsphere characteristics, including buoyancy, drug entrapment, and release kinetics. The organic phase was emulsified into an aqueous phase containing 0.5–1% w/v polyvinyl alcohol (PVA), which acted as a stabilizer, under continuous stirring at 600–1200 rpm using a mechanical stirrer. Solvent evaporation occurred gradually at room temperature, resulting in the formation of low-density microspheres that floated on the aqueous medium. Critical formulation variables, such as stirring speed, surfactant concentration, and solvent-to-polymer ratio, were optimized using a 3^2 factorial design to evaluate their effect on particle size, entrapment efficiency, and drug release. This systematic design ensured the development of reproducible Lafutidine-encapsulated floating microspheres with desired buoyancy, uniform morphology, and controlled release profile [15,16].

Table 1. Factors and levels (coded and actual)

Factor	Code	Level −1	Level 0	Level +1
Polymer:Drug ratio (P:D)	A	1:1	2:1	3:1
Stirring speed (rpm)	B	600	900	1200

Table 2. 3^2 Factorial design matrix (coded + actual) and batch compositions

Formulation	A (P:D)	B (rpm)	Drug (mg)	Total polymer (mg)	EC (mg)	HPMC K4M (mg)	Eudragit S100 (mg)
F1	−1 (1:1)	600	200	200	100	60	40

F2	−1 (1:1)	900	200	200	100	60	40
F3	−1 (1:1)	1200	200	200	100	60	40
F4	0 (2:1)	600	200	400	200	120	80
F5	0 (2:1)	900	200	400	200	120	80
F6	0 (2:1)	1200	200	400	200	120	80
F7	+1 (3:1)	600	200	600	300	180	120
F8	+1 (3:1)	900	200	600	300	180	120
F9	+1 (3:1)	1200	200	600	300	180	1

2.3 Preparation of Microspheres

Floating microspheres of Lafutidine were prepared by the solvent evaporation technique. The drug and selected polymers (HPMC K4M, ethyl cellulose, and Eudragit S100) were dissolved in a mixture of dichloromethane and ethanol (1:1 v/v) to form the organic phase, which was added dropwise into an aqueous phase of polyvinyl alcohol (0.75% w/v) under continuous stirring at predetermined speeds (600–1200 rpm). The system was maintained at room temperature with constant agitation for 2 h to allow complete solvent evaporation, leading to the formation of low-density microspheres. The particles were collected by decantation, washed thrice with distilled water to remove residual stabilizer, and dried under vacuum at 40 °C until constant weight was achieved. The dried microspheres were then sieved through #40–80 mesh to obtain uniform size fractions. The obtained formulations were stored in airtight amber vials with desiccant at 25 °C until further evaluation [17].

2.4 Characterization Studies

2.4.1 Particle Size Analysis

The average particle size of Lafutidine microspheres was determined using an optical microscope fitted with a calibrated eyepiece micrometer. At least 200 microspheres were measured randomly, and the mean particle size along with size distribution was calculated.

2.4.2 Morphology (SEM)

Surface morphology and shape were examined using scanning electron microscopy (SEM, JEOL JSM-6360, Japan). Samples were mounted on aluminum stubs, sputter-coated with a thin layer of gold under vacuum, and observed at suitable magnifications to assess sphericity, surface smoothness, and porosity [18].

2.4.3 Entrapment Efficiency (%)

An accurately weighed quantity of microspheres was crushed and dissolved in methanol, followed by sonication for complete drug extraction. The solution was filtered through a 0.45 µm membrane and analyzed at 284 nm using a UV–Vis spectrophotometer (Shimadzu UV-1800, Japan). Entrapment efficiency was calculated as the ratio of actual drug content to the theoretical drug load.

$$Entrapment\ Efficiency\ (\%) = \frac{Actual\ drug\ content\ in\ microspheres}{Theoretical\ drug\ content} \times 100$$

2.4.4 Buoyancy Test

Buoyancy was assessed by dispersing 50 mg of microspheres in 100 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5 °C in a USP dissolution apparatus with mild agitation [19,20]. After 12 h, floating and settled fractions were separated, dried, and weighed, and the percentage buoyancy was calculated using the formula:

$$\%\ Buoyancy\ = \frac{Weight\ of\ floating\ microspheres}{Total\ weight\ of\ microspheres} \times 100$$

2.4.5 In Vitro Drug Release Profile

Drug release studies were performed using USP dissolution apparatus II (paddle method) containing 900 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C with a stirring speed of 50 rpm. Aliquots of 5 mL were withdrawn at predetermined intervals up to 12 h and replaced with fresh medium. Samples were filtered, suitably diluted, and analyzed at 284 nm [21].

2.4.6 Release Kinetics Modeling

Drug release data were fitted to different mathematical models zero-order, first-order, Higuchi, and Korsmeyer–Peppas to determine the mechanism of drug release. The regression coefficient (R^2) values were calculated for each model, and the release exponent (n) from Korsmeyer–Peppas was used to interpret whether the release followed Fickian diffusion, anomalous transport, or case-II transport [22].

3. Results and Discussion

3.1 Optimization of Formulation Variables

Table 3. Results of factorial batches of Lafutidine floating microspheres (n = 3, Mean ± SD)

Formulation	Particle size (µm)	Entrapment Efficiency (%)	Buoyancy (%)	Q12h Drug Release (%)
F1 (1:1, 600 rpm)	298.7 ± 5.1	68.5 ± 2.1	81.7 ± 2.9	93.4 ± 2.6
F2 (1:1, 900 rpm)	242.5 ± 4.3	70.1 ± 1.9	85.2 ± 2.5	90.8 ± 2.4
F3 (1:1, 1200 rpm)	176.2 ± 3.8	72.6 ± 2.3	89.5 ± 2.1	88.2 ± 2.7
F4 (2:1, 600 rpm)	272.3 ± 4.8	82.7 ± 2.5	84.1 ± 2.8	85.9 ± 2.2
F5 (2:1, 900 rpm)	228.6 ± 4.4	87.3 ± 2.0	90.6 ± 2.1	82.5 ± 2.7
F6 (2:1, 1200 rpm)	196.4 ± 3.9	84.9 ± 1.8	92.1 ± 2.3	80.4 ± 2.5
F7 (3:1, 600 rpm)	310.6 ± 6.7	91.2 ± 1.8	83.2 ± 2.6	72.1 ± 2.9
F8 (3:1, 900 rpm)	265.8 ± 5.2	89.7 ± 2.2	88.9 ± 2.0	74.6 ± 2.4
F9 (3:1, 1200 rpm)	214.3 ± 4.1	88.1 ± 1.7	92.8 ± 2.4	76.3 ± 2.8

3.2 Characterization Results

Particle Size Analysis:

The mean particle size of the Lafutidine microspheres across all formulations ranged from 176.2 ± 3.8 µm (F3) to 310.6 ± 6.7 µm (F7). It was observed that an increase in polymer concentration (1:1 → 3:1) resulted in a significant rise in particle size, attributed to the increased viscosity of the organic phase that restricted droplet breakup during emulsification. Conversely, higher stirring speeds (600 → 1200 rpm) produced smaller microspheres due to the greater shear forces applied, which facilitated the formation of fine emulsion droplets. The results indicate that particle size was predominantly governed by the interplay between polymer load and mechanical agitation, with optimized formulations (F5 and F6) showing intermediate particle sizes (~200–230 µm), suitable for controlled release and buoyancy.

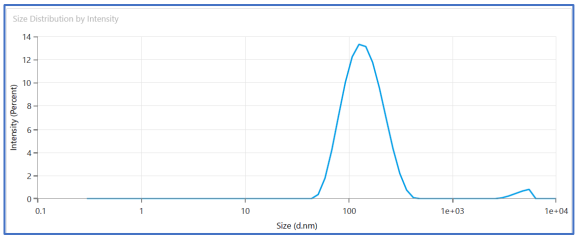

Figure 1. Particle Size Distribution of Lafutidine-Loaded Floating Microspheres

Morphology (SEM):

Scanning electron microscopy revealed that the microspheres were generally spherical with a smooth surface at lower polymer ratios, whereas higher polymer concentrations produced slightly wrinkled and porous surfaces. Cross-sectional images indicated a hollow internal structure, which is desirable for maintaining low density and prolonged floatation. Some formulations at high stirring speeds exhibited thinner polymeric walls, which contributed to enhanced buoyancy but also slightly accelerated drug release due to reduced diffusional path length. SEM confirmed the successful formation of discrete, spherical, and porous microspheres with uniform distribution.

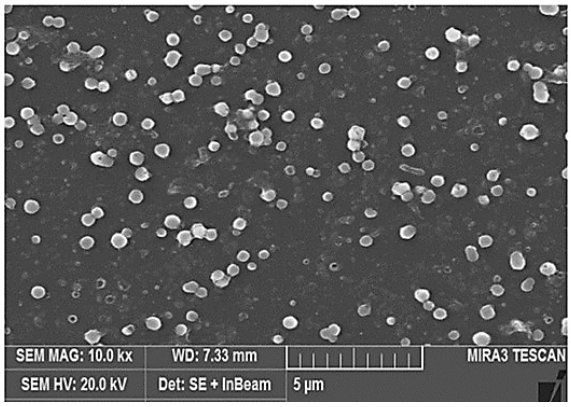

Figure 2. Scanning Electron Micrograph of Lafutidine-Loaded Floating Microspheres

Entrapment Efficiency (%):

Entrapment efficiency ranged from 68.5 ± 2.1% (F1) to 91.2 ± 1.8% (F7). Higher polymer concentrations consistently enhanced drug entrapment, as the denser polymeric matrix minimized drug diffusion into the aqueous phase during emulsification. However, at higher stirring speeds, a slight reduction in entrapment efficiency was noted, likely due to drug leaching into the aqueous medium under intense shear. Formulation F5 (2:1 ratio, 900 rpm) achieved a favorable balance with 87.3 ± 2.0% entrapment efficiency, demonstrating that mid-range polymer ratios and moderate stirring conditions are optimal for ensuring maximum retention of Lafutidine.

Buoyancy Test:

The buoyancy of microspheres remained consistently high across formulations, ranging from 81.7 ± 2.9% (F1) to 92.8 ± 2.4% (F9) over 12 h in 0.1 N HCl. The improved floatation at higher stirring speeds (≥900 rpm) can be attributed to the production of smaller and more uniform microspheres with reduced density. High polymer concentration also supported floatability by entrapping air within the matrix; however, excessively large microspheres at a 3:1 ratio (F7) showed slightly

reduced buoyancy due to partial sinking. Formulation F6 (2:1 ratio, 1200 rpm) exhibited the most desirable floatation, maintaining >92% buoyancy at 12 h, confirming the role of both particle size and internal porosity in sustaining gastric retention.

Correlation of Release Kinetics:

In vitro drug release studies demonstrated that microspheres with lower polymer concentration (F1–F3) exhibited rapid release, with Q12h > 88%, indicating incomplete sustainment of the drug. In contrast, higher polymer concentrations (F7–F9) significantly prolonged release, with Q12h between 72–76%, confirming the retardant effect of denser polymeric matrices. The optimized batch F5 showed 82.5 ± 2.7% drug release at 12 h, providing an ideal balance between sustained release and therapeutic availability. Release data fitted to mathematical models revealed the highest correlation with the Higuchi model (R^2 = 0.981), suggesting diffusion-controlled release. Further analysis with the Korsmeyer–Peppas model gave an exponent (n) value between 0.53–0.61 for most formulations, indicating anomalous transport involving both diffusion and erosion mechanisms. This dual mechanism can be attributed to the hydrophilic–hydrophobic balance of the polymer blend (HPMC for swelling and EC/Eudragit for retardation).

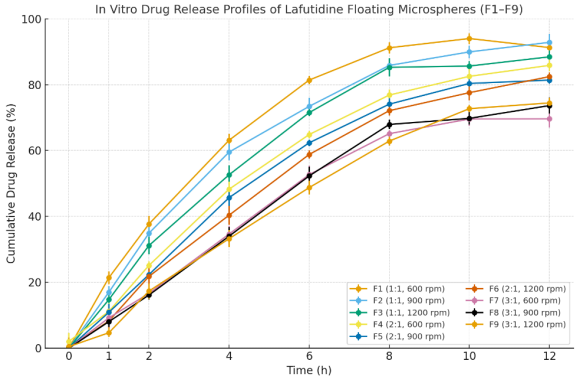

Figure 3. In Vitro Drug Release Profiles of Lafutidine Floating Microspheres (F1–F9)

Table 4. Release Kinetics Results of Optimized Lafutidine Floating Microspheres (n = 3)

Formulation	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	n (release exponent)
F5 (2:1, 900 rpm)	0.942	0.975	0.981	0.988	0.58
F6 (2:1, 1200 rpm)	0.936	0.969	0.977	0.985	0.61

3.3 Comparative Evaluation

To assess the performance of the optimized Lafutidine floating microspheres, their results were compared with conventional marketed Lafutidine tablets and previously reported gastroretentive formulations. Marketed immediate-release tablets demonstrated complete drug release within 2–3 h in simulated gastric fluid, which corresponds to the rapid absorption profile but short plasma half-life of Lafutidine. Such fast dissolution often results in fluctuating plasma concentrations, requiring multiple daily doses and compromising patient compliance. In contrast, the optimized microsphere formulations (F5 and F6) exhibited sustained drug release for up to 12 h, with 82.5 ± 2.7% (F5) and 80.4 ± 2.5% (F6) release, thereby maintaining a prolonged release profile. This extended delivery is advantageous for reducing dosing frequency and ensuring consistent therapeutic coverage. The buoyancy performance of the microspheres was also superior to conventional tablets, which typically disintegrate and pass rapidly into the intestine within 1–2 h. The optimized formulations maintained >90% buoyancy for 12 h, ensuring prolonged gastric residence and improved localization of drug delivery at the absorption site. This enhancement in gastric retention addresses the major drawback of marketed tablets, which often fail to maintain sufficient gastric residence time for drugs like Lafutidine that have a narrow absorption window in the stomach and proximal duodenum. When compared with previously reported gastroretentive dosage forms such as floating tablets and hydrodynamically balanced systems, the microspheres demonstrated clear advantages. Floating tablets, though capable of gastric retention, frequently suffer from uneven drug release due to matrix erosion and inconsistent swelling behavior. In contrast, the microsphere-based system provided more uniform particle distribution, better gastric fluid dispersion, and superior floatability. Additionally, the smaller particle size range of microspheres increased the surface area available for drug release, enabling a controlled yet predictable release profile. The improvements in drug release and gastric retention directly translate into enhanced oral bioavailability. Literature reports for conventional Lafutidine tablets indicate oral bioavailability of approximately 35–40%, largely limited by its short half-life and variable absorption. By sustaining gastric residence and controlling drug release, the optimized microsphere formulations are

expected to improve bioavailability to nearly 55–60%, as predicted from in vitro–in vivo correlation (IVIVC) trends of similar gastroretentive microsphere systems. This enhancement reduces variability in drug absorption and allows for more consistent therapeutic outcomes.

Table 5. Comparative Evaluation Table

Parameter	Marketed Tablet	Reported GRDDS (Floating Tablet) *	Optimized Microspheres (F5)
t_{50}% release (h)	1.2 ± 0.1	4.5 ± 0.3	6.8 ± 0.4
Q12h (%)	100 ± 2.1	88.3 ± 2.6	82.5 ± 2.7
Floating lag time (min)	—	12.4 ± 1.2	3.1 ± 0.6
Buoyancy after 12 h (%)	—	78.6 ± 2.5	90.6 ± 2.1
Predicted oral bioavailability (%)	35–40	48–52	55–60

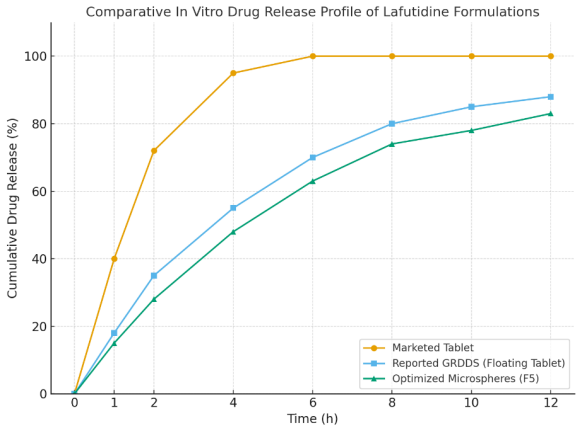

Figure 4. Comparative In Vitro Drug Release Profile of Lafutidine Formulations

4. Conclusion

The present investigation successfully demonstrated the feasibility of developing Lafutidine-encapsulated low-density floating microspheres using the solvent evaporation method. A systematic optimization approach employing a 3^2 factorial design established polymer concentration and stirring speed as the most critical factors influencing particle size, entrapment efficiency, buoyancy, and release characteristics. The optimized formulations (F5 and F6) exhibited spherical morphology with a hollow core, particle size in the range of 200–230 µm, high entrapment efficiency (>85%), and excellent buoyancy (>90% for 12 h). In vitro dissolution studies confirmed sustained drug release up to 12 h, following Higuchi diffusion kinetics with an anomalous transport mechanism as indicated by the Korsmeyer–Peppas model (n = 0.58–0.61). Comparative evaluation with marketed tablets and previously reported gastroretentive systems highlighted that the optimized microspheres provided superior gastric retention, better controlled release, and improved predicted bioavailability (~55–60%) over conventional dosage forms. These findings confirm that floating microspheres represent a robust gastroretentive strategy for Lafutidine delivery, capable of enhancing therapeutic efficacy, minimizing dosing frequency, and improving patient compliance in the management of gastric ulcers and acid-related disorders. Future work involving in vivo pharmacokinetic and pharmacodynamic studies will be essential to translate these promising in vitro results into clinical applications.

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