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Innovative SMEDDS Design for Selexipag: Boosting Solubility and Dissolution Efficiency

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Abstract: Selexipag (SeLx), a selective prostacyclin receptor agonist for pulmonary arterial hypertension (PAH), suffers from poor aqueous solubility, leading to limited oral bioavailability and variable therapeutic response. To overcome this challenge, a self-microemulsifying drug delivery system (SMEDDS) was designed and optimized using a simplex centroid mixture design. Nine formulations were developed by varying composition of oil (Capryol 90, X1: 10–15%), surfactant (Cremophor EL, X2: 55–65%), and co-surfactant (Transcutol HP, X3: 25–30%), followed by systematic evaluation of critical quality attributes (CQAs) such as self-emulsification time (R1), drug release at 30 min (R2), and globule size (R3). The formulations exhibited rapid self-emulsification (21–33 s), high drug release (83.89–93.81% within 30 min), and nanoscale globules (16.63–143.5 nm). Overlay plot analysis identified an optimized composition (X1 = 13.3%, X2 = 58.3%, X3 = 28.3%) that demonstrated superior performance with rapid emulsification (23 s), enhanced drug release (91.32%), nanosized globules (38.56 nm), and stable zeta potential (−12.8 mV), confirming colloidal stability upon dilution. The optimized SeLx-SMEDDS markedly improved dissolution and stability, offering a promising strategy to enhance the solubility, absorption, and ultimately oral bioavailability of SeLx. Improved dissolution is expected to translate into enhanced bioavailability and ultimately improved therapeutic efficacy, making this formulation approach clinically meaningful.

KEYWORDS: Selexipag, pulmonary arterial hypertension, SMEDDS, simplex centroid mixture design, dissolution enhancement

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1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive, and life-threatening cardiovascular disorder characterized by abnormal remodeling of the pulmonary vasculature, leading to elevated pulmonary arterial pressure (PAP) and increased pulmonary vascular resistance (PVR) (Galiè et al., 2016; Richter et al., 2016). If left untreated, the disease culminates in right ventricular hypertrophy, heart failure, and premature mortality (Bruderer et al., 2017; Schermuly et al., 2011). Clinically, PAH is classified under Group 1 pulmonary hypertension and is defined by a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest, pulmonary arterial wedge pressure (PAWP) ≤15 mmHg, and PVR >3 Wood units in the absence of significant parenchymal or thromboembolic pathology (Galiè et al., 2016). The global prevalence of PAH is estimated at 15–50 cases per million, with a higher incidence among females and individuals carrying genetic mutations such as BMPR2 (Anderson & Lau, 2022). Although rare, PAH imposes a disproportionate burden on healthcare systems, patient quality of life,

and socioeconomic resources, underscoring the need for novel therapeutic and formulation-based interventions.

The pathophysiology of PAH is multifactorial, involving endothelial dysfunction, dysregulated vascular tone, inflammatory signaling, and excessive proliferation of pulmonary artery smooth muscle cells (Humbert & Ghofrani, 2016; Tuder et al., 2013). A pathological imbalance between vasodilatory mediators (e.g., prostacyclin, nitric oxide) and vasoconstrictive/mitogenic mediators (e.g., endothelin-1, thromboxane A2, serotonin) drives progressive vascular remodeling. Advances in molecular pharmacology have identified the prostacyclin, endothelin, and nitric oxide pathways as critical therapeutic drug targets (Bruderer et al., 2017; Richter et al., 2016; Zhao et al., 2024). Current pharmacotherapies, including prostacyclin analogues (e.g., epoprostenol, treprostinil), endothelin receptor antagonists (e.g., bosentan, ambrisentan), and phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil) are employed either as monotherapy or in combination to improve hemodynamics, delay progression, and extend survival (Anderson & Lau, 2022). Despite these advances, PAH remains incurable, and median survival continues to be significantly lower than in the general population, emphasizing the urgent need for optimized treatment strategies.

Among prostacyclin pathway modulators, Selexipag (SeLx) has emerged as a next-generation therapeutic. It is the first orally available, non-prostanoid, selective prostacyclin receptor (IP receptor) agonist, specifically designed to overcome the limitations of traditional prostacyclin analogues (Panagiotidou et al., 2021; Wang et al., 2024). Unlike prostacyclin derivatives, SeLx possesses a non-prostanoid chemical structure that confers greater receptor selectivity and stability while reducing off-target activity at EP and TP receptors (Wang et al., 2024). Following oral administration, SeLx undergoes rapid hydrolysis by carboxylesterases to yield its active metabolite, ACT-333679, which demonstrates high potency and a prolonged half-life at the IP receptor (Kaufmann et al., 2015). Through selective receptor activation, SeLx induces vasodilation, inhibits vascular smooth muscle proliferation, and exerts anti-remodeling effects (Park et al., 2025). Clinical efficacy was firmly established in the landmark GRIPHON trial, which showed that SeLx significantly reduced the composite risk of disease progression and hospitalization while improving functional outcomes in PAH patients (Duggan et al., 2017; Galiè et al., 2022; Hardin & Chin, 2016). Based on these findings, SeLx has been incorporated into PAH treatment guidelines, with recommended dosing starting at 200 µg twice daily and titration up to 1600 µg twice daily depending on tolerability (Name Maryann Gordon & Garnett, 2015).

Despite these therapeutic advantages, SeLx exhibits notable biopharmaceutical limitations that compromise its oral effectiveness. Classified as a Biopharmaceutics Classification System (BCS) Class II drug, SeLx has high permeability but poor aqueous solubility (Alwan & Rajab, 2021). Its slow dissolution in gastrointestinal fluids results in incomplete absorption, variable plasma concentrations, and interpatient variability in therapeutic response. These issues are further complicated by dose-dependent gastrointestinal adverse effects (e.g., nausea, diarrhea, abdominal pain), which restrict higher dosing and may lead to suboptimal exposure (Asaki et al., 2015; Kaufmann et al., 2015; *Uptravi® (Selexipag) Prescribing Information. Actelion Pharmaceuticals US Inc.; 2023.*, s. d.). Enhancing the solubility and dissolution rate of SeLx is therefore essential to maximize therapeutic efficacy, reduce variability, and improve patient outcomes.

Several formulation strategies have been explored to address aforementioned challenges. Nanotechnology-based approaches have demonstrated considerable potential. For instance, SeLx nanocrystals prepared via solvent–antisolvent precipitation with ultrasonication exhibited markedly enhanced dissolution, compared to raw drug (Alwan & Rajab, 2021). Similarly, nanosuspensions stabilized with polymers such as Soluplus® achieved complete drug release within 60 min (Alwan & Rajab, 2021). Mesoporous silica nanoparticles (e.g., SBA-15 systems) have been shown to improve dissolution through nanoconfinement and amorphization (Attia & Ghazy, 2023), while nanoemulsion formulations provided nanoscale droplets with rapid release and improved bioavailability in preclinical models (Patel & Kiritkumar Patel, s. d.). Collectively, these studies highlight the promise of nanotechnology-enabled systems, although concerns regarding scalability, cost, and long-term stability limit their widespread clinical translation. Although several nanotechnology-based strategies have been investigated to enhance the dissolution of SeLx,

many of these systems rely on complex fabrication processes, high-energy inputs, or specialized materials that may limit scalability, reproducibility, and long-term physical stability. Moreover, such approaches often prioritize dissolution enhancement without adequately addressing manufacturability and clinical translatability, which are critical for chronic diseases such as PAH. In this context, lipid-based delivery systems, particularly self-micro-emulsifying drug delivery systems (SMEDDS), offer a pragmatic alternative by combining effective solubilization with formulation simplicity, industrial feasibility, and established regulatory acceptance. Despite the widespread application of SMEDDS for BCS Class II drugs, their systematic development and optimization for SeLx have not yet been reported, highlighting a clear and clinically relevant formulation gap.

Self-micro emulsifying drug delivery systems (SMEDDS) represent an especially attractive alternative for overcoming solubility-limited absorption. SMEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine, thermodynamically stable microemulsions upon exposure to gastrointestinal fluids. These formulations generate droplets typically below 100 nm, thereby enhancing solubilization of poorly water-soluble drugs and bypassing the dissolution step required for absorption of BCS Class II compounds (Pandey & Kohli, 2017). In addition to improving dissolution, SMEDDS reduce inter- and intra-patient variability, minimize food effects, and enhance lymphatic transport. The success of SMEDDS in marketed formulations including Neoral® (cyclosporine A), Fortovase® (saquinavir), and Agenerase® (amprenavir) demonstrates their clinical viability (Porter et al., 2008). Furthermore, numerous studies with poorly soluble molecules such as tolvaptan, simvastatin, pioglitazone, and candesartan confirm that SMEDDS significantly enhance dissolution, systemic exposure, and therapeutic efficacy compared with conventional formulations (Emad et al., 2023; Kang et al., 2004; Lee & Lee, 2022; Nekkanti et al., 2010). While nanocrystals, nanosuspensions, and mesoporous carriers show promise, their scalability and stability remain major hurdles. In contrast, SMEDDS combine simplicity in manufacturing, reproducibility in performance, and clinical translatability, making them an ideal platform for SeLx delivery. However, no comprehensive study has yet reported the systematic design and optimization of a SeLx-loaded SMEDDS to overcome its dissolution-limited oral absorption.

The present study therefore aims to develop and evaluate a SeLx-loaded SMEDDS with the objective of enhancing its dissolution rate. By employing systematic formulation optimization, characterization, and dissolution testing, this investigation seeks to establish a novel and clinically relevant approach to SeLx delivery. Successful development of such a system could reduce interpatient variability, mitigate side effects associated with higher doses, and ultimately improve therapeutic outcomes in the management of pulmonary arterial hypertension.

2. MATERIALS AND METHODS

Selexipag (Mw: 441.49 g mol^{-1}; purity > 98%) was provided as a gift sample by Alembic Pharmaceuticals Ltd. (Vadodara, India). Capryol 90 (0.92 g cm^{-3}), Labrafac Lipophile WL 1349 (0.93 g cm^{-3}), and Labrasol ALF (1.03 g cm^{-3}) were procured from Gattefossé Pvt. Ltd. (Mumbai, India). Miglyol® 812 (0.95 g cm^{-3}) was obtained from Fagron (India), while Captex® 200P (0.929 g cm^{-3}) was purchased from ABITEC Corporation (USA). Olive oil (0.91 g cm^{-3}) and castor oil (0.96 g cm^{-3}) were supplied by BASF India Ltd. (Mumbai, India). Cremophor® EL (1.05 g cm^{-3}) was sourced from Oryn Healthcare LLP (Ahmedabad, India). Polysorbates, including Tween® 20 (1.1 g cm^{-3}) and Tween® 80 (1.06 g cm^{-3}), along with polyethylene glycol 400 (PEG 400; 1.13 g cm^{-3}), were purchased from Sigma-Aldrich (St. Louis, USA). Propylene glycol (1.04 g cm^{-3}) was obtained from Loba Chemie Pvt. Ltd. (Mumbai, India), while Transcutol® HP (1.07 g cm^{-3}) was procured from Gattefossé Pvt. Ltd. (Mumbai, India). All chemicals and solvents used were of analytical grade and employed as received without further purification.

2.1. Solubility Studies in Various Vehicles

The solubility of SeLx, was evaluated in various oils, surfactants, and co-surfactants to identify suitable excipients for formulation development. An excess quantity of SeLx was added to 1 mL of each selected vehicle contained in screw-capped glass vials. The mixtures were subjected to agitation in an orbital shaker at 25 ± 1 °C for 48 h to facilitate equilibrium

solubilization. After equilibration, the samples were centrifuged at 3000 rpm for 15 min, and the undissolved drug was separated by filtration using a 0.45 µm membrane filter. The concentration of dissolved SeLx in the clear supernatant was quantified spectrophotometrically at the predetermined λmax (306 nm) as reported previously (Panchal et al., 2025). The UV spectrophotometric method showed linearity at 306 nm with a regression equation of ($y = 0.0349x + 0.0171$) and correlation coefficient ($R^2 = 0.9932$).

2.2. Construction of Pseudo-ternary Phase Diagram

Based on the solubility screening results, Capryol 90 was selected as the lipid phase due to its superior solubilizing capacity for SeLx, while Cremophor EL and Transcutol HP were employed as surfactant and co-surfactant, respectively. To delineate the self-micro emulsifying region, pseudo-ternary phase diagrams were established using the aqueous titration method at 25 ± 1 °C. Binary blends of surfactant and co-surfactant (S_{mix}) were prepared at different weight ratios (S_{mix} = 1:1, 1:2, 1:3, 2:1, and 3:1). Each S_{mix} was combined with Capryol 90 at weight ratios ranging from 1:9 to 9:1 to generate a wide compositional matrix. The mixtures were subjected to dropwise titration with double-distilled water under continuous magnetic stirring (200 rpm) at room temperature until equilibrium was reached. The resulting dispersions were visually inspected and classified as clear isotropic microemulsions, turbid emulsions, or phase-separated systems. Pseudo-ternary phase diagrams were constructed by assigning oil, S_{mix}, and water as the three vertices using ProSim Ternary Diagram software (ProSim, France). The self-microemulsifying domain was delineated graphically, and formulations exhibiting spontaneous emulsification, optical clarity, and thermodynamic stability were considered suitable for further optimization of SeLx-loaded SMEDDS(Vlaia et al., 2021).

2.3. Formulation of Selexipag-Loaded SMEDDS

Based on preliminary solubility screening and pseudo-ternary phase diagram (PTPD) analysis, the most suitable excipients were identified and employed for the development of SMEDDS containing SeLx. The optimized formulation consisted of Capryol 90 (oil phase), Cremophor EL (surfactant), and Transcutol HP (co-surfactant).

Table 1. Independent variables and their concentration levels for simplex centroid mixture design

Factor	Component	Low Level (%)	High Level (%)
X_1	Oil (Capryol 90)	10	15
X_2	Surfactant (Cremophor EL)	55	60
X_3	Co-surfactant (Transcutol HP)	25	30

Table 2. Experimental layout of SeLx SMEDDS batches using simplex centroid mixture design

Batch no.	Amount of oil (%)	Amount of surfactants (%)	Amount of co-surfactant (%)
B1	10.00	60.00	30.00
B2	13.33	58.33	28.33
B3	15.00	57.50	27.50
B4	12.50	60.00	27.50
B5	10.00	60.00	30.00
B6	15.00	55.00	30.00
B7	12.50	57.50	30.00
B8	15.00	60.00	25.00
B9	15.00	55.00	30.00

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Precisely weighed quantity of SeLx and the excipients were transferred into borosilicate vials according to the predetermined ratios. The mixture was subjected to gentle magnetic stirring (200 rpm, 25 ± 1 °C), followed by vortex homogenization, until a clear, homogeneous, and isotropic system was obtained. This ensured the complete solubilization of SeLx within the lipid–surfactant matrix. To enhance molecular dispersion and mitigate the risk of localized supersaturation, the isotropic formulations were further processed using probe ultrasonication (20 kHz, 15 min) under controlled conditions. The resultant systems were evaluated visually for clarity, transparency, and absence of phase separation. They were subsequently stored at ambient temperature for 48 h to assess physical stability and exclude any signs of metastability or delayed precipitation. The successful formation of a visibly transparent and optically isotropic dispersion upon aqueous dilution validated the spontaneous emulsification potential of the developed formulations. This behavior is characteristic of oil-in-water (o/w) microemulsions and confirmed the generation of a stable SMEDDS system (Prajapat et al., 2017).

2.4. Optimization of SMEDDS Using Simplex Centroid Mixture Design

To systematically optimize the composition of SeLx -loaded SMEDDS, a simplex centroid mixture design was employed. Based on the self-microemulsifying region identified in the pseudo-ternary phase diagrams, three formulation variables were selected: oil (X_1: Capryol 90), surfactant (X_2: Cremophor EL), and co-surfactant (X_3: Transcutol HP). The design explored two concentration levels for each component, covering the feasible microemulsion region. The independent variables and their corresponding concentration ranges are presented in Table 1. Based on this design, nine experimental batches (B1–B9) were prepared, each representing a distinct combination of the three components. Batch B1 and B5 were intentionally included as replicate formulations to evaluate experimental reproducibility and estimate experimental error. The complete formulation matrix of the simplex centroid mixture design is outlined in Table 2.

2.5. Characterization of SMEDDS

2.5.1. Dilution Test

The dilution test was performed to determine the external phase of the developed SeLx-loaded microemulsion. For this, the formulation was independently diluted at 1:10, 1:100, and 1:1000 ratios using both distilled water and phosphate buffer (pH 6.8) at 25 ± 1 °C. Each sample was gently mixed and visually inspected against a contrasting background for clarity, transparency, or signs of instability such as turbidity, phase separation, or creaming.

2.5.2. Thermodynamic Stability Study

To assess the thermodynamic stability of the developed SeLx-loaded SMEDDS, a three-step stress evaluation was performed, consisting of heating–cooling cycles, centrifugation, and freeze–thaw cycles. Initially, the formulations were subjected to six alternate heating–cooling cycles between 4 °C and 45 °C, with a minimum holding time of 48 h at each temperature. Formulations that remained stable without phase separation or turbidity were further evaluated by centrifugation at 3500 rpm for 30 min. The samples that passed centrifugation stability were subsequently exposed to three freeze–thaw cycles between −16 °C and 25 °C, each with a storage period of not less than 48 h at the respective temperatures. Following each stress condition, the formulations were carefully examined for visual clarity, phase separation, precipitation, or color change, and only those maintaining isotropic stability across all conditions were considered suitable for further characterization (Panchal et al., 2025).

2.5.3. Globule Size Analysis

The mean droplet size and polydispersity index (PDI) of the optimized SeLx-loaded SMEDDS were determined using a dynamic light scattering (DLS) technique with a Malvern Zetasizer Nano ZS (Malvern Instruments, UK). For analysis, each formulation was freshly diluted (1:100 v/v) with double-distilled water to ensure appropriate scattering intensity and to mimic in vivo aqueous dispersion. Measurements were carried out at 25 ± 0.1 °C, under a scattering angle of 90°, and each sample was analyzed in triplicate to ensure reproducibility. The results were expressed as Z-average droplet diameter

(nm) and PDI, which reflects the homogeneity of the particle size distribution. A PDI value below 0.3 was considered indicative of a uniform and monodisperse system, suitable for efficient self-emulsification and drug delivery (Chawnani et al., 2024; Dave et al., 2025).

2.5.4. Zeta Potential Analysis

The zeta potential of SeLx-loaded SMEDDS was measured using dynamic light scattering on a HORIBA Scientific SZ-100 Nanoparticle Analyzer (HORIBA Scientific, Japan) equipped with clear disposable zeta cells. Fresh dispersions were prepared by appropriate dilution of the formulations with double-distilled water (1:100, v/v) to ensure optimal count rates. Prior to measurement, the diluted samples were gently inverted to achieve homogeneity and allowed to equilibrate for 2 min to remove entrapped air bubbles; any visible bubbles were carefully eliminated. The cuvettes were thoroughly rinsed with methanol followed by ultrapure water before sample loading to avoid cross-contamination. Measurements were performed at 25 ± 0.1 °C in triplicate, and results were expressed as mean zeta potential values (mV) ± standard deviation (SD).

2.5.5. Transmission Electron Microscopy

The morphological characteristics of the optimized SeLx-loaded SMEDDS formulation were investigated using transmission electron microscopy (TEM; SICART Laboratory, Anand, India) as reported previously (Bahloul et al., 2015). The formulation was diluted 100-fold with distilled water to ensure optimal dispersion of globules. A drop of the diluted dispersion was carefully placed on a carbon-coated copper grid and allowed to stand for one minute to facilitate adsorption. Excess fluid was removed with filter paper, and the grid was air-dried prior to analysis. Micrographs were captured using a digital camera attached to the TEM under an accelerating voltage of 80 kV. The obtained images were used to evaluate the shape, surface characteristics, and uniformity of the nanoemulsion globules.

2.5.6. Determination of Self-emulsification Time

The self-emulsification efficiency of SeLx-loaded SMEDDS was evaluated using a USP type II dissolution apparatus (paddle method, USP 22 guidelines). Precisely 1 mL of each formulation was introduced dropwise into 500 mL of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C. The medium was agitated using a paddle speed of 50 rpm to provide gentle hydrodynamic conditions mimicking gastrointestinal motility. The time required for the complete and uniform formation of a transparent or slightly bluish emulsion, without any phase separation or drug precipitation, was recorded as self-emulsification time. All measurements were performed in triplicate, and results were expressed as mean ± SD (Bashir et al., 2023a).

2.5.7. *In-vitro* Drug Release Study

The *in-vitro* release profile of SeLx from SMEDDS was evaluated using a USP type II dissolution apparatus (paddle method). Formulations equivalent to 8 mg of SeLx were filled into size "000" hard gelatin capsules and introduced into 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C. The paddles were rotated at 50 rpm to provide gentle agitation simulating intestinal fluid dynamics. At predetermined time intervals, 5 mL aliquots were withdrawn and filtered through a 0.45 µm membrane filter. To maintain sink conditions, each withdrawn volume was immediately replaced with an equal volume of fresh dissolution medium maintained at the same temperature. The amount of SeLx released at each time point was quantified by UV–Visible spectrophotometry against a suitable blank, and cumulative drug release (%) was calculated (Attama & Nkemnele, 2005). All experiments were performed in triplicate, and results were reported as mean ± SD.

3. RESULT AND DISCUSSION

3.1. Solubility Study of SeLx

The solubility screening of the oil phase plays a vital role in the design of SMEDDS, as it determines the achievable drug loading, minimizes the risk of precipitation, and influences both droplet size and formulation stability. In the present study, the equilibrium solubility method was employed to assess the solubility of SeLx in various oils, surfactants, and co-surfactants. Among the tested oils, Capryol 90 exhibited the highest solubilization potential, indicating its suitability as the lipid phase for SMEDDS development. Within the

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surfactant group, Cremophor EL was identified as the most effective solubilizer, while Transcutol HP emerged as the superior co-surfactant, showing a remarkable ability to enhance solubility compared with other candidates. The combination of Capryol 90, Cremophor EL, and Transcutol HP is therefore considered the most promising excipient system for formulating SeLx-loaded SMEDDS. Their synergistic interaction is expected to provide enhanced solubilization, improved microemulsion stability, and efficient drug dispersion, thereby laying the foundation for constructing pseudo-ternary phase diagrams and optimizing the formulation.

Table 3. Solubility study of SeLx in various oils, surfactants, and cosurfactants

Excipients	Solubility (mg/mL)
Miglyol 812	3.63
Labrafac lipophile WL1349	4.40
Oleic acid	3.03
Captex 200P	2.50
Capryol 90	9.33
Castor oil	3.02
Tween 80	12.20
Labrasol ALF	10.23
Cremophor EL	12.83
Tween 20	10.39
Transcutol HP	51.26
Polyethylene glycol 400	25.47
Propylene glycol	1.70

3.2. Pseudo-ternary Phase Diagram

The pseudo-ternary phase diagram was constructed using the selected components, namely oil (Capryol 90), S_{mix} (a blend of Cremophor EL and Transcutol HP), and water. Various surfactant-to-co-surfactant ratios (S_{mix}) were evaluated, including 1:1, 1:2, 1:3, 2:1and 3:1, following the standard procedure (Figure 1). The microemulsion region was identified as the transparent isotropic phase, which is critical for formulating a stable SMEDDS. Upon analysis, S_{mix} ratios of 1:1, 1:2, and 1:3 exhibited only narrow microemulsion regions, indicating limited water incorporation capacity and therefore were excluded from further consideration. In contrast, the S_{mix} ratio of 3:1 showed higher water consumption due to the increased surfactant content; however, formulations at this ratio displayed haziness after storage, suggesting compromised long-term stability. The S_{mix} ratio of 2:1 revealed the broadest microemulsion region and demonstrated optimal water incorporation, while maintaining stability for

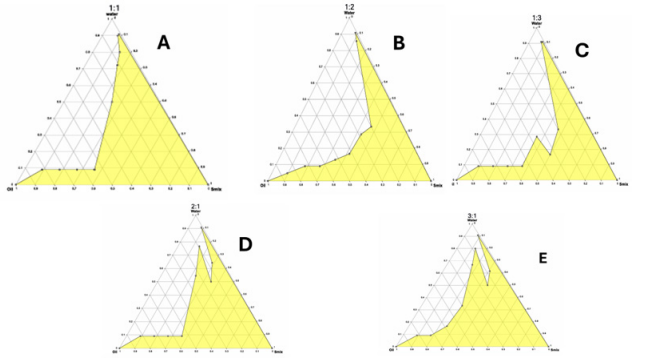


Figure 1. Ternary diagrams of (A) S_{mix} = 1:1; (B) S_{mix} = 1:2; (C) S_{mix} = 1:3; (D) S_{mix} = 2:1; and (E) S_{mix} = 3:1

over 20 days without phase separation or haziness. Based on these findings, the pseudo-ternary phase diagram constructed at a 2:1 ratio of Cremophor EL to Transcutol HP was selected as the optimized system for SeLx-loaded SMEDDS development. The enhanced microemulsion stability at this ratio is attributed to the higher proportion of surfactants, which reduced interfacial tension and improved drug solubilization.

3.3. Generation of Full Model and Reduced Model for Simplex Centroid Mixture Design

The effect of formulation variables on emulsification time (Y1) was analyzed using Design-Expert® 11.

Table 4. Experimental runs and measured responses for simplex centroid mixture design of SeLx-loaded SMEDDS

Experimental runs	X1 Amount of oil (%)	X2 Amount of surfactant (%)	X3 Amount of co-surfactants (%)	Y1 Emulsification time (sec)	Y2 Drug release in 30 min (%)	Y3 Globule size (nm)
1	10	60	30	21	86.14	16.63
2	13.33	58.33	28.33	23	91.32	38.56
3	15	57.5	27.5	25	92.33	72.84
4	12.5	60	27.5	24	89.19	29.3
5	10	60	30	32	84.65	16.63
6	15	55	30	33	93.81	143.5
7	12.5	57.5	30	28	90.92	58.59
8	15	60	25	23	83.89	31.69
9	15	55	30	33	93.31	143.5

Table 5. Statistical analysis of response Y1 (Emulsification time)

Response Y1	A	B	C	AB	AC	BC	ABC	R^2
Coefficient	21	32.5	23	5	8	-11	-73.5	0.996
p-value	0.0035	0.0035	0.0035	0.1548	0.0762	0.0426	0.0505	—
Model Type	Polynomial equation							
Full Model	Y1 = (21)X1 + (32.5) X2 + (23)X3 + (5) (X1X2) + (8) (X1X3) + (-11) (X2X3) + (-73.5) (X1X2X3)							
Reduced Model	Y1 = (21)X1 + (32.5) X2 + (23)X3 + (-11) (X2X3)							

The results are illustrated in the contour plot (Figure 2A) and the statistical analysis of the response is presented in Table 5. The regression model was statistically significant ($p < 0.01$) with a high determination coefficient ($R^2 = 0.996$), confirming its suitability for predicting emulsification behavior. The reduced polynomial equation obtained for emulsification time was:

$$Y_1=21X_1+32.5X_2+23X_3-11(X_2X_3)$$

where X1, X2, and X3 represent the proportions of oil, surfactant, and co-surfactant, respectively. Analysis of the regression coefficients revealed that the surfactant concentration (X2) exerted the most significant influence on reducing emulsification time. A negative interaction was observed between surfactant (X2) and co-surfactant (X3), indicating that their combined increase shortened emulsification time, thereby enhancing formulation efficiency. The emulsification times of the designed batches ranged between 21–33 sec, which is consistent with rapid dispersion and efficient microemulsion formation. These findings highlight that increasing surfactant content, along with a balanced contribution of co-surfactant, facilitates faster emulsification by lowering interfacial tension and improving droplet breakage (Bashir et al., 2023b). Thus, the optimized ratio of surfactant to co-surfactant plays a pivotal

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role in achieving a stable and efficient SMEDDS formulation of SeLx.

3.4. Statistical Analysis of Response Y2 (drug release in 30 min)

The effect of formulation variables on the percentage cumulative drug release at 30 min (Y2) was evaluated using Design-Expert® 11.

Table 6. Statistical analysis of response Y_2 (Drug release in 30 min)

Response: Y2	A	B	C	AB	AC	BC	ABC	R^2
Coefficient	85.40	93.56	83.90	2.90	17.82	14.05	–	0.988
p-value	0.0018	0.0018	0.0018	0.3666	0.0084	0.0163	–	–

Model Type	Equation
Full Model	$Y_2 = (85.40)\,X_1 + (93.56)\,X_2 + (83.90)\,X_3 + (2.90)\,(X_1X_2) + (17.82)\,(X_1X_3) + (14.05)\,(X_2X_3)$
Reduced Model	$Y_2 = (85.40)\,X_1 + (93.56)\,X_2 + (83.90)\,X_3 + (17.82)\,(X_1X_3) + (14.05)\,(X_2X_3)$

The results are illustrated in the contour plot (Figure 2B), and the statistical analysis of the response is presented in Table 6 (Drug Release at 30 min).The regression model was statistically significant ($p < 0.01$) with a high coefficient of determination ($R^2 = 0.988$), indicating excellent model fit and predictive ability. The reduced polynomial equation obtained for drug release was:

$$Y2 = 85.40X1 + 93.56X2 + 83.90X3 + 17.82(X1X3) + 14.05(X2X3)$$

where X1, X2, and X3 denote the proportions of oil, surfactant, and co-surfactant, respectively. The cumulative drug release of the designed batches ranged between 83% and 94%. Regression analysis revealed that all three independent variables significantly influenced the drug release profile. The positive coefficients of X1 (oil) and X3 (co-surfactant) suggest that increasing their proportions enhanced the drug release at 30 min. This effect can be attributed to improved drug solubilization within the lipid phase (X1) and enhanced interfacial partitioning facilitated by the co-surfactant (X3). Moreover, the interaction terms (X1X3 and X2X3) were also positive, indicating a synergistic effect between oil–co-surfactant and surfactant–co-surfactant combinations in promoting rapid drug release. These findings confirm that careful modulation of the oil/S_{mix} composition is critical to optimizing release kinetics, thereby ensuring efficient delivery of SeLx from the SMEDDS formulation.

3.5. Statistical Analysis of Response Y3 (globule size)

The effect of formulation variables on globule size (Y3) was analyzed using a special cubic model in Design-Expert® 11.

Table 7. Statistical analysis of response Y3 (Globule size)

Response Y_3	A	B	C	AB	AC	BC	ABC	R^2
Coefficient	16.63	143.65	31.69	–86.2	20.56	–59.32	–311.73	0.968
p-value	<0.0001	<0.0001	<0.0001	<0.0001	0.0012	0.0001	0.0003	–

Model	Equation
Full model	$(16.63)\,X_1 + (143.65)\,X_2 + (31.69)\,X_3 + (-86.2)\,(X_1X_2) + (20.56)\,(X_1X_3) + (-59.32)\,(X_2X_3) + (-311.73)\,(X_1X_2X_3)$
Reduced model	$(16.63)\,X_1 + (143.65)\,X_2 + (31.69)\,X_3 + (-86.2)\,(X_1X_2) + (20.56)\,(X_1X_3) + (-59.32)\,(X_2X_3) + (-311.73)\,(X_1X_2X_3)$

The results are depicted in the contour plot (Figure 2C), and the statistical analysis of the response is presented in Table 7. The regression model was highly significant ($p < 0.0001$) with an excellent coefficient of determination ($R^2 = 0.968$), confirming

a strong predictive fit. The reduced polynomial equation describing globule size was:

$$Y3=16.63X1+143.65X2+31.69X3-86.2(X1X2)+20.56(X1X3)+59.32(X2X3)-311.73(X1X2X3)$$

Where X1, X2, and X3 represent the proportions of oil, surfactant, and co-surfactant, respectively. The droplet size of the designed formulations ranged between 16 and 145 nm. Analysis of regression coefficients indicated that surfactant concentration (X2) had the most pronounced effect, with an inverse relationship to droplet size: as the surfactant level increased, globule size decreased. This behavior reflects the role of surfactants in lowering interfacial tension and promoting the formation of smaller, more stable nanodroplets. Conversely, increasing the oil fraction (X1) resulted in larger droplet sizes due to enhanced lipophilicity and reduced emulsification efficiency. The co-surfactant (X3) also contributed positively to reducing globule size when combined with surfactant (X2), as evidenced by the positive interaction term (X2X3). However, the strong negative three-way interaction (X1X2X3) suggested a destabilizing effect when all components were present in high proportions simultaneously. Overall, the results demonstrated that achieving an optimal balance between oil and surfactant/co-surfactant ratios is critical to producing nano-sized droplets with enhanced stability, which is essential for maximizing drug solubilization of SeLx.

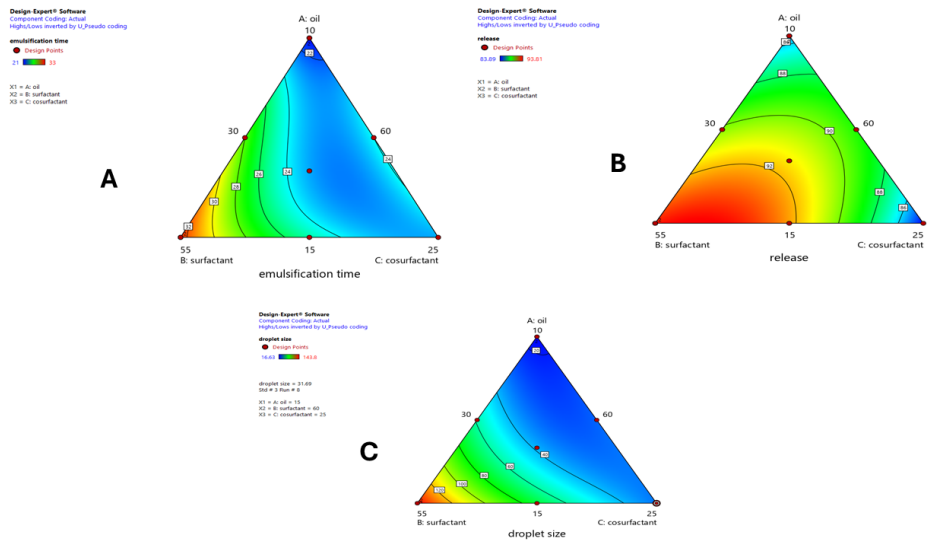


Figure 2. Contour plots of (A) emulsification time, (B) drug release at 30 min, and (C) globule size

3.6. Formulation Optimization Using Overlay Plot

The effect of formulation variables on the critical quality attributes of SeLx-loaded SMEDDS was systematically analyzed using Design-Expert® 11, and the results are presented in Figures 2 and 3. For emulsification time (Y1), a special cubic model ($R^2 = 0.996$, $p < 0.01$) was obtained, and the reduced polynomial equation highlighted surfactant concentration (X2) as the most significant factor, showing an inverse correlation with emulsification time. Interaction between surfactant and co-surfactant (X2X3) further reduced emulsification time, resulting in rapid dispersion with values ranging between 21 and 33 seconds. For drug release at 30 min (Y2), a quadratic model ($R^2 = 0.988$, $p < 0.01$) was established, yielding cumulative release between 83% and 94%. Positive coefficients of oil (X1) and co-surfactant (X3), along with synergistic interactions (X1X3 and X2X3), indicated that modulation of oil/S_{mix} ratios significantly enhanced drug release. For globule size (Y3), a special cubic model ($R^2 = 0.968$, $p < 0.0001$) confirmed that surfactant (X2) played the most dominant role, exhibiting an inverse relationship with droplet size, whereas oil (X1) increased droplet size due to higher lipophilicity. Interaction effects suggested

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that balanced contributions of X2 and X3 promoted nanoscale droplets, while excessive contributions from all three variables simultaneously destabilized the system. The simplex centroid mixture design was further employed for optimization through an overlay plot, with criteria set at Y1 = 21–30 s, Y2 = 90–100%, and Y3 = 16–150 nm. The design space identified a region of desirability, and the optimized formulation was predicted at X1 = 13.52% (oil), X2 = 58.90% (surfactant), and X3 = 27.59% (co-surfactant). Validation of a checkpoint batch prepared using this composition confirmed close agreement between predicted and experimental responses, thereby validating the robustness of the model. Collectively, these findings demonstrate that statistical modeling combined with overlay plot optimization provides a powerful strategy for designing SMEDDS formulations with rapid emulsification, enhanced release kinetics, and nanoscale droplet size, which are essential for improving dissolution efficacy of SeLx.

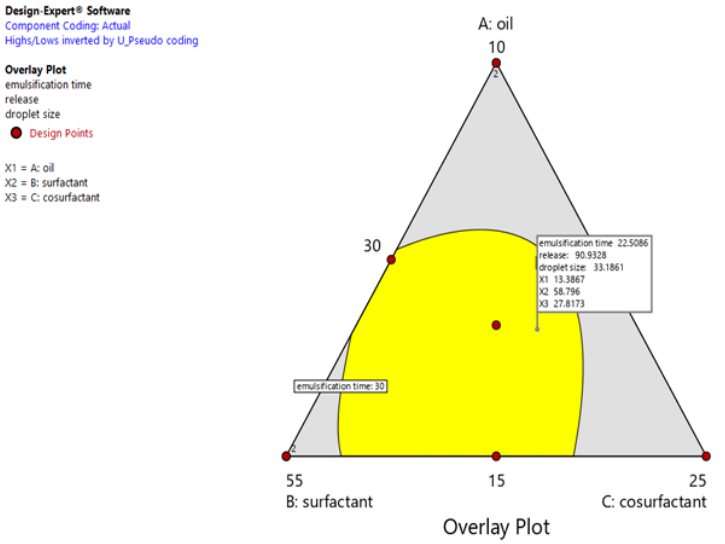


Figure 3. Overlay plot of response variables

Table 8. Check point batch evaluation

Response	Result of check point batch		Prediction Error (%)
	Experimental	Predicted	
Y1 – Emulsification time (sec)	23 sec	22.48 sec	2.31
Y2 – Drug release (%)	89.95%	90.72%	0.84
Y3 – Globule size (nm)	34.80 nm	33 nm	5.45

From the overlay plot, the validation (check point) batch was selected at X_1 = 13.52%, X_2 = 58.90%, and X_3 = 27.59%, which was very close to the optimized formulation. The check point batch was evaluated for critical formulation parameters including emulsification time (Y1), drug release (Y2), and globule size (Y3). The experimentally observed responses were found to be in close agreement with the predicted values generated by Design-Expert® 11 software. The low prediction error values (< 6%) indicated good predictability and robustness of the developed optimization model. Furthermore, residual analysis confirmed the absence of significant deviation between predicted and experimental responses, demonstrating the reliability and reproducibility of the established design space. Overall, the statistical optimization approach successfully identified an optimized SMEDDS formulation with rapid emulsification, enhanced drug release, and nanoscale globule size suitable for improving dissolution performance of SeLx.

3.6.1. Dilution Test

The optimized SeLx-loaded SMEDDS exhibited excellent dilution stability in both distilled water and phosphate buffer (pH 6.8). At all dilution levels (10, 100, and 1000fold), the dispersions appeared clear and transparent, with no signs of turbidity. Furthermore, no phase separation or drug precipitation was observed throughout the study. These findings confirm the robustness of the developed formulation, indicating its ability to maintain self-emulsification efficiency and stability under varying aqueous environments.

3.6.2. Thermodynamic Stability

The developed SeLx-loaded microemulsion exhibited excellent thermodynamic stability as confirmed by heating–cooling cycles, centrifugation, and freeze–thaw stress testing. During the heating–cooling cycle, the formulation remained clear and transparent without any signs of turbidity, indicating resistance to thermal stress. Centrifugation studies showed no evidence of phase separation, further supporting the stability of the dispersed system. Additionally, the formulation demonstrated no precipitation or color change under freeze–thaw conditions, confirming its robustness against temperature fluctuations. Collectively, these results suggest that the optimized formulation is physically stable under different stress conditions.

3.6.3. Globule Size and Polydispersity Index (PDI)

The globule size of the developed SeLx-loaded SMEDDS formulations was found to be highly dependent on the relative proportion of oil, surfactant, and co-surfactant. The particle size ranged from 16.63 nm to 143.50 nm across the experimental runs, indicating successful formation of nanometric globules characteristic of a self-micro-emulsifying system. The smallest globule size (16.63 nm) was observed in formulations with a lower oil concentration (10 %) combined with higher surfactant content, suggesting that sufficient surfactant facilitates efficient reduction of interfacial tension and stabilization of smaller droplets. In contrast, formulations containing higher oil fractions (15 %) exhibited larger globule sizes (up to 143.50 nm), which may be attributed to incomplete coverage of oil droplets at the interface due to limited surfactant-to-oil ratio. In addition, the polydispersity index (PDI) values of all formulations were found to be below 0.3, indicating a narrow size distribution and good uniformity of the globules. The low PDI values confirm the homogenous nature and

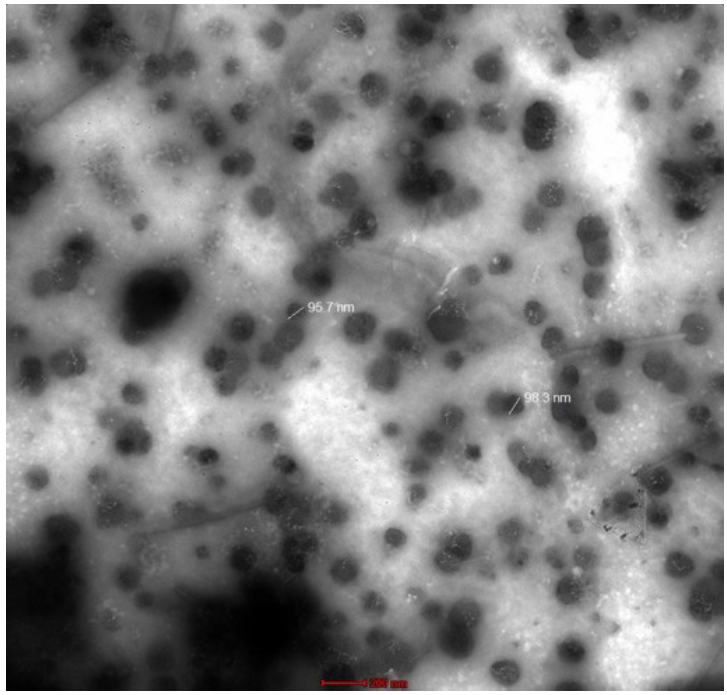


Figure 4. TEM images of optimized SMEDDS

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stability of the developed SMEDDS formulations. Overall, the results confirm the critical influence of component ratios on droplet size, with optimized compositions producing uniformly distributed nano-globules in the desirable range (< 100 nm) for enhanced drug dissolution.

3.6.4. Zeta Potential

The zeta potential of the optimized SeLx-loaded microemulsion was determined using a HORIBA Scientific SZ-100 analyzer and was found to be −12.8 mV, suggesting moderate surface charge–based stabilization of the dispersed globules. Although zeta potential values greater than ±30 mV are generally considered indicative of strong electrostatic stabilization, the developed SMEDDS system remained physically stable due to the presence of non-ionic surfactants such as Cremophor EL, which provide additional steric stabilization and prevent droplet coalescence. Furthermore, no phase separation, precipitation, or globule aggregation was observed during thermodynamic stability studies, confirming the adequate stability of the formulation. Furthermore, the measured conductivity value of 0.089 mS/cm confirmed the continuous aqueous phase, thereby substantiating that the developed formulation was of the oil-in-water (o/w) microemulsion type.

3.6.5. Transmission Electron Microscopy

Transmission electron microscopy analysis of the optimized SeLx-loaded SMEDDS formulation was performed, and representative micrographs are shown in Figure 4. The images revealed well-defined, spherical globules appearing as dark spheres against a light background, confirming the uniform morphology of the dispersed droplets. The globules were clearly separated from one another, with no evidence of aggregation or clumping, thereby validating the formation of a finely dispersed and stable microemulsion system.

3.6.6. Determination of Self-emulsification Time

The self-emulsification time of SeLx-loaded SMEDDS formulations was evaluated to assess the efficiency of spontaneous emulsification upon dilution in aqueous media. The developed formulations exhibited rapid emulsification with self-emulsification times ranging between 21 and 33 sec, confirming their ability to disperse readily in aqueous medium. The faster emulsification observed in surfactant-rich formulations highlights the role of surfactant concentration in lowering interfacial tension and promoting the spontaneous formation of stable nanometric droplets.

3.6.7. *In-vitro* Drug Release Study

The *in-vitro* release of SeLx pure API was evaluated in phosphate buffer (pH 6.8) as per FDA-recommended dissolution conditions. Being a BCS Class II drug, SeLx exhibits poor aqueous solubility and low oral bioavailability, primarily due to its dissolution-limited absorption. The cumulative drug release from pure SeLx (encapsulated in hard gelatin capsules) was found to be only 42 % within 60 min, confirming its dissolution-limited nature. In contrast, the developed SMEDDS formulations demonstrated a significant enhancement in drug release. The improvement can be attributed to

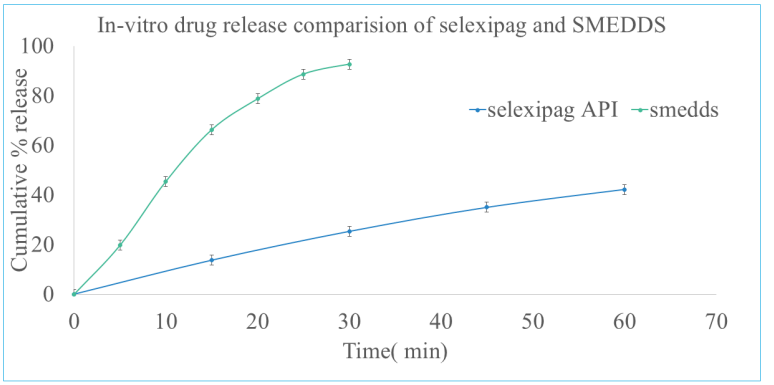


Figure 5. *In-vitro* drug release comparison of SeLx API and SMEDDS formulation

the spontaneous emulsification process, where the combination of surfactants and co-surfactants facilitated the formation of ultra-fine oil droplets (<150 nm). This resulted in a markedly increased interfacial surface area, thereby enhancing the drug solubilization and release into the dissolution medium. Among the tested formulations (B1–B9), batches B2, B3, B6, B7, and B9 exhibited > 90 % cumulative drug release within 30 min, whereas the remaining batches showed relatively lower release rates. Overall, the optimized SMEDDS formulations were able to achieve > 85 % release within 30 min, which was significantly higher compared to the pure drug (42 % in 60 min). The comparative drug release profiles are illustrated in Figure 5.

4. CONCLUSION

The present study successfully developed and optimized a SMEDDS of SeLx to overcome its poor aqueous solubility and dissolution-limited oral bioavailability. A systematic approach involving solubility screening, pseudo-ternary phase diagram construction, and simplex centroid mixture design enabled the rational selection of excipients and their optimal proportions. Capryol 90, Cremophor EL, and Transcutol HP were identified as the most suitable oil, surfactant, and co-surfactant, respectively, owing to their superior solubilization capacity and ability to form stable microemulsions. Statistical modeling through Design-Expert® 11 revealed that surfactant concentration had the most significant influence on emulsification time and globule size, while co-surfactant synergistically enhanced drug release in combination with oil. The optimized formulation demonstrated rapid emulsification (23 s), nanoscale globules (38.56 nm), and high drug release (> 90 % within 30 min), with favorable zeta potential confirming colloidal stability. Furthermore, thermodynamic stability tests and dilution studies confirmed the robustness of the formulation under physiological conditions. TEM analysis validated the formation of spherical, uniformly dispersed globules, consistent with the desired characteristics of a stable SMEDDS. In-vitro dissolution studies demonstrated a marked improvement in drug release compared with pure SeLx (91.32 % vs. 42 %), highlighting the efficiency of SMEDDS in enhancing dissolution and potentially indirectly improving bioavailability. Notably, the developed SeLx-loaded SMEDDS offers a novel lipid-based delivery strategy for improving the dissolution performance of poorly water-soluble drugs through rapid self-emulsification and nanosized droplet formation. Compared with conventional formulations of poorly soluble drugs, the optimized SMEDDS demonstrated significantly enhanced dissolution behavior, which may contribute to improved oral absorption and therapeutic performance. The incorporation of statistical optimization and quality-by-design principles further strengthens the translational relevance and reproducibility of the formulation approach. These findings underscore the potential of the developed formulation as a promising strategy for the effective management of PAH. Moreover, the formulation platform established in this study may be extended to other poorly soluble therapeutic agents, thereby offering broad clinical applicability and potential future clinical translation.

Data Availability

No datasets were generated or analysed during the current study.

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Conflict of Interest

The authors declare no competing interest.

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