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Development and optimization of a self-microemulsifying drug delivery system (SMEDDS) for lafutidine: enhancing solubility for effective gastric ulcer treatment

Gauri Rajendra Ghone[1], Paresh Ramesh Mahaparale[2*], Mohd Sayeed Shaikh[3*], Rijawan Rajjak Pathan[4], Sonali Paresh Mahaparale[5]

[1]Department of Pharmaceutics, Dr. D Y Patil College of Pharmacy, Pune 411044, India.
[2]Department of Pharmaceutics, Government College of Pharmacy, Karad 431005, India.
[3]Department of Pharmaceutical Chemistry, Y. B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad 431001, India.
[4]Department of Pharmaceutics, B. Pharmacy College, Ambajogai 431517, India.
[5]Department of Pharmaceutical Chemistry, Dr. D. Y. Patil College of Pharmacy, Pune 411044, India.

[*]**Correspondence to:** Paresh Ramesh Mahaparale, Department of Pharmaceutics, Government College of Pharmacy, Masur Rd, Karad 431005, India. E-mail: pareshmahaparale@gmail.com. Mohd Sayeed Shaikh, Department of Pharmaceutical Chemistry, Y. B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Dr. Rafiq Zakaria Marg, Aurangabad 431001, India. E-mail: sdsayeed@ybccpa.ac.in.

Author contributions
Ghone GR: Conceptualization, Investigation, Writing-original draft, Writing-review & editing, Data curation; Mahaparale PR: review & editing, Data Curation, Visualization, Validation, Analysis; Shaikh MS: Writing-review & editing, Data Curation, Visualization, Validation, Analysis; Pathan RR: Writing-review & editing, Formal Analysis, and Data Curation; Mahaparale SP: Formal Analysis, and Data Curation.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
CCD, central composite design; SMEDDS, self-microemulsifying drug delivery system.

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Abstract

Background: This study focused on developing and optimizing a self-microemulsifying drug delivery system (SMEDDS) to improve Lafutidine's solubility and bioavailability, thereby enhancing its effectiveness in treating gastric ulcers. Traditional formulations are less effective due to their limited water solubility and bioavailability. **Methods:** The study used solubility tests, pseudo-ternary phase diagrams, and central composite design (CCD) to optimize. The formulation was optimized by varying the oil concentration (10–40%) and surfactant/cosurfactant ratio (0.33–3.00), and then tested for droplet size, drug content, emulsification, phase stability, and in vitro dissolution. **Results:** The study found that the optimized formulation contained 14% Capmul PG 8NF oil, 62% Labrasol surfactant, and 24% Tween 80 cosurfactant. This combination generated an average droplet size of 111.02 nm and improved drug release properties. Furthermore, the formulation was stable without phase separation, with a drug content of 88.2–99.8%. **Conclusion:** SMEDDS significantly improves lafutidine delivery by increasing solubility and absorption, thereby overcoming oral administration challenges. The system quickly formed small droplets in water and released the drug in 15 min. Enhancing lafutidine's bioavailability may improve its efficacy in treating gastric ulcers, resulting in better patient outcomes and potentially lower dosing frequency.

Keywords: lafutidine; self-microemulsifying drug delivery system (SMEDDS); gastric ulcer treatment; enhancing solubility and bioavailability; Capmul PG 8NF oil

Introduction

Ulcers are open sores on the upper portion of the small intestine and the stomach's inner lining. It affected approximately 5–10% of the population with a lifetime risk [1]. Gastric ulcer is caused by an imbalance between protective and damaging factors. Protecting factors such as the epithelial cell renewal mechanism, and the mucus bicarbonate system protect mucosal cells and prevent damage to epithelial cells due to excessive secreted gastric acid, and prostaglandin also contributes to maintaining the mucus layer in the stomach [2, 3]. Damaging factors are pepsin, gastric acid, and *Helicobacter pylori* (*H. pylori*). Gastric acid is essential for the digestion of food, but excessive secretion leads to damage to the mucus lining. The imbalance between protective and damaging factors causes ulceration [4].

Essential for the treatment of gastric ulcers is to control the secretion of gastric acid. The common treatment for gastric ulceration is the use of H_2 blockers and proton pump inhibitors to control excessive secretion of gastric acid [3]. Drugs used for the treatment of gastric ulcers are histamine H_2 receptor antagonists and proton pump inhibitors. Prolonged use of proton pump inhibitors may cause systemic side effects such as an imbalance in gastric microbiota and nutritional deficiencies [1]. Therefore, the most common and safest treatment is the use of H_2 blockers. Different types of H_2 blockers used for treatment are currently marketed products such as ranitidine, cimetidine, nizatidine, roxatidine, famotidine, and lafutidine [5].

Conventional formulations used for treatment are tablets, capsules, and suspensions. These formulations are limited due to different challenges associated with the intrinsic system of the gastric environment and formulation [6, 7]. The challenges for this formulation for effective treatment of gastric ulceration are short gastric retention of the drug due to fast gastric emptying rate, degradation of the drug in the gastric environment, poor targeted delivery of the drug to the affected site, and systemic side effects of long-term treatment with the drug [7]. To overcome these challenges, formulations with targeted effects with less systemic side effects have been developed for the treatment of gastric ulcers.

In the present study, the lafutidine drug was used for formulation. Lafutidine is a second-generation histamine H_2-receptor antagonist. It shows additional benefits to earlier H_2 antagonistic drugs, such as gastric protection. Lafutidine is available in tablet form and is marketed under various brand names, such as Lafaxid (Zuventus Healthcare Ltd.), Lafudac (Torrent Pharmaceuticals Ltd.), Lafukem (Alkem Laboratories Ltd.), Lafty (Akumentis Healthcare Ltd.), Futaden (Emcure Pharmaceuticals Ltd.), Lafutax (Ajanta Pharma Ltd.), and Lafumac (Macleods Pharmaceuticals Pvt. Ltd.), for the prevention and treatment of gastric ulcers. The mechanism of action of lafutidine is an antagonistic effect on the gastric H_2 receptor on gastric parietal cells, resulting in inhibition of acid secretion. Some researchers also found that it stimulates the release of nitric oxide and prostaglandin, resulting in the protection of the gastric mucosa [8]. Lafutidine also shows a potential role in combination therapy with antibiotics. Although it's not an antibiotic, it creates a feasible environment by reducing gastric acid secretion for an antibiotic effect against *H. pylori.* Research has been carried out on lafutidine in the form of different novel formulations such as gastro-retentive, solid dispersion, oral strip, orally disintegrating tablet, and mucoadhesive formulation for prolonged delivery as well as higher bioavailability drug [7–10]. These formulations have advantages as well as some limitations, such as the issue of permeability of the drug. To overcome this problem, the present study was carried out for the formulation of self-microemulsifying drug delivery systems (SMEDDS) of lafutidine. SMEDDS is a mixture of oil, surfactant, and cosurfactant which is converted into a microemulsion on spontaneous stirring in an aqueous medium such as gastric fluid [11, 12]. This system, used to enhance the bioavailability and permeation rate of lipophilic drugs, belongs to the Biopharmaceutical Classification System (BCS) class II and IV. It bypasses the dissolution step and shows direct absorption of oil-soluble drugs through the gastrointestinal tract. Present research carried out on formulation optimization and evaluation of lafutidine SMEDDS. The study involved the factorial study of the oil phase, surfactant, and cosurfactant, and based on response-optimized formulation, F3* with droplet size distribution found between 100 and 200 nm was selected.

Materials and methods

Materials

The experiments were conducted using high-quality analytical-grade chemicals and reagents sourced from Research Lab Fine Chem and Mollychem Laboratory in Mumbai, India. Lafutidine active pharmaceutical ingredient powder was generously provided by Emcure Pharmaceuticals Ltd. (Pune, India). Additionally, Captex 200 and Capmul PG 8NF were generously provided as gift samples by Abitec Corporation (Janesville, WI, USA), and Labrasol was kindly supplied by Gattefossé Headquarters (Saint-Priest, France). Tween 80 was obtained from Marathon Icon (Mumbai, India).

Solubility studies

Lafutidine's solubility in various oils, surfactants, and cosurfactants was determined using the shake flask method. Excess lafutidine was added separately to vials containing 2 mL of each component, followed by manual mixing for 30 min and sonication for an additional 30 min. The mixtures were then shaken for 6 h with an orbital shaker. After equilibration, the samples were centrifuged at 3,000 rpm for 15 min, allowing any undissolved lafutidine to settle to the bottom. The supernatant was collected, diluted with methanol, and measured with a UV spectrophotometer. Components with the highest solubility were chosen for further investigation [13, 14].

Screening of surfactants for emulsification ability

The emulsification potential of various surfactants was determined by adding 150 mg of surfactant to an equal volume of oily phase. The mixtures were gently heated to 50–60 °C to achieve uniform blending. A 50 mg portion of each mixture was then diluted to 50 mL with distilled water in a stoppered conical flask. Emulsification ease was determined by the number of flask inversions required to form a homogeneous emulsion. After standing for 2 h, the % transmittance of the emulsions was measured at 650 nm using a UV–visible spectrophotometer (Shimadzu, Kyoto, Japan), with distilled water as the blank [15–17].

Screening of cosurfactants for emulsification ability

The selected oily phase and surfactant were used to test various co-surfactants for emulsification ability. Mixtures containing 100 mg co-surfactant, 200 mg Labrasol (surfactant), and 300 mg Capmul PG8 (oil) were heated to 50–60 °C to homogenize. A 50 mg sample of each mixture was diluted to 50 mL with distilled water, and emulsification was determined by the number of flask inversions required to achieve a homogeneous emulsion. After standing for 2 h, the % transmittance at 650 nm was measured using a UV-visible spectrophotometer (Shimadzu, Japan) with distilled water as a blank [15–17].

Construction of pseudo ternary phase diagram

A pseudo-ternary phase diagram is created to determine appropriate components and concentration ranges for a wide microemulsion region. Various surfactant-to-cosurfactant ratios (1:1, 1:2, 1:3, 2:1, and 3:1) were used, with Smix and oil mixed in different proportions (0.1:0.9 to 0.9:0.1) in pre-weighed vials. Distilled water was gradually added to these mixtures until turbidity was reduced to a clear or slightly bluish emulsion. The phase clarity and transmittance were then visually evaluated. The phase diagram was created using the Chemix School Ver. 9 software (MN, USA) [15–17].

Formulation optimization of lafutidine-loaded SMEDDS

Lafutidine-loaded SMEDDS were formulated by dissolving lafutidine in a mixture of oil, surfactant, and cosurfactant while stirring

continuously at room temperature, yielding a clear and transparent solution. The formulation was optimized using central composite design (CCD), with oil percentage and surfactant/cosurfactant ratio identified as key factors influencing SMEDDS properties. The feasible ranges for these parameters were determined using preliminary experiments and previous research. Oil percentage (X1) range 10%–40% and surfactant/cosurfactant ratio (X2) range 0.33–3.00 were used for SMEDDS formulation. Droplet size (Y1) and percent drug release (Y2) were identified as key responses for assessing SMEDDS quality. A two-factor, five-level CCD was used to investigate the main effects and interactions between these factors. The oil percentage and surfactant/cosurfactant ratio were varied as shown in Table 1, and the results were analyzed using classical second-order polynomial models [16–18].

Evaluation of liquid SMEDDS of lafutidine

Ease of emulsification. A 50 mg formulation was precisely weighed and diluted to 50 mL with distilled water to create a fine emulsion. The ease of emulsification was determined by counting the number of flask inversions required for uniformity. The emulsions were visually examined for turbidity and then left undisturbed for 2 h before being measured at 650 nm with a Shimadzu UV-1700 UV-Visible spectrophotometer [19–21].

Phase separation study. A 100 mg sample of each Liquid SMEDDS formulation was placed in a 100 mL volumetric flask and diluted with distilled water to the required volume. After gently inverting the flask 3–4 times, the mixture was stored for 2 h before being visually examined for phase separation [19, 20].

Drug content. A liquid SMEDDS formulation containing 15 mg of lafutidine was added to a 50 mL volumetric flask containing 0.1N HCl and inverted 2–3 times. A suitable portion of the solution was withdrawn, diluted with 0.1N HCl, and analyzed for drug content using a UV spectrophotometer at 650 nm [22, 23].

Globule size determination.

(a) By digital microscope. One milliliter (1 mL) of emulsion was mixed with an equal volume of double-distilled water, and the sample was placed on a glass slide. The mean globule size of the resulting emulsion was then measured using a LABOMED digital microscope.

(b) Instrumental method by Nanophox. A 1 mL emulsion was diluted with 100 mL of double-distilled water. The sample was placed in a transparent polystyrene cuvette (path length = 1 cm) inside a thermostatic chamber set to 25 °C. The mean globule size and polydispersity index were determined using photon cross-correlation spectroscopy (Nanophox, Sympatec, Clausthal-Zellerfeld, Germany). The sample was kept at 25 °C for three 60 s runs with detection at a 90° scattering angle [19, 20].

In vitro dissolution studies. A paddle-type dissolution apparatus (USP XXII) was used to dissolve liquid SMEDDS formulations in vitro. The formulations were encapsulated in size '0' capsules and placed in 900 mL of 0.1N HCl at 37 °C ± 0.5 °C. The paddle speed was set to 50 rpm. 10 mL samples were withdrawn at 15 min intervals and replaced with an equal volume of fresh medium. The samples were analyzed with a Shimadzu UV-1700 spectrophotometer at 650 nm [19, 20].

Results and discussion

The research attempted to develop and optimize an SMEDDS for lafutidine, addressing critical issues in oral drug delivery. Lafutidine, an H_2-receptor antagonist used to treat gastric ulcers, has low water solubility and bioavailability, which limits its therapeutic effectiveness. Conventional formulations face significant challenges such as low gastric retention, rapid drug degradation, and poor targeted delivery. SMEDDS are isotropic and thermodynamically stable mixtures of drug, lipid, and surfactants, usually with one or more hydrophilic cosolvents. This approach offers a promising solution for improving drug absorption through the gastrointestinal tract and lipophilic drug solubility. Using a CCD, we explored two key independent variables: oil percentage (10–40%) and surfactant/cosurfactant ratio (0.33–3.00). The droplet size (Y_{size} = 5.40 + 1.15A – 0.10B) showed a direct relationship between oil percentage and globule size, and an inverse relationship with surfactant/cosurfactant ratio. The drug release ($Y\%_{release}$ = 92.86 + 3.67A + 0.74B) showed that both variables had a positive influence on lafutidine release performance. The optimized formulation (F5) emerged as the most promising, achieving a remarkable globule size of 111.02 nm and superior lafutidine release characteristics. This method addresses the primary challenges of oral lafutidine administration by developing a microemulsion system that forms small droplets in water, thereby improving drug solubility, absorption, and bioavailability.

Solubility studies

Solubility studies were carried out to determine the optimal solubility of lafutidine for selecting the appropriate oil phase, surfactant, and cosurfactant to create a stable formulation. Because SMEDDS should prevent drug precipitation in the gastrointestinal tract, lafutidine must be soluble in all excipients [24]. The solubility analysis revealed that Capmul PG8 (190.7 mg/mL) and Peceol (144.5 mg/mL) had the highest drug solubility capacity among the oils (Figure 1). Labrasol (71.73 mg/mL) and Tween 80 (101.01 mg/mL) were the surfactants with the highest solubility (Figure 2). As a result, Capmul PG8, Labrasol, and Tween 80 were chosen as the oil phase, surfactant, and cosurfactant for the formulation of lafutidine's SMEDDS.

Table 1 Factor level and the corresponding values

Factors	Levels				
	–α	–1	0	1	+α
Oil percentage	10	14.40	25	35.60	40
Surfactant/cosurfactant ratio	0.33	0.72	1.66	2.60	3

(α = 1.414)

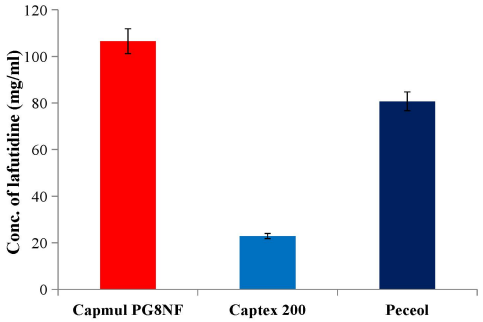

Figure 1 Solubility of lafutidine in different oils

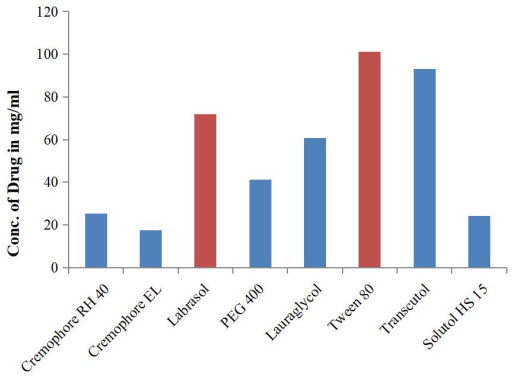

Figure 2 Solubility of lafutidine in different surfactants and cosurfactants

Screening of surfactants for emulsification ability

Based on the solubility analysis, three oils and three surfactants were chosen for further testing. Surfactants needed to be effective emulsifiers as well as drug solubilizers. As a result, the three selected surfactants were evaluated for their emulsification efficiency with three different oils. Nine surfactant-oil combinations were tested for ease of emulsification and percentage transmittance (Table 2). Following the emulsification screening, the combination of Peceol (oil) with Labrasol (surfactant) and Capmul PG8 (oil) with Labrasol (surfactant) had the highest transmittance. As a result, these two combinations were selected for further investigation.

Screening of co-surfactants for emulsification ability

According to preliminary surfactant screening, Peceol and Capmul PG8 were identified as suitable oils, with Labrasol selected as the surfactant for developing the SMEDDS formulation. Three cosurfactants were chosen based on previous solubility studies. In the emulsification study, six different cosurfactant combinations were tested using the flask inversion method, and their percent transmittance was recorded. The combination of Capmul PG8 (oil), Labrasol (surfactant), and Tween 80 (cosurfactant) emulsified in only 4–5 flask inversions and had the highest transmittance (94.7%) (Table 3).

Construction of pseudo-ternary phase diagrams

A pseudo-ternary phase diagram is constructed to evaluate the self-emulsification potential within an optimal range of oil phase, surfactant, and cosurfactant by gradually adding distilled water. This research contributes to the determination of the appropriate water, oil phase, surfactant, and cosurfactant concentrations required to form a stable microemulsion. Figure 3 shows the phase behavior of Capmul PG8 and a surfactant-cosurfactant mixture containing Labrasol and Tween 80 in various ratios (1:1, 1:2, 1:3, 2:1, and 3:1) (Table 4). The pseudo-ternary phase diagrams for 1:1, 1:2, 2:1, and 3:1 ratios show a coarser emulsion region and a smaller microemulsion region, implying that a larger surfactant mixture is required for stabilization. The 1:3 ratio exhibits the largest microemulsion region, indicating that a higher concentration of the cosurfactant Tween 80 is required to stabilize the microemulsion's interfacial film. Cui et al. (2009) investigated the effect of different surfactants on self-emulsifying microemulsions and found that Labrasol alone was a weak emulsifier when compared to others [25]. Their findings revealed that a co-surfactant is required for a stable self-emulsifying microemulsion. The optimal ratio was found to be 1:3, resulting in a larger microemulsion region. However, observations revealed that microemulsions with higher oil content were turbid and unstable. Based on these findings, the study concluded that an oil percentage of 10–40% and a surfactant-to-cosurfactant ratio of 0.33–3.00 are critical for optimizing SMEDDS formulations (Figure 3). The current SMEDDS-based approach made use of Capmul PG8, Labrasol, and Tween 80, which had a higher solubilizing potential for lafutidine (190.7 mg/mL, 71.73 mg/mL, and 101.01 mg/mL, respectively), ensuring efficient drug incorporation and microemulsion stability. Fule et al. used Soluplus® and Lutrol-grade surfactants (PEG 400, F127, F68) for solid dispersion, which improved dissolution but required a high energy input and resulted in amorphous dispersions that were susceptible to recrystallization risks [8]. Meanwhile, the taste-masked granules used a combination of ethylcellulose and hypromellose polymers to control release but lacked any solubilizing or emulsifying excipients, limiting solubility enhancement to dissolution kinetics [10].

Formulation optimization of lafutidine-loaded SMEDDS

CCD was used to optimize the oil content and surfactant/cosurfactant ratio for lafutidine self-emulsifying microemulsion drug delivery. The droplet size and drug release profile were used as dependent variables (responses). Table 4 summarizes the experimental findings of CCD, with the corresponding equations presented below.

$$Y_{SIZE} = 4.95665 + 0.165181A - 1.95044B + 0.045413AB - 0.003471A^2 - 0.059416B^2 \quad (r^2 = 0.9890, P < 0.0001) \tag{1}$$

$$Y\%_{release} = 93.05338 + 0.168397A + 1.97602B - 0.007276AB - 0.010063A^2 - 0.244030B^2 \quad (r^2 = 0.9607, P < 0.0001) \tag{2}$$

ANOVA results showed that model terms A and B were significant ($P < 0.05$), indicating that the oil percentage and surfactant/cosurfactant ratio had a significant impact on droplet size and drug release percentage. The droplet size equation indicates that the oil percentage has a greater impact on droplet size than the surfactant/cosurfactant ratio. Furthermore, the final equation revealed a positive coefficient for oil percentage, indicating a direct correlation with droplet size, while the surfactant/cosurfactant coefficient was negative, indicating an inverse relationship with droplet size (Figure 4).

The independent variable's influence on the responses was investigated, and the surfactant-to-cosurfactant ratio and percentage of the oil phase were found to have a significant impact. The effect of the surfactant-to-cosurfactant ratio was investigated using a 3D response surface curve, which revealed that as the surfactant concentration increased, droplet size decreased. A lower surfactant-to-cosurfactant ratio caused larger droplet sizes in the emulsion. Formulation F1, with a surfactant-to-cosurfactant ratio of 0.72, produced droplets measuring 6.1 ± 0.02 µm. Droplet size decreased with increasing concentration, with F5 (ratio 1.66) at 3.28 ± 0.008 µm and F3 (ratio 2.6) at 2.93 ± 0.009 µm. The response surface curve analysis revealed that droplet size is significantly influenced not only by the surfactant-to-cosurfactant ratio, but also by oil phase concentration. A decrease in the oil phase concentration reduces the size of the microemulsion's droplets. Although formulations F1 and F2 had the same surfactant-to-cosurfactant ratio of 0.72, the oil phase concentrations were different, with F1 containing 14.4% and F2 containing 35.6%. The resulting microemulsions had droplet sizes of 6.1 ± 0.02 and 6.29 ± 0.013, respectively. The observed increase in droplet size was attributed to increased oil phase concentration. A similar effect was observed in the

Table 2 Emulsification ability of different surfactants

Sr. No.	Oil	Surfactant	No. of flask inversions		Transmittance (%)	
			Batch A	Batch B	Batch A	Batch B
1	Peceol	Cremophor RH40	6	7	61.8	62.2
2	Peceol	Cremophor EL	10	9	53.8	55.7
3	Peceol	Labrasol	3	4	99.4	98.5
4	Capmul PG8	Cremophor RH40	9	10	28.6	29.9
5	Capmul PG8	Cremophor EL	12	13	29.7	29.2
6	Capmul PG8	Labrasol	4	5	97.4	97.6
7	Captex 200	Cremophor RH40	6	7	83.1	83.8
8	Captex 200	Cremophor EL	9	10	92.2	92.4
9	Captex 200	Labrasol	5	6	51.7	52.5

Table 3 Emulsification ability of different cosurfactants

Sr. No.	Oil	Surfactant	Cosurfactant	No. of flask inversions		Transmittance (%)	
				Batch A	Batch B	Batch A	Batch B
1			Tween 80	4	5	94.0	94.7
2	Capmul PG8	Labrasol	Lauroglycol	9	10	18.8	19.3
3			Transcutol	10	11	41.2	41.6
4			Tween 80	11	10	14.9	15.6
5	Peceol	Labrasol	Lauroglycol	9	10	12.1	12.2
6			Transcutol	10	12	5.8	6.2

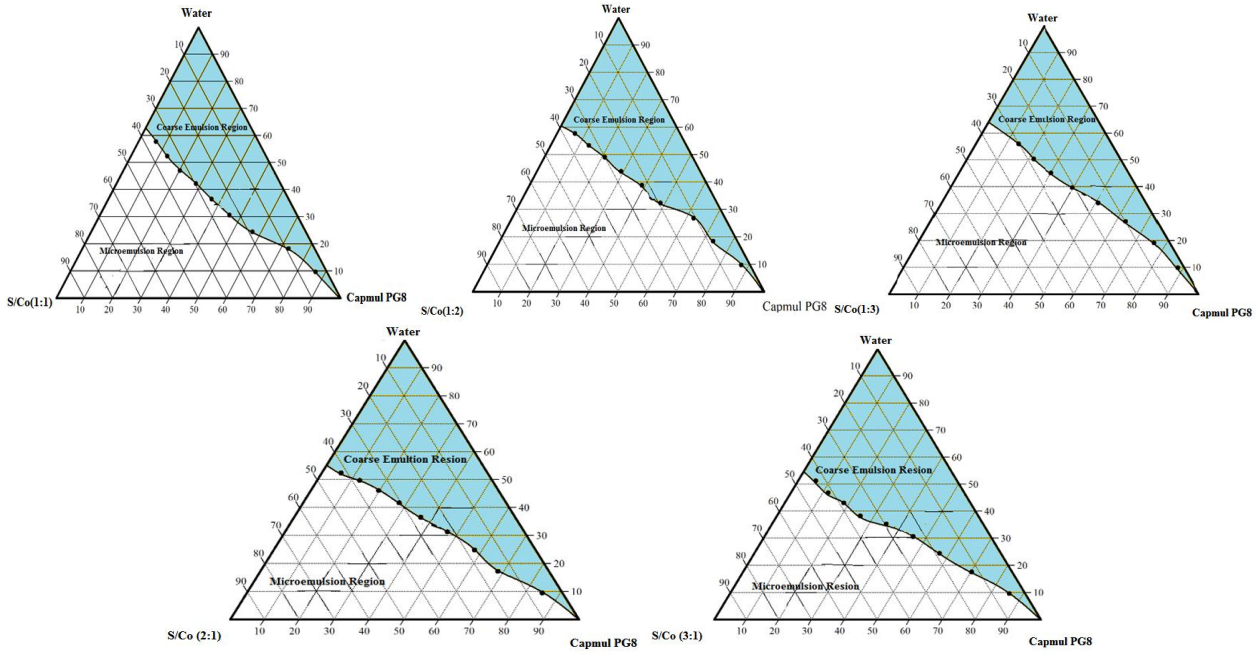

Figure 3 Ternary phase diagram of Capmul PG8 with ratios of Labrasol and Tween80

Table 4 Composition of lafutidine-based SMEDDS

Sr. No.	Oil (%)	Surfactant/Cosurfactant	Oil (mg)	Surfactant (mg)	Cosurfactant (mg)	Lafutidine (mg)
F1	14.4	0.72	10	56	34	10
F2	35.6	0.72	36	27	37	10
F3*	14.4	2.6	25	56	19	10
F4	35.6	2.6	14	37	49	10
F5	10.01	1.66	14	62	24	10
F6	39.99	1.66	25	19	56	10
F7	25.0	0.33	36	46	18	10
F8	25.0	2.99	40	37	23	10
F9–F13	25.0	1.66	25	47	28	10

F3* optimized formulation batch of SMEDDS. SMEDDS, self-microemulsifying drug delivery system.

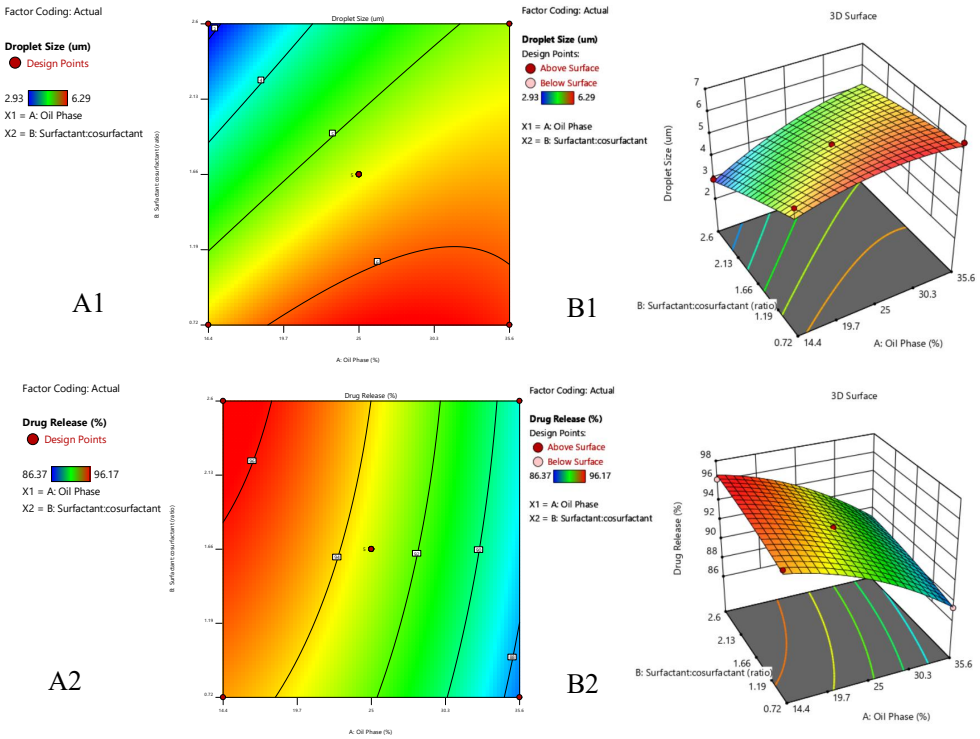

Figure 4 Response surfaces for (a) droplet size and (b) % drug release.
(A1) Contour plot of oil phase and surfactant-to-co-surfactant ratio on droplet size; (B1) 3D response plot of oil phase and surfactant-to-co-surfactant ratio on droplet size; (A2) Contour plot of oil phase and surfactant-to-co-surfactant ratio on percentage drug release; (B2) 3D response plot of oil phase and surfactant-to-co-surfactant ratio on percentage drug release.

formulations F3 and F4, with a surfactant-to-cosurfactant ratio of 2.6, produced droplet sizes of 2.93 ± 0.009 and 4.93 ± 0.011, respectively. These variations were attributed to increased oil concentration, which resulted in the formation of an interfacial film. However, at lower surfactant concentrations, film formation was less effective. In formulations F5 and F6, droplet sizes were 3.28 ± 0.008 and 5.75 ± 0.006, respectively, with a surfactant-to-cosurfactant ratio of 1.66 and oil phase percentages of 10% and 39%. This means that when the surfactant/cosurfactant ratio is constant, an increase in oil concentration causes an increase in droplet size.

The percentage drug release study found that a lower oil concentration combined with a higher surfactant ratio increased drug release from the microemulsion. Formulation F6, with the highest oil concentration, showed the lowest drug release at 86.37 ± 1.15%. Formulations with lower oil concentrations, such as F3 and F5, with 14.4% and 10% oil phase, respectively, exhibited the highest drug release (96.15 ± 1.24% and 96.17 ± 1.52%). Increasing surfactant concentration improved drug release, as seen in formulation F3, where a ratio of 2.66 resulted in 96.15 ± 1.24. A lower surfactant concentration in formulation F2, with a ratio of 0.72, resulted in a reduced drug release of 87.34 ± 0.57. Optimization studies revealed that the optimal oil phase concentration and surfactant-cosurfactant ratio for the optimized formulation F3 were 14.4 and 2.6, respectively. The formulation had a droplet size of 2.93 ± 0.009 and drug release of 96.15 ± 1.24. These findings are consistent with those reported by Zhao et al., who discovered that lower oil phase concentrations combined with higher surfactant and cosurfactant concentrations resulted in smaller droplet sizes in apigenin-loaded SMEDDS [26].

Evaluation of SMEDDS of lafutidine

Ease of emulsification, phase separation study, drug content determination. The transmittance study found that increasing surfactant concentration resulted in higher transmittance in the emulsions. A UV spectrophotometer was used to determine emulsification efficiency or rate of emulsion formation (Table 5). All formulations remained stable in distilled water for 2 h with no signs of phase separation (Table 5), indicating their suitability for further testing. The drug content of all formulations ranged from 88.2% to 99.8%, with formulation F5 having the highest at 99.8% (Table 5).

Droplet size determination. By digital microscope: the droplet size of a microemulsion is an important factor in determining drug release and bioavailability. A smaller droplet size leads to a larger interfacial surface area, which improves drug absorption [27]. Furthermore, the size of the emulsion droplets influences the rate and extent of drug release. A smaller droplet size increases the available surface area, which promotes better drug absorption. The droplet sizes of all nine formulations were measured using microscopy, as shown in Table 5. It was discovered that the concentration of surfactant and the surfactant-to-cosurfactant ratio had a significant impact on droplet size, with an increase in surfactant concentration resulting in a decrease.

Formulation F1 had a surfactant-to-cosurfactant ratio of 0.72, with droplets measuring 6.1 ± 0.02 µm. It was found that as the concentration increased, the droplet size decreased. Formulation F5, with a surfactant-to-cosurfactant ratio of 1.66, showed a smaller droplet size of 3.28 ± 0.008 µm, whereas F3, with a ratio of 2.6, showed a droplet size of 2.93 ± 0.009 µm. The percentage of oil in the formulation also had an effect on droplet size. Although F1 and F2 had the same surfactant-to-cosurfactant ratio of 0.72, their oil percentages differed, with F1 containing 14.4% and F2 containing 35.6%. The difference produced microemulsions with droplet sizes of 6.1 ± 0.02 µm and 6.29 ± 0.013 µm, respectively. The larger droplet size was attributed to the higher oil phase concentration. It was observed that keeping the surfactant/cosurfactant ratio constant while increasing the oil percentage resulted in larger droplet sizes. The droplet sizes for formulation batches F3*, F4, and F5 were 2.93 ± 0.009, 4.93 ± 0.011, and 3.28 ± 0.008, respectively. Cui et al. reported a similar trend in vinpocetine SMEDDS, demonstrating that as the surfactant concentration increased, droplet size decreased [25].

By Nanophox: after measuring droplet size with a digital microscope, the optimized batch with the smallest droplets from formulation F3 was examined further with Nanophox (Figure 5). The

analysis revealed that the droplet size distribution ranged from 100 to 200 nm.

In vitro dissolution study: Figure 6 shows that the SMEDDS formulation F5 released significantly more TFV than the other formulations. According to the observation table, both F5 and F8 demonstrated superior lafutidine release, 96.17 ± 0.52% and 94.97 ± 0.21% respectively, indicating that increasing the oil percentage improves drug release. In addition, increasing the surfactant-to-cosurfactant ratio while maintaining a constant oil percentage improved drug release. This can be attributed to a reduction in droplet size with a higher surfactant-to-cosurfactant ratio, which results in a larger effective surface area and allows for faster drug transfer from the oil phase to the aqueous phase. A comparison with previous studies demonstrates the superiority of the developed SMEDDS formulation for lafutidine. The floating microsphere approach improved gastric retention and sustained release, but resulted in larger particle sizes (3.78–10.62 µm) and delayed action due to swelling and buoyancy development [28]. Meanwhile, taste-masking granules in orally disintegrating tablets sought to improve palatability and rapid onset, but were limited to immediate release after a dissolution lag time and lacked solubility enhancement features [10]. In contrast, the optimized SMEDDS system in the current study provided a significant advantage by producing nano-sized droplets (111.02 nm), rapid emulsification, and over 96% drug release within 15 min, with no lag or floatation required. Furthermore, SMEDDS addressed lafutidine's solubility and permeability limitations, resulting in improved bioavailability and potentially lower dosing frequency, establishing it as a more effective and patient-friendly option for gastric ulcer therapy.

Conclusion

This study optimized an SMEDDS formulation of lafutidine to improve oral drug delivery for gastric ulcer treatment. Using CCD, the ideal formulation consisted of 14% Capmul PG 8NF, 62% Labrasol, and 24% Tween 80. This composition exhibited outstanding performance characteristics, including rapid spontaneous emulsification, excellent stability, and consistent drug content ranging from 88.2% to 99.8%. The optimized formulation produced impressive average droplet sizes of 111.02 nm, which is critical for increased absorption and bioavailability. In vitro dissolution studies revealed rapid drug release within 15 min, significantly faster than conventional formulations. Compared to previously reported formulations, the developed SMEDDS for lafutidine showed superior solubility enhancement and therapeutic efficacy. The floating microspheres provided gastric retention but had limited solubility enhancement and a slower release time [28]. Solid dispersion via hot melt extrusion improved dissolution but introduced stability and scalability issues [8]. The taste-masked ODT granules improved patient compliance but had no significant solubilizing effect [10]. In contrast, our optimized SMEDDS achieved rapid emulsification, nano-sized droplets (111.02 nm), and over 96% drug release in just 15 min. This system ensures increased lafutidine solubility and bioavailability, making it a promising option for gastric ulcer treatment by forming fine microemulsions in aqueous media for improved therapeutic efficacy.

Table 5 Ease of emulsification, phase separation, and drug content (%) of lafutidine-based SMEDDS

Formulation	Oil phase (%)	Surfactant: cosurfactant ratio	Droplet size (µm)	Drug release (%)	Transmittance (%)	Phase separation	Drug content (%)
F1	14.4	0.72	6.10 ± 0.02	94.97 ± 1.04	98.7	No	96.2 ± 1.04
F2	35.6	0.72	6.29 ± 0.013	87.34 ± 0.57	87.9	No	99.3 ± 1.51
F3*	14.4	2.6	2.93 ± 0.009	96.17 ± 1.24	98.7	No	97.8 ± 1.27
F4	35.6	2.6	4.93 ± 0.011	88.25 ± 0.79	98.8	No	93.2 ± 1.22
F5	10.01	1.66	3.28 ± 0.008	96.17 ± 0.52	99.6	No	99.8 ± 0.98
F6	39.99	1.66	5.75 ± 0.006	86.37 ± 1.15	99.5	No	88.2 ± 0.94
F7	25.0	0.33	6.28 ± 0.021	91.23 ± 1.20	96.4	No	96.8 ± 1.4
F8	25.0	2.99	4.10 ± 0.019	94.97 ± 0.21	97.9	No	97.8 ± 1.29
F9–F13	25.0	1.66	5.40 ± 0.014	93.28 ± 0.59	99.1	No	90.2 ± 0.98

F3* optimized formulation batch of SMEDDS. SMEDDS, self-microemulsifying drug delivery system.

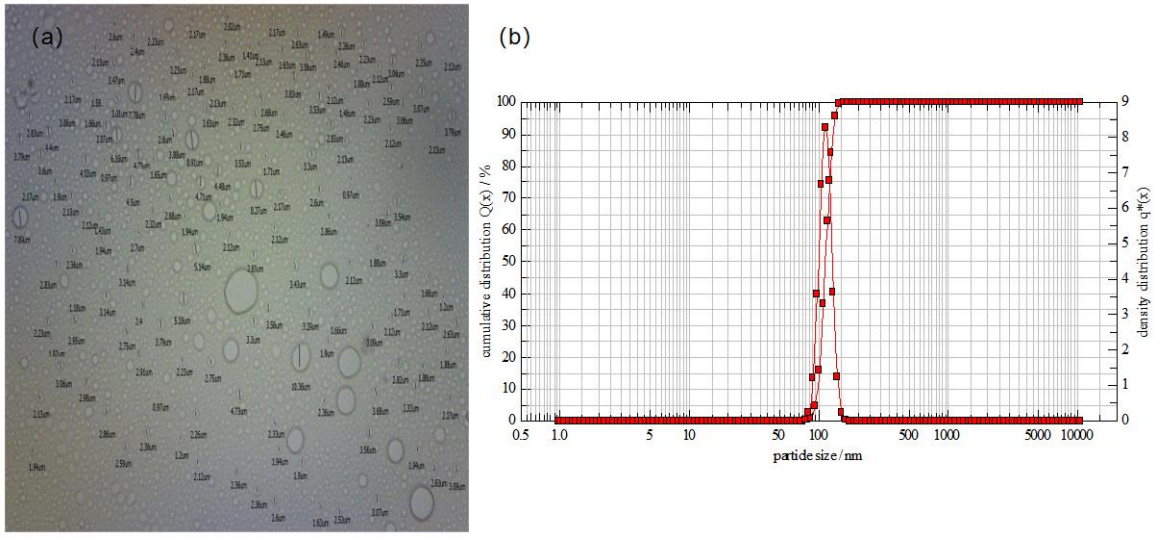

Figure 5 Microscopic characterization of F3 formulation batch. (a) Microscopy of F3; (b) Droplet size graph of Formulation F3.

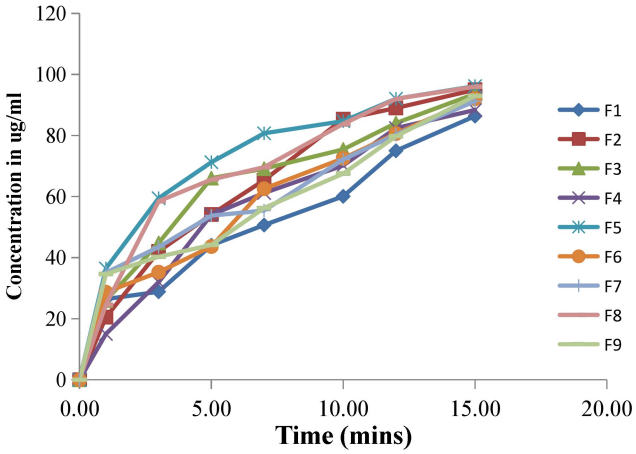

Figure 6 Dissolution profile of liquid SMEDDS. SMEDDS, self-microemulsifying drug delivery system.

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