

Formulation Development and In-Vitro Characterization of Posaconazole-Loaded Self-Microemulsifying Drug Delivery System (SMEDDS)

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Abstract

Posaconazole is a broad-spectrum, second-generation triazole antifungal agent classified under the Biopharmaceutics Classification System (BCS) as a Class II drug, characterized by poor aqueous solubility and dissolution rate-limited oral bioavailability. The present study was undertaken to develop, optimize, and evaluate a Posaconazole-loaded Self-Microemulsifying Drug Delivery System (SMEDDS) to overcome solubility limitations and enhance in-vitro drug dissolution. Preformulation screening identified Capryol 90 (oil phase), Tween 80 (surfactant), PEG 400, and Transcutol P (co-surfactants) as optimal excipients based on maximum drug solubilization and emulsification efficiency. Pseudo-ternary phase diagrams were constructed using various surfactant-to-co-surfactant (S_{mix}) ratios, and ten formulations (F1–F10) were prepared via the magnetic stirring method. The formulations were characterized for self-emulsification time, droplet size, polydispersity index (PDI), zeta potential, drug content, viscosity, and thermodynamic stability. Among all prepared formulations, F6 was selected as the optimized batch; it demonstrated a rapid self-emulsification time of 22 s (Grade A), an average droplet size of 36.8 nm, a low PDI of 0.196, a zeta potential of -22.6 mV, drug content of 99.4%, and a viscosity of 104 cP. Fourier-Transform Infrared (FTIR) spectroscopy confirmed the chemical stability of Posaconazole and the absence of deleterious drug-excipient interactions. The optimized F6 formulation passed all thermodynamic stress tests (centrifugation, heating-cooling, and freeze-thaw cycles) with negligible changes in droplet size (37.2 nm) and PDI (0.201). In-vitro drug dissolution in 0.1 N HCl revealed marked enhancement in drug release, achieving 93.5% at 60 min and 99.4% at 120 min. Mathematical release kinetic modeling demonstrated that the drug release from F6 obeyed first-order kinetics (R^2 highest), indicating concentration-dependent release along with diffusion-mediated transport. These findings confirm that the developed SMEDDS represents an efficient lipid-based oral drug delivery platform for poorly soluble Posaconazole.

Keywords: Posaconazole, SMEDDS, Capryol 90, Tween 80, Pseudo-ternary Phase Diagram, In-Vitro Dissolution, First-Order Kinetics.

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1. Introduction

Invasive fungal infections (IFIs) caused by opportunistic pathogens such as *Candida* spp., *Aspergillus* spp., and members of the order *Mucorales* are responsible for severe morbidity and mortality, particularly in immunocompromised patients, stem cell transplant recipients, and individuals undergoing intensive chemotherapy. Posaconazole—a broad-spectrum, second-generation triazole antifungal agent—acts by selectively inhibiting the fungal cytochrome P450-dependent enzyme lanosterol (CYP51), thereby preventing ergosterol biosynthesis and disrupting cell membrane integrity.

Despite its high antifungal efficacy, Posaconazole belongs to BCS Class II, presenting extremely low aqueous solubility (<0.01 mg/mL) at neutral/alkaline pH) and high lipophilicity. Consequently, its oral absorption from conventional solid and suspension dosage forms is slow, dissolution rate-limited, and erratic. Posaconazole absorption is strongly subject to

the "food effect," where co-administration with high-fat meals improves systemic exposure while fasting or altered gastric motility leads to sub-therapeutic plasma concentrations.

To address the limitations of poorly soluble drugs, lipid-based drug delivery systems have gained prominent interest. Self-Microemulsifying Drug Delivery Systems (SMEDDS) are isotropic, thermodynamically stable mixtures of oils, surfactants, co-surfactants/co-solvents, and drugs that spontaneously form fine oil-in-water (O/W) microemulsions with droplet sizes between 10 and 100 nm upon contact with gastrointestinal fluids under mild gastrointestinal motility. SMEDDS maintain the drug in a molecularly dissolved state, generate an extensive interfacial surface area, bypass dissolution barriers, facilitate lymphatic transport, and minimize food-dependent variability.

The objective of the present investigation was to systematically develop, optimize, and evaluate a Posaconazole-loaded SMEDDS formulation using

Capryol 90, Tween 80, PEG 400, and Transcutol P, followed by comprehensive physicochemical evaluation, FTIR compatibility studies, thermodynamic stability testing, and in-vitro drug release kinetic modeling.

2. Materials and Methods

2.1 Materials

Posaconazole was procured from Sigma-Aldrich. Capryol 90 was obtained from Chemdyes / Gattefossé. Tween 80 (Polysorbate 80) and Oleic Acid were supplied by Sigma-Aldrich. Transcutol P and Polyethylene Glycol 400 (PEG 400) were obtained from Loba Chemie. Methanol and Acetonitrile (HPLC grade) were procured from Thermo Fisher Scientific. Distilled and deionized water was prepared using an in-house Milli-Q system (Merck Millipore).

2.2 Preformulation Studies

- **Melting Point Determination:** The melting point of Posaconazole was determined using an automated capillary melting point apparatus.
- **Solubility Screening:** Excess Posaconazole was added into screw-capped glass vials containing 2 mL of various selected oils (Capryol 90, Oleic Acid), surfactants (Tween 80), and co-surfactants (PEG 400, Transcutol P). The mixtures were vortexed for 5 min and equilibrated in an orbital shaking water bath maintained at 37 ± 0.5 °C for 72 h. The samples were centrifuged at 5000 rpm for 15 min, filtered through a 0.45 μ m membrane, diluted with methanol, and quantified by UV-Visible spectrophotometry at 262 nm.
- **pH-Dependent Solubility:** The solubility of Posaconazole was assessed across buffer media of varying pH values (pH 1.2, 3.0, 5.0, 6.8, and 7.4).
- **Determination of Analytical Wavelength and Calibration Curve:** Standard Posaconazole solutions were scanned across 200–400 nm using a UV-1900i spectrophotometer (Shimadzu). A standard calibration curve in 0.1 N HCl was constructed in the concentration range of 10–60 μ g/mL at 262 nm.
- **FTIR Compatibility Studies:** Compatibility between Posaconazole and excipients was assessed using a Spectrum Two FTIR spectrophotometer (PerkinElmer) by the KBr pellet method across 4000–400 cm^{-1} at a resolution of 4 cm^{-1} .

2.3 Construction of Pseudo-Ternary Phase Diagrams

Surfactant (Tween 80) and co-surfactants (PEG 400 and Transcutol P) were mixed in varying weight ratios (S_{mix} 1:1:1, 2:1:1, 3:1:1, and 4:1:1). Capryol 90 (oil phase) was combined with each S_{mix} ratio at

weight ratios ranging from 9:1 to 1:9. Each mixture was titrated with distilled water under gentle magnetic stirring at ambient temperature. Formulations were visually inspected for transparency, phase clarity, and spontaneity of emulsification to identify the boundaries of the self-microemulsifying region.

2.4 Preparation of Posaconazole-Loaded SMEDDS (F1–F10)

Ten SMEDDS formulations (F1–F10) were prepared by blending designated amounts of Capryol 90, Tween 80, PEG 400, and Transcutol P. The excipients were mixed using a magnetic stirrer at 500–700 rpm for 15–20 min at room temperature to form an isotropic mixture. Posaconazole (10% w/w) was gradually incorporated with continuous stirring for 30–45 min, heating mildly to 40 ± 2 °C where necessary to ensure complete dissolution. Formulations were equilibrated for 24 h to eliminate entrapped air bubbles and stored in amber glass containers.

2.5 Physicochemical Characterization

Self-Emulsification Time and Visual Grading: 1 mL of each SMEDDS formulation was introduced into 250 mL of distilled water maintained at 37 ± 0.5 °C in a USP Type II paddle apparatus rotated at 50 rpm. The time required to form a clear dispersion was recorded, and formulations were classified according to Pouton's grading scale (Grade A to E).

Droplet Size, PDI, and Zeta Potential: Formulations were diluted 1:100 with distilled water and analyzed at 25 °C using Dynamic Light Scattering (DLS) on a Zetasizer Nano ZS90 (Malvern Panalytical).

Drug Content Analysis: An amount of SMEDDS equivalent to 10 mg of Posaconazole was dissolved in methanol, sonicated for 15 min, filtered 0.45 μ m, and analyzed at 262 nm.

Viscosity: Viscosity of the undiluted formulations was measured using a Brookfield Digital Viscometer at 25 ± 1 °C.

2.6 Thermodynamic Stability Studies

The optimized SMEDDS formulation (F6) was subjected to sequential thermodynamic stress tests:

Centrifugation: Centrifuged at 3500 rpm for 30 min and checked for phase separation or precipitation.

Heating-Cooling Cycles: Six cycles between 4 °C and 45 °C with storage at each temperature for not less than 48 h.

Freeze-Thaw Cycles: Three cycles between -20 °C and 25 °C with storage for 48 h at each temperature.

Post-stress droplet size and PDI were determined by DLS to assess structural robustness.

2.7 In-Vitro Drug Release and Kinetic Modeling

In-vitro dissolution of the optimized formulation (F6) was conducted using USP Dissolution Apparatus Type II (Paddle method) in 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5 °C and 50 rpm. SMEDDS equivalent to 100 mg of Posaconazole was filled into

hard gelatin capsules and placed in the vessel. Aliquots (5 mL) were withdrawn at 5, 10, 15, 20, 30, 45, 60, 75, 90, and 120 min, filtered through 0.45 µm filter, replaced with an equal volume of fresh media, and quantified spectrophotometrically at 262 nm.

To evaluate the release mechanism, data were fitted to the following mathematical models:

• **Zero-Order Model:**

$$Q_t = Q_0 + K_0 t$$

• **First-Order Model:**

$$\log(100 - Q) = \log 100 - \frac{K_1}{2.303} t$$

• **Higuchi Model:**

$$Q = K_H \sqrt{t}$$

• **Korsmeyer-Peppas Model:**

$$\frac{M_t}{M_\infty} = K t^n$$

3. Results and Discussion

3.1 Preformulation and Physicochemical Evaluation of Drug

Posaconazole was obtained as a white to off-white crystalline powder. The melting point of the drug was determined to be 171 °C, which matches the reported pharmacopoeial range of 171 – 172 °C, confirming drug purity. Solubility screening showed that Posaconazole was practically insoluble in water, slightly soluble in ethanol, and freely soluble in methanol and acetonitrile.

The pH-dependent solubility profiling revealed a marked decline in solubility with rising pH: 0.82 mg/mL at pH 1.2, 0.58 mg/mL at pH 3.0, 0.21 mg/mL at pH 5.0, 0.03 mg/mL at pH 6.8, and 0.01 mg/mL at pH 7.4. This pronounced drop emphasizes the weak base behavior of Posaconazole and explains its poor absorption in the intestinal milieu unless formulated in a solubilizing vehicle.

UV spectrophotometric scanning of Posaconazole in 0.1 N HCl exhibited a prominent, sharp λ max at 262 nm with an absorbance of 1.02. The constructed calibration curve over 10–60 µg/mL obeyed Beer-Lambert's law, yielding the linear regression equation:

$$y = 0.0166x - 0.0577 \quad (R^2 = 0.999)$$

3.2 FTIR Compatibility Studies

FTIR spectra of pure Posaconazole, individual excipients, and the optimized formulation (F6) were compared. The pure drug exhibited distinctive vibrational bands at 3420 cm⁻¹ (O–H stretching), 3125 cm⁻¹ (aromatic C–H), 2920 cm⁻¹ (aliphatic C–H), 1695 cm⁻¹ (C=O stretching), 1605 cm⁻¹ (C=N stretching of triazole ring), 1510 cm⁻¹ (aromatic C=C), 1245 cm⁻¹ (ether linkage C–O), 1115 cm⁻¹ (C–N

stretching), and 845 cm⁻¹ (difluorophenyl C–F stretching).

In the FTIR spectrum of the optimized SMEDDS formulation, all principal drug absorption peaks were retained with negligible shifts: broad O–H stretching at 3428 cm⁻¹, aliphatic C–H stretching at 2924 and 2854 cm⁻¹, ester carbonyl at 1736 cm⁻¹, C=N stretching at 1620 cm⁻¹, aromatic C=C at 1508 cm⁻¹, and C–F stretching at 1086 cm⁻¹. The absence of any new peak formation or peak disappearance confirmed chemical compatibility and suggested that Posaconazole was molecularly dispersed in the lipid matrix without covalent interaction.

3.3 Pseudo-Ternary Phase Diagram and Formulation Screening

Phase behavior investigations revealed that increasing the surfactant-to-co-surfactant ratio enhanced the microemulsion region. Compositions prepared at a 1:1:1 S_{mix} ratio showed slight turbidity when oil content reached 30%. At a 3:1:1 ratio, 30% oil resulted in slight phase separation. The 4:1:1 S_{mix} ratio (Tween 80 : PEG 400 + Transcutol P) containing 20% Capryol 90, 70% S_{mix}, and 10% water formed a clear, homogeneous, transparent microemulsion upon dilution with rapid self-emulsification, identifying it as the optimal composition space.

3.4 Physicochemical Characterization of SMEDDS Batches (F1–F10)

The experimental results for formulations F1 through F10 are summarized in the following table:

Table 3.1 Physicochemical Characterization of SMEDDS Batches (F1–F10)

Formulation Code	Self-Emulsification Time (s)
F1	42
F2	38
F3	34
F4	30
F5	27
F6	22
F7	26
F8	31
F9	36
F10	40

The self-emulsification times of all batches ranged from 22 to 42 s. Formulation F6 exhibited the fastest emulsification time (22 s), corresponding to Grade A visual efficiency (spontaneous bluish clarity within 1 min). The mean droplet size varied between 36.8 nm and 118.4 nm, with F6 yielding the smallest size (36.8 nm). The PDI of F6 was 0.196, confirming a unimodal and narrow droplet size distribution (PDI < 0.3).

Zeta potential is critical in predicting dispersion physical stability against coalescence. F6 exhibited the highest magnitude of negative surface charge (-22.6 mV), offering strong electrostatic repulsion. The drug content of F6 was highest at 99.4%, and its viscosity was 104 cP, which facilitated prompt phase dispersal upon contact with aqueous media. Based on these criteria, F6 was selected as the optimized batch.

3.5 Thermodynamic Stability Testing of F6

Thermodynamic stability assessment confirmed that formulation F6 is physically stable and non-labile:

- Centrifugation Test (3500 rpm, 30 min): No phase separation, cracking, or precipitation observed.
- Heating-Cooling Cycles (4 °C - 45 °C): Formulations remained transparent and homogeneous.
- Freeze-Thaw Cycles (-20 °C - 25 °C): Passed without evidence of phase breakdown.
- Post-Stability DLS Evaluation: The droplet size of F6 shifted only marginally from 36.8 nm to 37.2 nm, and PDI changed from 0.196 to 0.201, verifying high thermodynamic stability.

3.6 In-Vitro Dissolution and Kinetic Analysis

The in-vitro drug release profile of the optimized F6 formulation in 0.1 N HCl (pH 1.2) is presented below: *In-Vitro Dissolution and Kinetic Analysis*

Table 3.2 In-Vitro Dissolution and Kinetic Analysis

Time (min)	Cumulative Posaconazole Release (%)
0	0.0
5	18.5
10	34.2
15	48.6
20	60.4
30	74.8
45	86.7
60	93.5
75	96.8
90	98.2
120	99.4 ↓

Table - In-vitro Cumulative Drug Release (%)

Time (min)	Cumulative Drug Release (%)
0	0.0
5	18.5
10	34.2
15	48.6
20	60.4
30	74.8
45	86.7
60	93.5
75	96.8
90	98.2
120	99.4

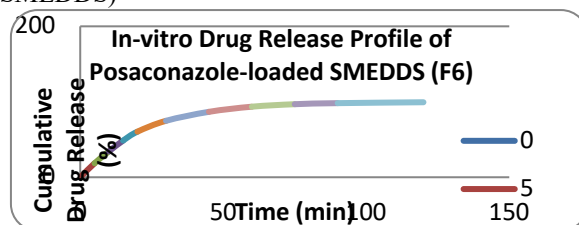


Figure 3.1 Cumulative Drug Release Profile (%)

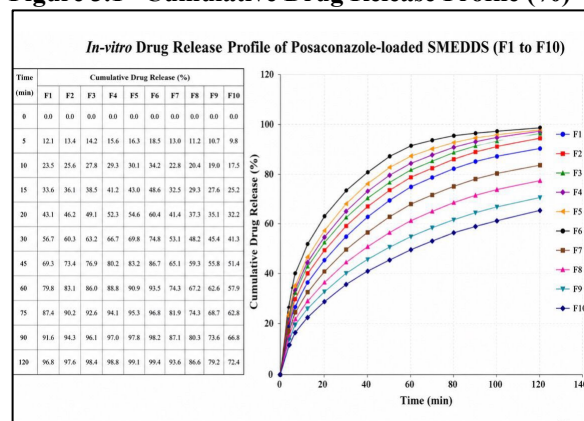


Figure 3.2 In-vitro drug release profile of posaconazole-loaded SMEDDS (F1 TO F10)

Formulation F6 produced a rapid and nearly complete dissolution profile, releasing 74.8% of Posaconazole within 30 min, 93.5% at 60 min, and 99.4% at 120 min. In contrast to unformulated crystalline Posaconazole, which exhibits severe dissolution rate limitations in GI fluids, the spontaneous generation of nanosized droplets (36.8 nm) drastically increased the effective surface area for drug partition and solubilization according to the Noyes-Whitney equation.

Mathematical kinetic modeling showed that the drug release from F6 demonstrated the highest correlation coefficient with the First-Order kinetic model, indicating that Posaconazole release was concentration-dependent under sink conditions. Good correlation was also observed with the Higuchi and Korsmeyer-Peppas models, indicating that diffusion processes contribute to the partitioning of the solubilized drug from oil droplets into the bulk dissolution medium.

3.6 Drug Release Kinetic

The optimized Posaconazole-loaded SMEDDS formulation (F6) showed excellent self-emulsification characteristics with an emulsification time of 22 seconds, indicating rapid spontaneous microemulsion formation upon dilution with aqueous media. The formulation was classified as Grade A, demonstrating efficient self-emulsifying performance and suitability for oral drug delivery.

The optimized formulation (F6) exhibited rapid drug release, with approximately 99% cumulative drug release within 120 minutes. The kinetic analysis showed that the formulation best fitted the First-order kinetic model, indicating that the release rate was concentration-dependent. The Higuchi and

Korsmeyer–Peppas models also demonstrated good correlation, suggesting that diffusion contributed to the release mechanism.

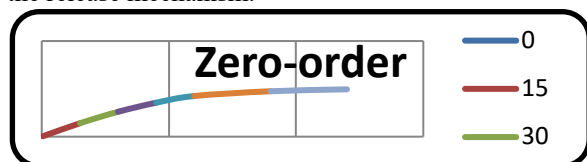


Figure 3.3 Zero order Kinetics

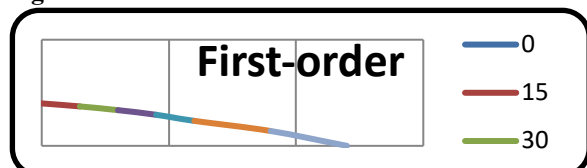


Figure 3.4 First order Kinetics

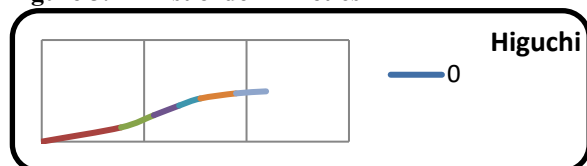


Figure 3.5 first order Kinetics

These observations are consistent with published findings by Sanaei Oskouei et al. (2023) and Gorle et al. (2022), who observed that self-emulsifying and nano-dispersed lipid systems dramatically enhance the in-vitro release rates of Posaconazole by overcoming poor aqueous wettability and crystal lattice barrier properties.

4. Conclusion

A stable, self-microemulsifying drug delivery system (SMEDDS) for Posaconazole was successfully developed and evaluated. Preformulation screening identified Capryol 90, Tween 80, PEG 400, and Transcutol P as compatible and effective excipients. Formulation F6, optimized via pseudo-ternary phase diagram analysis, displayed superior physicochemical characteristics: spontaneous self-emulsification in 22 s (Grade A), nanometric droplet size (36.8nm), narrow polydispersity (PDI = 0.196), robust electrokinetic stability (zeta potential = -22.6mV), high drug loading (99.4 %), and complete thermodynamic stability. FTIR spectra confirmed that the drug remained chemically stable without detrimental excipient interactions. In-vitro dissolution testing demonstrated complete drug release (99.4% at 120 min), which followed first-order release kinetics. Therefore, the developed SMEDDS represents a highly viable oral platform to enhance the dissolution and oral bioavailability of poorly water-soluble Posaconazole.

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