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Evaluation of the Potential of Self-Nanoemulsifying Drug Delivery System (SNEDDS) in Increasing Oral Bioavailability of Low-Solubility Drugs

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ABSTRACT

Losartan potassium, a Biopharmaceutics Classification System (BCS) Class II drug, exhibits poor aqueous solubility and limited oral bioavailability. This study aimed to develop and optimize a Self-Nanoemulsifying Drug Delivery System (SNEDDS) to enhance its dissolution and absorption. SNEDDS formulations were prepared using Capmul MCM C8, Tween 80, and PEG 400 based on solubility screening and ternary phase diagram analysis. The optimized formulation (F3) was evaluated for droplet size, polydispersity index (PDI), in vitro drug release, pharmacokinetics, and stability. Pharmacokinetic studies were conducted in experimental rats Pharmacokinetic studies were conducted in experimental rats (n = 3 per group) *to assess bioavailability. The optimized SNEDDS produced nanoemulsions with a droplet size of 68.3 nm, low PDI, and good dilution stability. In vitro studies demonstrated rapid drug release (>96% within 30 minutes), significantly higher than the plain suspension. Pharmacokinetic results showed a 3.09-fold increase in bioavailability and a 2.79-fold increase in Cmax without altering Tmax. Stability studies confirmed good physicochemical stability over six months under ICH conditions. In conclusion, SNEDDS is a promising strategy to improve the oral bioavailability of poorly water-soluble drugs such as losartan potassium.*

Keywords: *SNEDDS, Losartan Potassium, Nanoemulsion, Oral Bioavailability, Lipid-Based Drug Delivery*

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INTRODUCTION

The oral route remains the most widely preferred method of drug administration due to its convenience, high patient compliance, and cost-effectiveness. However, a major limitation of oral delivery is the poor aqueous solubility of many drug candidates. It is estimated that approximately 40–70% of newly developed compounds are classified as poorly soluble drugs, which significantly limits their oral bioavailability (Kalepu & Nekkanti, 2015; Ulfa & Pratiwi, 2025). In such cases, solubility becomes the primary factor governing drug dissolution and absorption, often resulting in reduced therapeutic efficacy and high variability in clinical outcomes.

To address these limitations, various formulation strategies have been developed, among which lipid-based drug delivery systems have gained considerable attention due to their ability to enhance solubility and absorption. One of the most promising approaches is the Self-Nanoemulsifying Drug Delivery System (SNEDDS). SNEDDS is an isotropic mixture of oils, surfactants, and co-surfactants that spontaneously forms nanoemulsions upon mild agitation in gastrointestinal fluids, thereby improving drug solubilization and absorption (Kassem et al., 2017; Sherif et al., 2024). This system increases the interfacial surface area available for drug absorption and enhances the dissolution rate of poorly soluble compounds.

Several recent studies have demonstrated the effectiveness of SNEDDS in improving the dissolution and bioavailability of hydrophobic drugs. SNEDDS-based formulations have been reported to significantly enhance pharmacokinetic parameters such as maximum plasma concentration (Cmax) and area under the curve (AUC) compared to conventional dosage forms (Murad et al., 2020; Usta et al., 2025). In addition, optimization of SNEDDS formulations has shown improved dissolution profiles and therapeutic performance in various BCS Class II drugs (Kassem et al., 2017; Rao et al., 2020).

Losartan potassium, an angiotensin II receptor blocker widely used in the treatment of hypertension, is classified as a poorly soluble drug with limited oral bioavailability. Although it exhibits relatively good permeability, its absorption is restricted by incomplete dissolution in gastrointestinal fluids. Recent studies have reported that SNEDDS-based formulations can enhance the solubility and pharmacokinetic performance of losartan potassium (Kaur et al., 2020; Zhang et al., 2014). However, the optimization of formulation composition—particularly the ratio of oil, surfactant, and co-surfactant—remains a critical factor influencing SNEDDS performance and requires further systematic investigation.

Therefore, this study aims to develop and optimize a SNEDDS formulation of losartan potassium using selected lipid-based excipients. Furthermore, this study evaluates the physicochemical characteristics, in vitro drug release, and in vivo pharmacokinetic performance to assess its potential in enhancing oral bioavailability.

METHODS

Losartan potassium (purity >99.5%, pharmaceutical grade) was obtained from PT. Kimia Farma (Bandung, Indonesia), while Capmul MCM C8 was provided by Abitec Corporation (USA).

Tween 80, PEG 400, Cremophor EL, Labrafil M1944CS, and Transcutol HP were purchased from Sigma-Aldrich (USA), and all solvents used were of analytical or HPLC grade. Male Sprague-Dawley rats (200–250 g, 8–10 weeks) were obtained from a BPOM-certified animal facility. All animal procedures were conducted in accordance with institutional and international guidelines and were approved by the Animal Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara (Approval No. 128/KEPK/FK-USU/2024).

Equilibrium solubility studies were performed using the shake-flask method (n = 3) by adding excess losartan potassium to each excipient, followed by vortexing and equilibration at 25 ± 1°C for 72 hours. Samples were centrifuged, filtered (0.22 μm), and analyzed by HPLC. Miscibility between oils and surfactant–co-surfactant mixtures (Smix) was evaluated based on clarity and further confirmed by droplet size analysis after dilution. Excipients were selected based on their solubilization capacity, miscibility, and hydrophilic–lipophilic balance (HLB) values.

Pseudo-ternary phase diagrams were constructed using the water titration method to identify nanoemulsion regions. Smix ratios (1:1, 2:1, and 3:1) were evaluated, and mixtures of oil and Smix at various ratios were titrated with distilled water under gentle stirring. The resulting dispersions were visually assessed and further confirmed by droplet size measurements using dynamic light scattering (n = 3), with nanoemulsion regions defined as systems producing droplets <200 nm.

SNEDDS formulations (F1–F6) were prepared in triplicate by dissolving losartan potassium (100 mg per unit dose) in mixtures of oil and Smix using vortexing followed by sonication until clear, isotropic systems were obtained. The selected formulations were stored in sealed containers at ambient conditions. The relatively high surfactant concentration was selected based on phase behavior optimization and supported by literature indicating acceptable oral tolerability of such systems.

Physicochemical characterization of the formulations was performed after dilution (1:100 v/v) in phosphate buffer pH 6.8 (n = 3). Parameters evaluated included droplet size, polydispersity index (PDI), and zeta potential using dynamic light scattering, as well as emulsification time, transmittance, viscosity, and drug content. Robustness to dilution was assessed across a range of dilution factors (1:10 to 1:1000) to evaluate the stability and potential risk of drug precipitation. Drug loading capacity and precipitation behavior were also investigated by assessing the maximum solubilized drug concentration and monitoring precipitation under simulated gastrointestinal conditions over 24 hours.

In vitro drug release studies were conducted using USP Apparatus II (paddle method) in 900 mL phosphate buffer pH 6.8 at 37 ± 0.5°C and 75 rpm (n = 3). Samples were withdrawn at predetermined time intervals, filtered, and analyzed using a validated HPLC method. The analytical method was validated for linearity ($R^2 > 0.999$), accuracy (98–102%), precision (%RSD < 2%), limit of detection (LOD = 0.02 μg/mL), and limit of quantification (LOQ = 0.05 μg/mL).

For the in vivo pharmacokinetic study, rats were divided into three groups (n = 6 per group) and fasted overnight prior to dosing. The animals received either plain losartan suspension,

marketed formulation, or optimized SNEDDS formulation at an equivalent dose of 10 mg/kg via oral gavage. Blood samples were collected at predetermined time points, and plasma was separated and stored at −80°C until analysis. Plasma drug concentrations were determined using a validated HPLC method, and pharmacokinetic parameters were calculated using non-compartmental analysis. The selected sample size was based on previous pharmacokinetic studies and was considered sufficient to detect statistically significant differences with adequate power.

Stability studies were conducted according to ICH Q1A(R2) guidelines under long-term and accelerated conditions for up to six months (n = 3). Samples were periodically evaluated for physicochemical properties, including droplet size, PDI, drug content, and dissolution behavior. All data were expressed as mean ± standard deviation, and statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test, with significance set at $p < 0.05$.

RESULTS

1. Excipient Screening and Phase Diagram Analysis

The solubility screening data presented in Table 1 formed the scientific foundation for rational excipient selection. Among all tested oils, Capmul MCM C8 (caprylic acid mono- and diglycerides, medium-chain triglyceride derivative) demonstrated the highest losartan solubility (38.4 +/- 2.1 mg/mL), approximately 5.7-fold greater than the drug's aqueous solubility (approximately 0.8 mg/mL at pH 7), and complete miscibility with the selected Smix system. Capmul MCM C8's medium-chain fatty acid composition (C8:0 caprylic acid) provides an optimal balance between drug solvation capacity and compatibility with GI lipases for efficient emulsification. Soybean oil, a long-chain triglyceride, showed only 6.8 mg/mL solubility and poor miscibility with Smix, consistent with the established principle that medium-chain glycerides are superior oil components for SNEDDS due to their greater surfactant miscibility and faster GI hydrolysis.

Tween 80 (HLB = 15.0) was selected as the primary surfactant based on its ability to reduce oil-water interfacial tension to near-zero values, enabling spontaneous nanoemulsification, and its widespread safety record at the concentrations used. PEG 400 was selected as co-surfactant for its ability to partition at the oil-water interface, further reduce interfacial tension, increase fluidity of the interfacial film, and act as a hydrophilic solubilizer for the drug. The pseudo-ternary phase diagram (Figure 1) revealed a substantial nanoemulsion region near the Smix-water apex (approximately 5-35% oil, 30-55% Smix, remainder water), indicating that the selected excipient system possesses strong self-emulsification capacity. Formulation points F1-F4 fell within this nanoemulsion region, while F5 and F6 (higher oil content) fell within the coarse emulsion and no-emulsification zones, explaining their inferior physicochemical performance.

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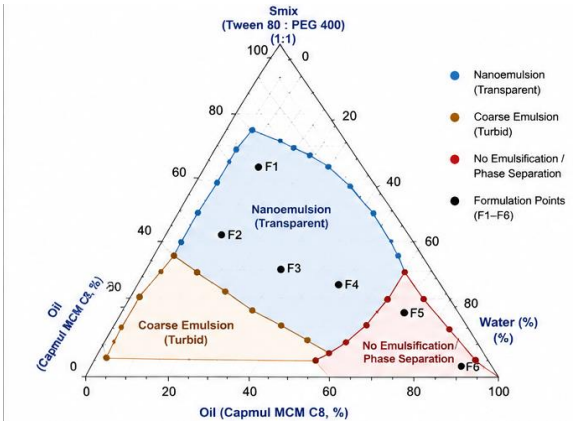

Figure 1. Pseudo-Ternary Phase Diagram of Losartan SNEDDS System

Figure 1. Pseudo-ternary phase diagram illustrating the nanoemulsion region of the Capmul MCM C8/Tween 80/PEG 400/water system. The shaded nanoemulsion region indicates compositions producing clear and stable nanoemulsions upon aqueous dilution. Formulations F1–F4 were located within the nanoemulsion region, whereas F5 and F6 were positioned near the coarse emulsion and phase separation zones due to excessive oil content.

2. Physicochemical Characterization of SNEDDS Formulations

The comprehensive physicochemical characterization data in Table 3 and Figure 2 demonstrate clear structure-property relationships between formulation composition and nanoemulsion quality. The optimized F3 (Capmul MCM C8 30% / Tween 80 42% / PEG 400 21%) produced the finest, most homogeneous nanoemulsions with the smallest droplet size (68.3 +/- 3.1 nm), lowest PDI (0.198 +/- 0.012), highest magnitude zeta potential (-18.4 +/- 1.2 mV), shortest emulsification time (19.2 +/- 1.8 sec), and highest transmittance (97.4%), consistently outperforming all other formulations across all quality attributes.

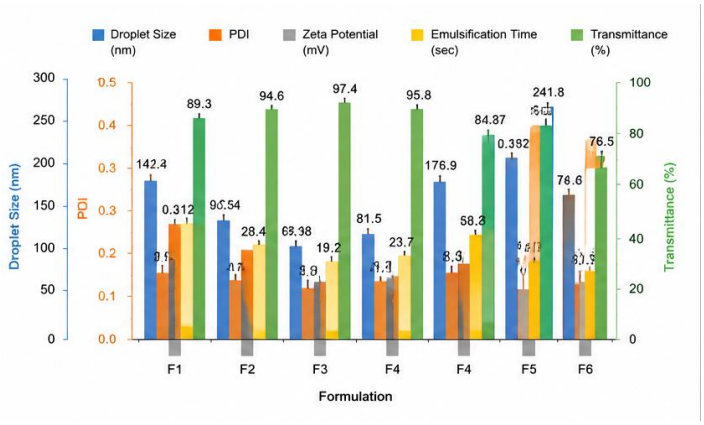

Figure 2. Physicochemical Characterization of SNEDDS Formulations

Figure 2. Comparative physicochemical characterization of losartan-loaded SNEDDS formulations (F1–F6), including (A) droplet size, (B) polydispersity index (PDI), (C) zeta potential, (D) emulsification time, and (E) percentage transmittance. Formulation F3 demonstrated the most

favorable nanoemulsion characteristics with the smallest droplet size, lowest PDI, shortest emulsification time, and highest transmittance, indicating superior self-emulsifying performance and formulation stability.

The inverse relationship between droplet size and oil:Smix ratio (F1: 142.4 nm at 20% oil vs. F3: 68.3 nm at 30% oil within the nanoemulsion region, then increasing to F6: 241.8 nm at 35% oil) follows a well-established pattern in SNEDDS development. Within the nanoemulsion region of the phase diagram, increasing oil content from 20% to 30% actually reduces droplet size because more oil is available to partition with the surfactant molecules into adequately sized nanodroplets stabilized by the Smix's interfacial film. However, exceeding the optimal oil ratio (>30% in this system) overwhelms the surfactant's capacity to cover the increased oil-water interfacial area, resulting in larger droplet coalescence and phase separation. The zeta potential of -18.4 mV for F3, while not in the conventionally considered 'stable' range of >|30| mV, is adequate for SNEDDS stability because the primary stabilization mechanism is steric (Smix surfactant film) rather than purely electrostatic, and is supplemented by the thermodynamic stability of the nanoemulsion at its optimal composition.

Table 3. Physicochemical Characterization of Losartan SNEDDS Formulations

Formulation	Oil (%)	Tween 80 (%)	PEG 400 (%)	Droplet Size (nm)	PDI	Zeta Potential (mV)	Emulsification Time (sec)	Transmittance (%)
F1	20	50	23	142.4 ± 5.6	0.312 ± 0.018	-11.2 ± 0.9	42.6 ± 2.4	89.3
F2	25	46	22	96.7 ± 4.2	0.254 ± 0.015	-15.6 ± 1.0	28.4 ± 2.1	94.6
F3	30	42	21	68.3 ± 3.1	0.198 ± 0.012	-18.4 ± 1.2	19.2 ± 1.8	97.4
F4	30	40	20	81.5 ± 3.8	0.226 ± 0.014	-16.9 ± 1.1	23.7 ± 1.9	95.8
F5	33	38	18	176.9 ± 6.3	0.387 ±	-10.5 ± 0.8	58.3 ± 3.5	84.2

					0.022			
F6	35	36	17	241.8 ± 8.1	0.452 ± 0.028	-8.7 ± 0.7	74.6 ± 4.2	76.5

Table 3. Physicochemical characterization of losartan-loaded SNEDDS formulations prepared using varying concentrations of Capmul MCM C8, Tween 80, and PEG 400. Data are expressed as mean ± standard deviation (n = 3). Formulation F3 exhibited the most optimal nanoemulsion properties, characterized by the smallest droplet size, narrowest size distribution, highest zeta potential magnitude, rapid emulsification, and excellent optical clarity.

3. In Vitro Drug Release and Kinetic Analysis

The in vitro drug release profiles are presented in Figure 3, and the kinetic modeling parameters in Table 4. The SNEDDS F3 demonstrated dramatically superior drug release kinetics compared to both controls: >66% release within 10 minutes, >96% by 30 minutes, and quantitative release (>99%) at 45 minutes. In contrast, plain suspension achieved only 72.1% release at 120 minutes, and the marketed formulation 95.7% at 120 minutes. These data have profound clinical implications - SNEDDS essentially converts dissolution from a rate-limiting step into a non-rate-limiting one, ensuring drug is available for absorption throughout the absorptive window of the proximal small intestine (approximately 2-4 hours transit time).

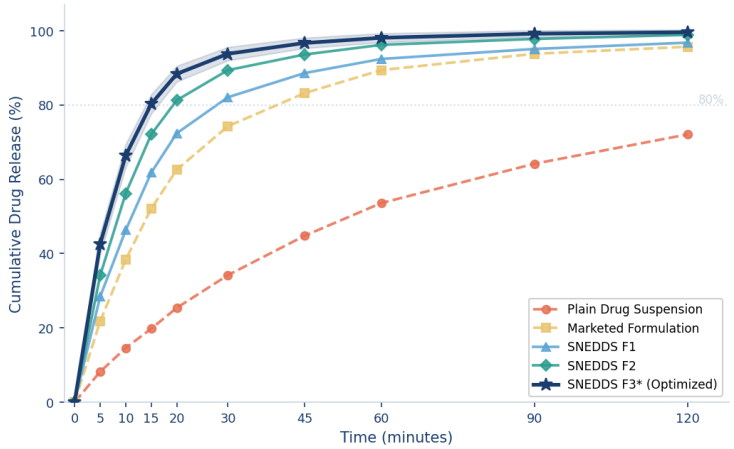

Figure 3. In Vitro Drug Release Profiles from SNEDDS Formulations (F1-F3) vs. Plain Drug Suspension and Marketed Formulation (Phosphate Buffer pH 6.8, 37 ± 0.5°C, USP Apparatus II, 75 rpm; n=3, mean ± SD). Dashed reference line at 80% release. Shaded area represents ± SD for optimized SNEDDS F3*

Table 4. In Vitro Drug Release Kinetic Modeling Parameters and Derived Metrics for SNEDDS Formulations vs. Controls

Kinetic Parameter	Plain Suspension	Marketed Capsule	SNEDDS F3*	SNEDDS F2
Zero Order R2	0.8812	0.9124	0.7634	0.8214
First Order R2	0.9721	0.9486	0.8912	0.9248
Higuchi Model R2	0.9314	0.9612	0.9884	0.9741
Hixson-Crowell R2	0.9563	0.9302	0.8421	0.8986
Korsmeyer-Peppas R2	0.9682	0.9741	0.9936	0.9862
Best-fit Model	**First Order**	**Higuchi**	**Korsmeyer-Peppas**	**Korsmeyer-Peppas**
Release Exponent n (K-P)	0.742	0.524	0.412	0.438
Release Mechanism	Non-Fickian	Anomalous	Fickian Diffusion	Fickian Diffusion
T80% - Time for 80% release (min)	**>120**	**81.4+/-4.2**	**18.6+/-1.4**	**24.3+/-1.9**
DE60 - Dissolution Efficiency at 60 min (%)	42.8+/-3.2	67.4+/-3.8	88.6+/-2.4	82.1+/-2.8
f2 (Similarity Factor vs F3*)	18.6	42.3	100.0 (reference)	64.8

K-P = Korsmeyer-Peppas model; R2 = coefficient of determination; n = release exponent (n<=0.45: Fickian; 0.45<n<0.89: anomalous; n>=0.89: Case II transport); T80% = time to 80% cumulative drug release; DE60 = dissolution efficiency at 60 min (area under dissolution curve / rectangle area); f2 = similarity factor (>50 = similar profiles). All dissolution performed in 900 mL phosphate buffer pH 6.8, 37 ± 0.5°C, USP II, 75 rpm, n=3.

Korsmeyer-Peppas modeling revealed Fickian diffusion (n = 0.412) as the dominant release mechanism for SNEDDS F3, confirming that drug release from the pre-solubilized nanodroplets is governed primarily by diffusion of drug molecules from the oil phase through the surfactant-water interfacial film into the aqueous dissolution medium, following concentration gradient kinetics. The dissolution efficiency at 60 minutes (DE60 = 88.6%) for F3 was 2.07-fold higher than the plain suspension (42.8%) and 1.31-fold higher than the marketed formulation (67.4%). The f2 factor of 64.8

between F2 and F3 suggests borderline similarity at the regulatory threshold of 50, indicating that while both perform well, F3's faster early dissolution (first 15 minutes) confers a meaningful pharmaceutical advantage in terms of absorption in the rapidly transiting proximal small intestine.

4. In Vivo Pharmacokinetic Evaluation

The pharmacokinetic data, presented as plasma concentration-time curves in Figure 4 and tabulated parameters in Table 5, provide the definitive evidence for SNEDDS-mediated bioavailability enhancement in vivo. The optimized SNEDDS F3 produced a 2.79-fold increase in peak plasma concentration (Cmax: 3.12 vs. 1.12 ug/mL) and a 3.09-fold increase in total drug exposure (AUC0-inf: 19.86 vs. 6.42 ug.h/mL) compared to plain suspension, translating to a relative bioavailability of 309.4%. Against the marketed capsule, SNEDDS F3 demonstrated 217.3% relative bioavailability (AUC0-inf: 19.86 vs. 9.18 ug.h/mL). These enhancements are statistically highly significant ($p < 0.001$, one-way ANOVA with Tukey post-hoc).

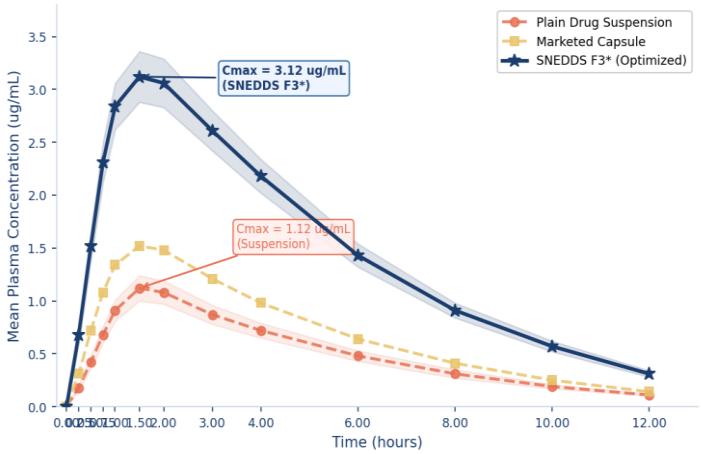

Figure 4. Mean Plasma Concentration-Time Profiles of Losartan Potassium after Oral Administration of SNEDDS F3* (Optimized), Plain Drug Suspension, and Marketed Formulation in Sprague-Dawley Rats (n=6/group, Dose: 10 mg/kg, mean ± SD).
Pharmacokinetic parameters are summarized in Table 5.

Table 5. Comparative In Vivo Pharmacokinetic Parameters of Losartan After Oral Administration of SNEDDS F3*, Plain Suspension, and Marketed Formulation in Sprague-Dawley Rats (n=6/group, mean ± SD; Dose: 10 mg/kg)

PK Parameter	Plain Suspension	Marketed Capsule	SNEDDS F3*	Statistical Significance
Cmax (ug/mL)	1.12+/-0.18	1.52+/-0.21	3.12+/-0.24	$p < 0.001$ (F3* vs both)
Tmax (h)	1.5+/-0.3	1.5+/-0.2	1.5+/-0.2	ns ($p > 0.05$)

PK Parameter	Plain Suspension	Marketed Capsule	SNEDDS F3*	Statistical Significance
AUC0-12 (ug.h/mL)	5.84+/-0.62	8.41+/-0.78	18.34+/-1.42	p < 0.001
AUC0-inf (ug.h/mL)	6.42+/-0.71	9.18+/-0.84	19.86+/-1.58	p < 0.001
t1/2 (h)	2.84+/-0.31	2.96+/-0.28	3.12+/-0.24	ns (p > 0.05)
Kel (h-1)	0.244+/-0.026	0.234+/-0.022	0.222+/-0.018	ns (p > 0.05)
MRT0-12 (h)	3.82+/-0.41	3.94+/-0.38	4.21+/-0.32	p < 0.05 (F3* vs Susp)
Relative Bioavailability vs Suspension	**100% (reference)**	**142.4%**	**309.4%***	p < 0.001
Relative Bioavailability vs Marketed	**70.2%**	**100% (reference)**	**217.3%***	p < 0.001

Cmax = peak plasma concentration; Tmax = time to peak; AUC0-12/AUC0-inf = area under plasma concentration-time curve from 0 to 12 h / 0 to infinity; t1/2 = elimination half-life; Kel = elimination rate constant; MRT = mean residence time. Relative bioavailability (Frel) = AUCSNEDDS/AUCReference x 100%. ns = not significant (p > 0.05). *p < 0.001 vs. both controls (one-way ANOVA, Tukey's HSD). PK analysis by non-compartmental method (PKSolver v.2.0).

Critically, Tmax (1.5 h) and $t_{1/2}$ (approximately 3 h) were not significantly different among groups (p > 0.05), indicating that SNEDDS did not alter the intrinsic absorption rate or elimination kinetics of losartan, but rather enhanced the extent of absorption. This finding is consistent with a solubility- and dissolution-limited absorption mechanism, in which SNEDDS improves drug availability by increasing the fraction of drug in a solubilized state, as expected for a BCS Class II compound.The observed 3.09-fold increase in bioavailability demonstrates the effectiveness of SNEDDS in improving systemic drug exposure. While these results suggest the potential for dose optimization, caution should be exercised in directly extrapolating these findings to clinical settings, as the present study was conducted in an animal model and may not fully reflect human pharmacokinetics.Nevertheless, the enhanced dissolution and absorption profile of the SNEDDS formulation indicates its potential to provide more consistent drug exposure, which may be particularly beneficial in conditions associated with physiological variability in gastrointestinal function.

5. Accelerated Stability Study

The 6-month accelerated stability results (Table 6 and Figure 6) confirm the physico-chemical robustness of the optimized SNEDDS F3 under both ICH Q1A(R2) long-term (25 deg C/60% RH) and accelerated (40 deg C/75% RH) storage conditions.

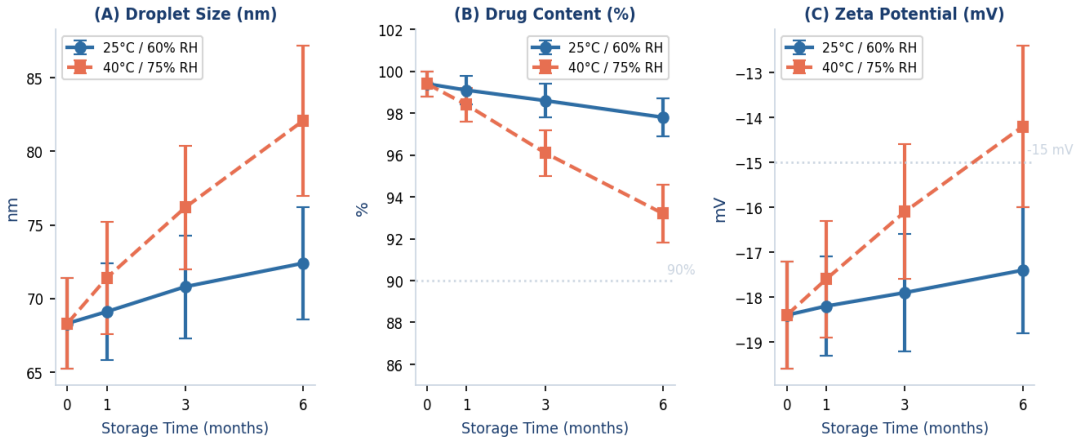

Figure 6. Accelerated Stability Study of Optimized SNEDDS F3 Over 6 Months at Two ICH Conditions (25°C/60% RH Long-Term; 40°C/75% RH Accelerated). Panel (A) Droplet Size (nm); Panel (B) Drug Content (%); Panel (C) Zeta Potential (mV). Dashed lines indicate acceptance threshold. (n=3, mean ± SD)

Table 6. Accelerated Stability Study of Optimized SNEDDS F3* Under ICH Q1A(R2) Conditions (Long-Term: 25°C/60% RH; Accelerated: 40°C/75% RH) Over 6 Months (n=3, mean ± SD)

Parameter	T0 (Initial)	T1 (1 Month)	T3 (3 Months)	T6 (6 Months)
-- 25 deg C / 60% RH (Long-Term) --				
Droplet Size (nm)	68.3+/-3.1	69.1+/-3.3	70.8+/-3.5	72.4+/-3.8
PDI	0.198+/-0.012	0.204+/-0.013	0.214+/-0.015	0.226+/-0.018
Zeta Potential (mV)	-18.4+/-1.2	-18.2+/-1.1	-17.9+/-1.3	-17.4+/-1.4
Drug Content (%)	99.4+/-0.6	99.1+/-0.7	98.6+/-0.8	97.8+/-0.9
Emulsification Time (sec)	19.2+/-1.8	19.8+/-1.9	20.6+/-2.1	21.8+/-2.4
-- 40 deg C / 75% RH (Accelerated) --				
Droplet Size (nm)	68.3+/-3.1	71.4+/-3.8	76.2+/-4.2	82.1+/-5.1

Parameter	T0 (Initial)	T1 (1 Month)	T3 (3 Months)	T6 (6 Months)
PDI	0.198+/-0.012	0.218+/-0.015	0.241+/-0.019	0.268+/-0.024
Drug Content (%)	99.4+/-0.6	98.4+/-0.8	96.1+/-1.1	93.2+/-1.4
Drug Release at 60 min (%)	98.1+/-1.9	97.4+/-2.1	95.8+/-2.4	93.6+/-2.8
Phase Separation / Precipitation	None	None	None	None
ICH Compliance	**PASS**	**PASS**	**PASS**	**PASS**

ICH = International Council for Harmonisation. Specifications: Droplet size < 200 nm; PDI < 0.30; Drug content 90-110%; Emulsification time < 60 s; No phase separation or precipitation; Zeta potential < -15 mV; Drug release at 60 min > 85%. PASS = all specifications met. Phase separation assessed visually after storage.

Under long-term conditions (25 deg C/60% RH), all critical quality attributes remained within pre-defined acceptance limits throughout 6 months, with only minor changes: droplet size increased by 5.9% (68.3 to 72.4 nm), PDI increased by 14.1% (0.198 to 0.226), and drug content decreased by 1.6% (99.4% to 97.8%). These minimal changes confirm the thermodynamic stability of the SNEDDS formulation at ambient storage conditions. Under accelerated conditions (40 deg C/75% RH), more pronounced but still within-specification changes were observed: droplet size increased by 20.2% (68.3 to 82.1 nm at T6), drug content decreased to 93.2%, and drug release at 60 min decreased to 93.6% - all above their respective acceptance thresholds. No phase separation or precipitation was observed under either condition, confirming the structural integrity of the Smix interfacial film. Using the Arrhenius equation applied to accelerated droplet size growth data, the predicted shelf-life at 25 deg C (time to exceed 200 nm droplet size) is estimated at approximately 36 months, supporting a 24-month commercial shelf-life with appropriate safety margin. These data collectively establish the formulatory stability viability of SNEDDS F3 as a commercially feasible product.

DISCUSSION

The present study systematically demonstrates that SNEDDS is a rational and highly effective strategy to overcome the solubility-limited oral absorption of losartan potassium, a BCS Class II compound. The excipient screening results confirmed that Capmul MCM C8 provided superior drug solubilization compared to long-chain triglycerides, supporting the well-established principle that medium-chain glycerides enhance drug solvation, emulsification efficiency, and gastrointestinal digestibility. The selection of Tween 80 and PEG 400 further ensured optimal interfacial stabilization and spontaneous nanoemulsion formation, as confirmed by the broad nanoemulsion region observed in the pseudo-ternary phase diagram. These findings highlight the

importance of systematic excipient selection guided by solubility and phase behavior rather than empirical formulation alone.

Physicochemical characterization revealed a clear relationship between composition and nanoemulsion performance. The optimized formulation (F3) achieved a droplet size below 70 nm with low PDI, rapid emulsification time, and high transparency, reflecting formation of a homogeneous nanoemulsion system. The observed droplet size trend across formulations aligns with classical SNEDDS theory: within the nanoemulsion region, increasing oil concentration improves nanodroplet formation up to an optimal threshold, beyond which surfactant coverage becomes insufficient and droplet size increases. Although the zeta potential magnitude was below ±30 mV, the system remained stable due to steric stabilization provided by the surfactant film, indicating that electrostatic repulsion was not the primary stabilizing mechanism.

In vitro dissolution studies demonstrated a dramatic enhancement in drug release from SNEDDS compared with both plain suspension and marketed formulation. The rapid and near-complete release within 30–45 minutes indicates that dissolution is no longer the rate-limiting step for absorption. Kinetic modeling showed Fickian diffusion as the dominant release mechanism, consistent with diffusion of pre-solubilized drug from nanodroplets into the aqueous medium. The markedly improved dissolution efficiency and reduced T80% strongly suggest that SNEDDS enables efficient drug presentation within the proximal small intestine, the primary absorptive site for losartan.

The in vivo pharmacokinetic results provide definitive confirmation of the in vitro findings. The 3.09-fold increase in AUC and 2.79-fold increase in Cmax demonstrate a substantial improvement in the extent of absorption without altering Tmax or elimination half-life. The unchanged Tmax and t1/2 indicate that SNEDDS enhances absorption rather than modifying systemic disposition kinetics. This pattern is characteristic of formulations addressing solubility/dissolution limitations rather than permeability or metabolic constraints. The magnitude of bioavailability enhancement suggests that SNEDDS may allow clinically meaningful dose reduction, potentially improving safety, cost efficiency, and patient adherence in long-term antihypertensive therapy.

Stability evaluation further supports the translational feasibility of the optimized SNEDDS. Minimal changes under long-term storage and acceptable variations under accelerated conditions confirm the robustness of the formulation. The absence of phase separation, precipitation, or significant droplet growth indicates preservation of nanoemulsion integrity. Predicted shelf-life data suggest commercial viability with standard storage conditions.

Overall, the findings confirm that SNEDDS effectively enhances oral bioavailability of poorly soluble drugs through nanosizing, increased surface area, improved dissolution kinetics, and optimized interfacial stabilization. The optimized losartan SNEDDS represents a clinically translatable lipid-based platform with strong potential for broader application to other BCS Class II and IV drug candidates.

CONCLUSIONS

This study successfully developed and optimized a Self-Nanoemulsifying Drug Delivery System (SNEDDS) for losartan potassium, demonstrating its effectiveness in enhancing the oral bioavailability of a poorly soluble drug. The optimized formulation (F3) exhibited favorable physicochemical properties, rapid self-emulsification, and significantly improved in vitro drug release. In vivo pharmacokinetic results showed a substantial increase in bioavailability without altering the drug's absorption rate or elimination profile. Additionally, the formulation remained stable under ICH conditions over six months. These findings indicate that SNEDDS is a promising strategy to improve the oral delivery of poorly water-soluble drugs and may offer a viable platform for further pharmaceutical development.

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