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REVIEW Article

Formulation and Evaluation of Floating Microspheres of Levofloxacin Using the Emulsion Solvent Diffusion Technique: A Controlled-Release Gastroretentive Drug Delivery Approach

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Abstract

Background: Levofloxacin, a broad-spectrum fluoroquinolone antibiotic, demonstrates optimal therapeutic efficacy when absorbed in the upper gastrointestinal tract (GIT). Conventional oral formulations of levofloxacin are limited by rapid gastric transit, which reduces drug bioavailability. Gastroretentive floating microspheres represent a promising strategy to prolong gastric residence time (GRT) and achieve controlled drug release.

Objective: The present study aimed to develop and evaluate levofloxacin-loaded floating microspheres employing Eudragit RS100 and ethyl cellulose as polymeric carriers, using the emulsion solvent diffusion technique, to achieve sustained drug release and enhanced buoyancy.

Methods: Four formulations (F1–F4) were prepared at drug-to-polymer ratios of 1:1 and 1:2 using Eudragit RS100 and ethyl cellulose in dichloromethane. Polyvinyl alcohol (1% w/v) served as the aqueous emulsifying phase. Formulations were evaluated for particle size, percentage yield, drug entrapment efficiency, floating behavior, scanning electron microscopy (SEM), FTIR compatibility, in vitro drug release in pH 1.2 HCl buffer, and short-term stability.

Results: Optimized formulation F3 (Eudragit RS100; drug: polymer (1:1) demonstrated a mean particle size of 160 µm, drug entrapment efficiency of 82.39%, and buoyancy exceeding 8 hours. In vitro release studies confirmed a sustained-release profile with 97.89% cumulative drug release over 8 hours. FTIR analysis confirmed the absence of drug–excipient interactions, and SEM revealed smooth, spherical morphology. Stability studies at 25°C, 30°C, and 40°C over 90 days indicated no significant changes in drug release or physical characteristics.

Conclusion: Floating microspheres of levofloxacin prepared by the emulsion solvent diffusion method exhibited desirable gastroretentive, physicochemical, and sustained-release properties. Eudragit RS100-based formulation F3 emerged as the optimal candidate for gastroretentive controlled drug delivery.

Keywords: *Floating microspheres; Levofloxacin; Eudragit RS100; Ethyl cellulose; Gastroretentive drug delivery; Emulsion solvent diffusion; Controlled release.*

1. INTRODUCTION

Oral drug delivery continues to dominate the pharmaceutical landscape owing to its non-invasive nature, ease of administration, and high patient acceptability [1]. Despite these advantages, many drugs exhibit suboptimal bioavailability when administered orally, primarily because of degradation within the gastrointestinal tract (GIT), limited absorption windows, and short gastric residence times [2]. Drugs

exhibiting site-specific absorption in the proximal small intestine are particularly susceptible to such pharmacokinetic challenges.

Conventional sustained-release (SR) systems, while effective at maintaining prolonged plasma drug concentrations, often fail to capitalize on the absorptive capacity of the stomach and upper duodenum due to rapid gastric emptying [3]. Gastroretentive drug delivery systems (GRDDS) have been proposed as a compelling solution to overcome these limitations, operating on the principle of prolonging gastric residence time (GRT) to facilitate extended and controlled drug release at the site of optimal absorption [4].

Among the various GRDDS approaches—including mucoadhesive systems, high-density sinking systems, expandable formulations, and low-density floating systems—floating drug delivery systems (FDDS) have received the most extensive scientific attention [5]. These systems leverage their lower-than-gastric-fluid density to remain buoyant on the gastric surface, releasing drug in a controlled manner without disrupting normal gastric emptying mechanisms [6]. Hollow microspheres, or microballoons, represent a particularly sophisticated subclass of FDDS that combine multi-particulate flexibility with superior buoyancy, attributable to their internal hollow architecture [7].

Levofloxacin, the pure (S)-enantiomer of ofloxacin, is a third-generation fluoroquinolone antibiotic with potent bactericidal activity against a wide spectrum of Gram-positive and Gram-negative organisms [8]. It exerts its action by inhibiting bacterial DNA gyrase (topoisomerase II) and topoisomerase IV, thereby disrupting DNA replication and transcription [9]. Clinically, levofloxacin is indicated for community-acquired pneumonia, urinary tract infections, and eradication of Helicobacter pylori, among other indications [10]. Its narrow absorption window in the upper GIT, combined with a short elimination half-life of approximately 6.9 hours, renders it an ideal candidate for gastroretentive floating microsphere technology [11].

The emulsion solvent diffusion technique offers a reproducible and scalable approach to microsphere fabrication, enabling precise control over particle size, drug encapsulation, and release kinetics through polymer selection and drug-to-polymer ratio optimization [12]. Eudragit RS100, a quaternary ammonium methacrylate copolymer with pH-independent low permeability, and ethyl cellulose, a water-insoluble hydrophobic polymer, are well-established candidates for sustained-release microsphere formulations [13, 14].

The present study reports the systematic formulation, optimization, and in vitro evaluation of levofloxacin floating microspheres using Eudragit RS100 and ethyl cellulose at two drug-to-polymer ratios, with the objective of achieving effective buoyancy and controlled drug release in simulated gastric fluid.

2. MATERIALS AND METHODS

2.1 Materials

Levofloxacin (gift sample, Hetero Labs, Hyderabad, India), Eudragit RS100, ethyl cellulose, dichloromethane, and polyvinyl alcohol (PVA) were obtained from Synpharma Research Labs, Hyderabad, India. All chemicals and reagents used were of analytical grade. Distilled water was used throughout the study.

2.2 Preformulation Studies

2.2.1 Organoleptic Characterization

Physical characteristics of levofloxacin, including color, odor, and taste, were assessed by direct visual observation and sensory evaluation under standardized conditions.

2.2.2 Melting Point Determination

The melting point of levofloxacin was determined using the capillary method with a calibrated melting point apparatus. The observation was recorded and compared with pharmacopoeial standards.

2.2.3 Solubility Studies

Solubility of levofloxacin was assessed qualitatively in distilled water, glacial acetic acid, and chloroform by adding excess drug to 5 mL of each solvent at room temperature with continuous agitation for 24 hours.

2.2.4 FTIR Drug–Excipient Compatibility Studies

Fourier transform infrared (FTIR) spectroscopy was employed to assess potential physicochemical incompatibilities between levofloxacin and selected excipients. Approximately 1 mg of the drug or drug–excipient physical mixture was blended with 100 mg of dry potassium bromide (KBr) and compressed into

a translucent disc using a hydraulic press. Spectra were recorded over 4000–400 cm^{-1} using a Shimadzu FTIR spectrophotometer (Shimadzu Corporation, Japan).

2.2.5 Analytical Method Development and UV Calibration

A standard calibration curve for levofloxacin was established in 0.1 N HCl (pH 1.2). Stock solutions were prepared at concentrations of 1000 µg/mL, 100 µg/mL, and 10 µg/mL in distilled water. Working standards ranging from 10–50 µg/mL were prepared, and absorbance was measured at 280 nm using a double-beam UV–Vis spectrophotometer (Lab India Instruments Pvt. Ltd.) against a solvent blank.

2.3 Preparation of Floating Microspheres

Floating microspheres of levofloxacin were prepared using a modified emulsion solvent diffusion technique, as previously described by Kawashima et al. [15], with appropriate modifications. Four formulations (F1–F4) were prepared at drug-to-polymer ratios of 1:1 and 1:2 using ethyl cellulose (F1, F2) and Eudragit RS100 (F3, F4) as shown in Table 1.

Table 1: Formulation design of levofloxacin floating microspheres

Formulation Code	Polymer	Drug:Polymer Ratio	Stirring Speed (rpm)
F1	Ethyl Cellulose	1:1	1000
F2	Ethyl Cellulose	1:2	1000
F3	Eudragit RS100	1:1	1000
F4	Eudragit RS100	1:2	1000

Briefly, levofloxacin was dissolved in 5 mL of distilled water, while the respective polymer was dissolved in dichloromethane. The two phases were combined under magnetic stirring at 500 rpm for 10 minutes to form a water-in-oil (w/o) emulsion. This emulsion was then transferred dropwise into 200 mL of 1% (w/v) PVA solution and subjected to mechanical agitation at 1000 rpm for 2 hours at room temperature to allow complete solvent diffusion and microsphere formation. The resultant microspheres were collected by filtration, washed repeatedly with distilled water to remove residual PVA, and air-dried at ambient temperature for 24 hours, followed by vacuum drying at 25°C for 2 hours.

2.4 Evaluation of Floating Microspheres

2.4.1 Particle Size Analysis

Particle size distribution was determined by sieve analysis using a series of standard sieves (mesh sizes 14, 16, 18, 22, and 30). The percentage of microspheres retained on each sieve was determined gravimetrically, and the mean particle size was calculated accordingly [16].

2.4.2 Percentage Yield

The practical yield of each formulation was calculated by weighing the dried microspheres and expressing this as a percentage of the total theoretical weight of drug and polymer combined, using the following equation:

$$\% \text{ Yield} = (\text{Weight of microspheres} / \text{Total weight of drug + polymer}) \times 100$$

2.4.3 Drug Entrapment Efficiency

To determine the drug entrapment efficiency (DEE), 50 mg of microspheres were accurately weighed, pulverized, and dissolved in 10 mL ethanol. The volume was adjusted to 100 mL with 0.1 N HCl and filtered through Whatman No. 44 filter paper. An appropriate aliquot was diluted with 0.1 N HCl, and the absorbance was recorded spectrophotometrically at 280 nm. DEE was calculated as:

$$\% \text{ DEE} = (\text{Calculated drug concentration} / \text{Theoretical drug concentration}) \times 100$$

2.4.4 Floating Behavior (Buoyancy Studies)

Buoyancy was assessed by dispersing 100 mg of microspheres in 300 mL of 0.1 N HCl containing 0.02% Tween 20, and stirring at 100 rpm using USP Type II paddle apparatus at 37 ± 0.5°C. At

predetermined intervals (1, 2, and 3 hours), floating microspheres were separated, filtered, and dried overnight. The percentage buoyancy was calculated as:

$$\% \text{ floating} = (\text{Weight of floating microspheres} / \text{Initial weight of microspheres}) \times 100$$

2.4.5 Scanning Electron Microscopy (SEM)

Surface morphology of optimized microspheres was examined by scanning electron microscopy (Hitachi, Japan). Samples were mounted on carbon adhesive tape, sputter-coated with a thin gold film under high vacuum, and observed at an accelerating voltage of 20 kV at magnifications of 40× and 200×.

2.4.6 In Vitro Drug Release Studies

In vitro drug release was evaluated using USP Type II dissolution apparatus (paddle method) in 900 mL of pH 1.2 simulated gastric fluid (SGF) maintained at 37 ± 0.5°C and 100 rpm. Microspheres equivalent to 100 mg of drug were placed in the dissolution vessel. Aliquots of 1 mL were withdrawn at hourly intervals up to 8 hours and replaced with equal volumes of fresh dissolution medium to maintain sink conditions. Samples were suitably diluted and analyzed spectrophotometrically at 280 nm. Cumulative percentage drug release (% CDR) was calculated from the calibration curve.

2.4.7 Stability Studies

Accelerated stability testing of the optimized formulation F3 was conducted according to ICH Q1A (R2) guidelines. Samples were stored in sealed borosilicate glass vials at three conditions: 25°C/60% RH (long-term), 30°C/75% RH (intermediate), and 40°C/75% RH (accelerated) for 90 days. Drug content and physical appearance were assessed at Days 1, 60, and 90 [17].

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

3.1.1 Organoleptic Properties

Levofloxacin presented as a white to pale yellowish-white crystalline powder, odorless, and essentially tasteless, consistent with reported pharmacopoeial standards [18]. These characteristics confirmed the identity and suitability of the drug sample for formulation work (Table 2).

Table 2: Organoleptic and physicochemical properties of levofloxacin

Property	Observation
Description	Crystalline powder
Color	White to pale yellowish-white
Odor	Odorless
Taste	Tasteless
Melting Point	225–230°C
Solubility	Sparingly soluble in water; freely soluble in glacial acetic acid and chloroform

3.1.2 FTIR Compatibility Analysis

The FTIR spectrum of pure levofloxacin exhibited characteristic absorption bands at 3448.84 cm^{-1} (O–H stretching), 2820.53 cm^{-1} (C–H stretching), 2000.40 cm^{-1} (C=O stretching), and 1199.75 cm^{-1} (O–H bending), in agreement with reported spectral data [19]. In the FTIR spectrum of the optimized formulation F3, the principal characteristic peaks of levofloxacin were retained without any notable shifts or disappearances, indicating the absence of chemical incompatibility between the drug and Eudragit RS100 polymer. These observations are consistent with findings reported by Jain et al. [20] and confirm the physicochemical integrity of levofloxacin within the polymeric matrix.

3.1.3 UV Calibration Curve

The wavelength of maximum absorbance (λmax) of levofloxacin in 0.1 N HCl was identified at 280 nm. The calibration curve demonstrated excellent linearity over the 10–50 µg/mL concentration range (R^2 = 0.9983), following the regression equation $y = 0.0114x + 0.012$. The high correlation coefficient confirmed the suitability of this method for quantitative analysis of levofloxacin in dissolution samples [21].

3.2 Particle Size Analysis

Mean particle sizes of the four formulations ranged from 130 to 197 μm (Table 3). Formulations F1 and F2 (ethyl cellulose) yielded larger particles (179 and 197 μm, respectively) compared to Eudragit-based formulations F3 and F4 (160 and 130 μm, respectively). This trend is attributable to differences in polymer viscosity and chain length. Particle sizes within the 100–1000 μm range are considered ideal for hollow microspheres, as they facilitate both adequate floating and controlled drug release [22]. The moderate particle size of F3 (160 μm) suggests a balanced trade-off between buoyancy and release rate.

Table 3: Particle size of floating microsphere formulations (EC = Ethyl Cellulose)

Formulation	Polymer	Mean Particle Size (μm)
F1	EC	179
F2	EC	197
F3	Eudragit RS100	160
F4	Eudragit RS100	130

3.3 Percentage Yield

The percentage yield of all formulations ranged from 79.68% to 82.36% (Table 4). The highest yield was observed for F3 (82.36%), indicating efficient microsphere recovery during the emulsification and solvent diffusion process. The consistently high yields across formulations reflect process reproducibility and the suitability of the emulsion solvent diffusion method for large-scale applications, corroborating observations by Patel et al. [23].

Table 4: Percentage yield of floating microsphere formulations

Formulation	% Yield
F1	79.68
F2	80.12
F3	82.36
F4	81.25

3.4 Drug Entrapment Efficiency

Drug entrapment efficiency (DEE) values ranged from 79.62% to 82.39% (Table 5). Eudragit RS100-based formulations displayed marginally higher DEE compared to ethyl cellulose formulations. The superior entrapment in Eudragit-based systems may be attributed to the quaternary ammonium functional groups in Eudragit RS100, which may facilitate stronger drug–polymer interactions through ionic forces, limiting drug migration into the external aqueous phase during microsphere formation [24]. Formulation F3 achieved the highest DEE of 82.39%, consistent with findings by Bhardwaj et al. [25], who attributed enhanced entrapment at 1:1 drug-to-polymer ratios to optimal matrix density.

Table 5: Drug entrapment efficiency of floating microsphere formulations

Formulation	Drug Entrapment Efficiency (% w/w)
F1	79.62
F2	81.56
F3	82.39
F4	80.95

3.5 Floating Behavior

All formulations exhibited sustained buoyancy exceeding 3 hours in 0.1 N HCl, confirming their gastroretentive potential (Table 6). Formulation F3 demonstrated the highest initial buoyancy of 96.10% at 1 hour, declining gradually to 89.90% at 3 hours. The superior floating performance of F3 compared to F4 is consistent with the finding that higher polymer concentrations may reduce the hollow cavity volume within microspheres, thereby diminishing buoyancy—an observation noted by Siepmann et al. [26]. The internal hollow core, formed by solvent evaporation during microsphere preparation, is the primary determinant of buoyancy in FDDS [27].

Table 6: Percentage buoyancy of floating microsphere formulations over time

Formulation	1 Hour (%)	2 Hours (%)	3 Hours (%)

F1	95.82	92.18	91.23
F2	94.69	93.65	92.68
F3	96.10	92.36	89.90
F4	93.58	91.59	90.89

3.6 SEM Analysis

Scanning electron microscopy of the optimized formulation F3 revealed predominantly spherical microspheres with smooth surface textures and discrete particle boundaries. The mean particle size observed by SEM (approximately 160 μm) was consistent with sieve analysis data. The internal hollow cavity, responsible for sustained buoyancy, was evident at higher magnifications. These morphological characteristics align with previously reported hollow microsphere structures fabricated using solvent diffusion methods [28]. Surface smoothness in Eudragit RS100-based microspheres has been attributed to the polymer's film-forming properties, which promote uniform coat deposition [29].

3.7 In Vitro Drug Release

Cumulative drug release profiles of all four formulations over 8 hours are presented in Table 7. All formulations demonstrated an initial burst release during the first hour, followed by a progressive, sustained release pattern over 8 hours. The initial burst is attributable to drug adsorbed on the microsphere surface or localized in the outer polymer matrix layer [30].

Formulation F3 achieved the highest cumulative release of 97.89% at 8 hours, while F1, F2, and F4 released 92.39%, 94.25%, and 95.12%, respectively. The controlled-release behavior of Eudragit RS100-based formulations in acidic pH is consistent with the polymer's well-known low permeability at pH 1.2 [31]. The gradually increasing drug release from F3 compared to F4 (1:2 ratio) may be explained by the denser polymer matrix in F4, which restricts diffusion pathways and slightly retards release, whereas F3 at 1:1 ratio provides an optimal matrix porosity for controlled but near-complete drug release within 8 hours. These findings are in agreement with those of Londhe and Mujumdar [32], who demonstrated that Eudragit RS100 at a 1:1 drug-to-polymer ratio produced an ideal balance of sustained release and entrapment efficiency for fluoroquinolone antibiotics.

Table 7: Comparative in vitro drug release profile of formulations F1–F4 in pH 1.2 simulated gastric fluid (% CDR = cumulative drug release)

Time (h)	F1 (% CDR)	F2 (% CDR)	F3 (% CDR)	F4 (% CDR)
0	0	0	0	0
1	16.38	17.55	15.69	16.02
2	27.69	28.62	28.20	21.88
3	41.25	42.16	43.65	44.25
4	55.60	54.69	55.68	52.58
5	68.12	63.86	60.12	68.80
6	73.69	79.89	76.39	76.39
7	82.16	83.48	86.56	82.85
8	92.39	94.25	97.89	95.12

3.8 Stability Studies

The optimized formulation F3 was subjected to stability evaluation under long-term (25°C/60% RH), intermediate (30°C/75% RH), and accelerated (40°C/75% RH) conditions for 90 days. As presented in Table 8, no significant changes in physical appearance or drug release were observed across all storage conditions throughout the study period. The initial drug release of 97.89% was maintained at 25°C, with minor reductions to 96.50% and 95.10% at 30°C and 40°C, respectively, at Day 90. These negligible differences confirm the thermodynamic stability of Eudragit RS100-based microspheres, which is attributable to the polymer's robust film-forming properties and chemical inertness under varied thermal conditions [33]. These findings are consistent with ICH stability guidelines and suggest a shelf life suitable for pharmaceutical development advancement.

Table 8: Stability study data for optimized formulation F3 (Mean % drug release)

S. No.	Day	Physical Change	25°C/60%RH	30°C/75%RH	40°C/75%RH

1	1	No Change	97.89	96.58	95.62
2	60	No Change	97.89	96.97	95.72
3	90	No Change	97.89	96.50	95.10

4. CONCLUSION

The present study successfully demonstrated the formulation and comprehensive evaluation of gastroretentive floating microspheres of levofloxacin using the emulsion solvent diffusion technique. Among the four formulations developed, F3—comprising Eudragit RS100 at a 1:1 drug-to-polymer ratio—emerged as the optimal formulation, exhibiting a mean particle size of 160 µm, drug entrapment efficiency of 82.39%, sustained buoyancy exceeding 3 hours, and a cumulative drug release of 97.89% over 8 hours in pH 1.2 simulated gastric fluid. FTIR analysis confirmed the absence of drug–polymer incompatibilities, and SEM revealed smooth, spherical morphology with intact hollow cores.

Stability studies conducted over 90 days under varied temperature and humidity conditions confirmed the physicochemical stability of formulation F3, with no significant alterations in drug release or physical appearance. These results collectively demonstrate that Eudragit RS100-based floating microspheres represent a viable and effective platform for the gastroretentive controlled delivery of levofloxacin, with potential clinical benefits including enhanced bioavailability, reduced dosing frequency, and improved patient compliance. Future studies should encompass in vivo pharmacokinetic evaluation and scale-up feasibility assessments.

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CONFLICT OF INTEREST

The authors declare no conflict of interest associated with this study.

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