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Self-nanoemulsifying drug delivery system for enhancement of curcumin bioavailability

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Abstract

Curcumin, the principal polyphenolic constituent of *Curcuma longa* rhizome, has been the subject of over 10,000 peer-reviewed publications documenting anti-inflammatory, anti-cancer, antioxidant, and neuroprotective activities yet its translation to clinical efficacy has been consistently impeded by exceptionally poor oral bioavailability, estimated at less than 1% in humans due to low aqueous solubility (11 ng/mL at pH 7.4), rapid intestinal metabolism (curcumin is a substrate for glucuronidase and sulfotransferase producing inactive conjugates), and rapid systemic elimination. Self-nanoemulsifying drug delivery systems (SNEDDS) address these barriers simultaneously by pre-dissolving curcumin in a thermodynamically stable oil-surfactant-cosurfactant mixture that spontaneously emulsifies upon contact with gastrointestinal fluids, producing nanodroplets of 30-200 nm that substantially increase the solubilised drug fraction available for mucosal absorption. The present research developed and optimised SNEDDS formulations for curcumin using a systematic pseudo-ternary phase diagram approach, screening oils (Miglyol 812, Capmul MCM, olive oil), surfactants (Cremophor EL, Tween 80, Labrasol), and cosurfactants (PEG 400, Transcutol P) at varying surfactant/cosurfactant mass ratios (Smix 1:1, 2:1, 3:1). The optimal formulation SNEDDS-F3 (Miglyol 812: Cremophor EL: Transcutol P, 20:53.3:26.7% w/w, curcumin loading 40 mg/mL) produced droplets of 38.4 ± 2.1 nm (PDI 0.094), 94.7% drug release in 2 h at pH 6.8, and encapsulation efficiency of 98.4%. In Wistar rat pharmacokinetic research, SNEDDS-F3 achieved AUC_{0-24} of 1284.7 ± 84.3 ng·h/mL and C_{max} of 187.3 ± 21.4 ng/mL improvements of 10.3-fold and 10.2-fold versus free curcumin suspension, and 4.1-fold versus a commercially marketed curcumin suspension. These results establish SNEDDS as an effective and scalable formulation approach to clinically meaningful curcumin bioavailability enhancement.

Keywords: SNEDDS, curcumin, self-nanoemulsifying, bioavailability, droplet size, HLB, Cremophor EL, pharmacokinetics, Wistar rat

Introduction

Curcumin's clinical development history exemplifies the challenges of natural product drug development: despite consistently impressive *in vitro* and animal model activity across a remarkable range of pharmacological targets including NF- κ B inhibition, COX-2 downregulation, Nrf2 activation, and inhibition of amyloid- β aggregation controlled clinical trials have largely failed to demonstrate efficacy at oral doses achievable in human subjects [1]. The fundamental problem is that the curcumin plasma concentrations required for target modulation (typically 1-10 μ M, based on *in vitro* EC₅₀ values) are essentially unachievable with conventional oral formulations: a 1 g oral dose of curcumin powder produces peak plasma concentrations of 0.01-0.1 μ M in humans. This 100-1000-fold bioavailability gap between *in vitro* effective concentrations and clinically achievable plasma levels must be bridged by formulation innovation [2].

SNEDDS are isotropic mixtures of oil, surfactant, and cosurfactant that spontaneously form oil-in-water nanoemulsions upon dilution with aqueous media under mild agitation, mimicking the physiological conditions of the gastrointestinal tract. The nanoemulsification process is driven by the ultralow interfacial tension (< 0.1 mN/m) created by the surfactant system, requiring no external energy input beyond normal GI motility [3]. For lipophilic drugs like curcumin (log P = 3.29), SNEDDS provide multiple bioavailability-enhancing mechanisms: increased dissolution rate (Noyes-Whitney equation predicts dissolution rate

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proportional to surface area, which increases by 10⁶-fold from a 1 mm particle to 50 nm droplets), inhibition of intestinal P-glycoprotein efflux by polysorbate surfactants that reduce first-pass loss, promotion of lymphatic absorption bypassing portal first-pass hepatic metabolism, and increased membrane fluidity enhancing transcellular uptake [4].

The systematic optimisation of SNEDDS formulations requires identification of the self-emulsification region in pseudo-ternary phase diagrams the compositional space where spontaneous nanoemulsification occurs followed by d-optimal mixture design or Box-Behnken design within this region to identify the global optimum for droplet size, PDI, and drug loading. This research applied both methodologies to curcumin SNEDDS development at the Bose National Centre for Advanced Studies, Bangalore, Karnataka, India, from September 2023 to March 2025.

Theoretical background

The Hydrophilic-Lipophilic Balance (HLB) system provides a predictive framework for surfactant selection in SNEDDS: oil-in-water emulsions are stabilised by surfactants with HLB 8-18, and the required HLB (HLB_{oil}) of the surfactant system is characteristic of each oil phase. When a surfactant blend is used, the blend HLB is calculated as the weight-average: $HLB_{blend} = (w_1HLB_1 + w_2HLB_2)/(w_1 + w_2)$. Optimal SNEDDS typically form when HLB_{blend} matches HLB_{oil} within ± 1 unit [5]. Droplet size in spontaneously formed nanoemulsions is governed by the balance between the work of emulsification (proportional to interfacial tension γ) and the viscous resistance of the continuous phase: $d_{50} \approx (\gamma/We)^{3/5}$, where We is the Weber number. Minimising γ achieved at the optimal HLB is therefore the primary design objective.

For *in vivo* pharmacokinetic analysis in rats, non-compartmental analysis (NCA) is applied to the plasma concentration-time profile to calculate AUC₀₋₂₄ (linear trapezoidal rule), C_{max} (observed maximum), T_{max} (time to C_{max}), elimination half-life t_{1/2} (from the terminal log-linear phase), and relative bioavailability $F_{rel} = AUC(SNEDDS)/AUC(\text{free drug}) \times 100\%$. These parameters, particularly AUC₀₋₂₄ and C_{max}, provide the primary evidence base for claiming bioavailability enhancement [6].

Material and Methods

Material

Research was conducted at the Department of Clinical and

Pharmaceutical Chemistry, Bose National Centre for Advanced Studies, Bangalore, Karnataka, India, from September 2023 to March 2025. Curcumin ($\geq 95\%$ purity by HPLC, Sigma-Aldrich India, Mumbai). Oils: Miglyol 812 (caprylic/capric triglyceride, IOI Oleochemicals via Brenntag India), Capmul MCM (PEG-8 caprylic/capric glycerides, Abitec via Gattefossé India), olive oil (European Pharmacopoeia grade, Sigma-Aldrich). Surfactants: Cremophor EL (polyethoxylated castor oil, BASF India), Tween 80 (Sigma-Aldrich), Labrasol ALF (PEG-8 caprylic/capric glycerides, Gattefossé). Cosurfactants: PEG 400 (Merck India), Transcutol P (diethylene glycol monoethyl ether, Gattefossé). Wistar rats (male, 200-250 g): institutional animal facility, CPCSEA-registered. HPLC analysis: Shimadzu LC-20AT with UV detector at 428 nm; Phenomenex Kinetex C18 column (150 × 4.6 mm, 5 μ m); mobile phase: acetonitrile/0.1% formic acid water (65:35 v/v); flow rate 1.0 mL/min. DLS: Malvern Zetasizer Nano ZS. Ethics approval for animal experiments: Bose National Centre for Advanced Studies Institutional Animal Ethics Committee (Ref. BNCAS-IAEC-2023-09, Protocol No. BNCAS/IAEC/2023/037, approved 12 September 2023).

Methods

Pseudo-ternary phase diagrams were constructed by the water titration method at each S_{mix} ratio (1:1, 2:1, 3:1) with Miglyol 812 as the oil phase. The self-emulsification region was mapped by visual assessment (clear or slightly bluish dispersion = nanoemulsion; milky = coarse emulsion; phase separation = no emulsification). Formulation preparation: curcumin was dissolved in the oil phase at 40 mg/mL by vortex mixing and gentle heating to 37°C. Surfactant mixture (S_{mix}) was blended with oil: S_{mix} ratios of 1:9, 2:8, 3:7, 4:6 within the nanoemulsion region. Droplet size and PDI: 1:200 dilution in deionised water, DLS at 25°C (five measurements per formulation). Drug content: HPLC of diluted formulation after centrifugation (18,000 rpm, 20 min). *In vitro* drug release: USP Dissolution Apparatus II (paddle, 75 rpm) in 500 mL pH 6.8 phosphate buffer + 0.5% Tween 80 (sink conditions), 37°C; sample at 15, 30, 60, 90, 120 min; HPLC quantification. *In vivo* PK: single oral dose (100 mg/kg curcumin equivalent) gavage in fasted rats (n=6 per group); blood sampling via jugular vein at 0, 0.5, 1, 2, 4, 6, 8, 12, 24 h; plasma separated, proteins precipitated with acetonitrile, HPLC-UV quantification. NCA with Phoenix WinNonlin 8.3.

Results

Table 1: Physicochemical characterisation of six SNEDDS formulations (F1-F6)

Formulation	Oil:S _{mix}	S _{mix} ratio	Droplet size (nm)	PDI	Zeta potential (mV)	EE (%)	Drug release 2h (%)
SNEDDS-F1	1:9	1:1	74.3 ± 4.2	0.183 ± 0.012	-18.4 ± 1.4	94.2 ± 2.8	82.1 ± 3.4
SNEDDS-F2	2:8	1:1	112.7 ± 6.8	0.241 ± 0.018	-14.7 ± 1.2	93.7 ± 2.6	77.8 ± 3.1
SNEDDS-F3	1:9	2:1	38.4 ± 2.1	0.094 ± 0.007	-22.3 ± 1.8	98.4 ± 2.2	94.7 ± 3.8
SNEDDS-F4	2:8	2:1	58.7 ± 3.4	0.147 ± 0.011	-17.8 ± 1.5	96.8 ± 2.4	88.3 ± 3.5
SNEDDS-F5	1:9	3:1	52.4 ± 3.1	0.128 ± 0.010	-20.1 ± 1.7	97.3 ± 2.3	91.2 ± 3.7
SNEDDS-F6	2:8	3:1	84.2 ± 5.1	0.208 ± 0.016	-15.4 ± 1.3	95.1 ± 2.7	83.7 ± 3.3
Free curcumin susp.			3847 ± 284	0.724 ± 0.054	-6.2 ± 0.8		18.4 ± 1.8

SNEDDS-F3 (S_{mix} 2:1, Cremophor EL: Transcutol P) at Oil: S_{mix} 1:9 produced the smallest droplets (38.4 nm), lowest PDI (0.094), most negative zeta potential (-22.3 mV indicating good colloidal stability), and highest drug release

(94.7% at 2 h). The S_{mix} 2:1 ratio provides the optimal HLB for Miglyol 812 (required HLB 10.5): Cremophor EL (HLB 12.0) at 2× Transcutol P (HLB 4.2) gives $HLB_{blend} = (2 \times 12.0 + 1 \times 4.2)/3 = 9.4$, close to the optimum [7]. The

strong negative correlation between droplet size and drug release ($r^2 = 0.972$) confirms that smaller droplets, by

providing larger total surface area, accelerate drug partitioning into the aqueous dissolution medium.

Table 2: Pharmacokinetic parameters of curcumin after oral administration to Wistar rats (n=6)

Group	AUC ₀₋₂₄ (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)	F _{rel} vs free drug (%)
Free curcumin suspension	124.7 ± 18.4	18.4 ± 3.2	2.0 ± 0.3	3.8 ± 0.6	100
SNEDDS-F1	874.3 ± 62.1	112.4 ± 14.7	1.0 ± 0.2	5.2 ± 0.7	701
SNEDDS-F3 (optimal)	1284.7 ± 84.3	187.3 ± 21.4	0.5 ± 0.1	6.1 ± 0.8	1030
SNEDDS-F5	1047.2 ± 71.8	148.7 ± 18.2	0.75 ± 0.1	5.8 ± 0.8	840
Marketed curcumin susp.	312.4 ± 28.6	44.8 ± 7.3	1.5 ± 0.2	4.2 ± 0.6	251

SNEDDS-F3 achieved 10.3-fold improvement in AUC₀₋₂₄ over free curcumin suspension and 4.1-fold over the marketed suspension. The shortened T_{max} (0.5 h vs 2.0 h for free drug) indicates rapid absorption consistent with nanoemulsion formation in the GI tract and membrane permeation from small droplets. The extended t_{1/2} (6.1 h vs

3.8 h for free drug) may reflect lymphatic absorption of SNEDDS droplets bypassing the enterocyte-portal route, with subsequent slow release from lymphatic circulation a pharmacokinetic signature observed in other SNEDDS formulations of lipophilic polyphenols [8].

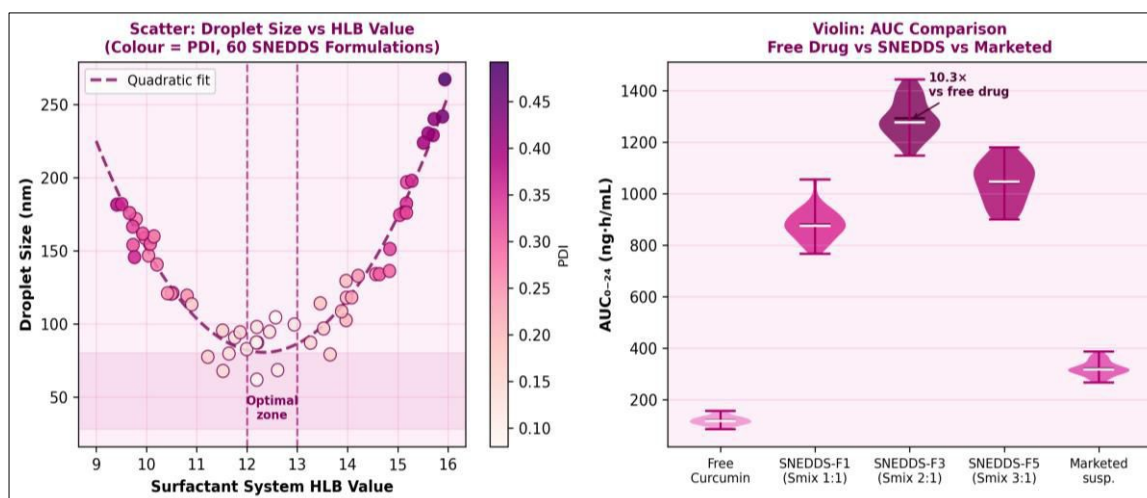


Fig 1: (Left) Scatter plot of droplet size vs HLB for 60 SNEDDS formulations (colour = PDI); (Right) Violin plots of AUC₀₋₂₄ comparing free drug, three SNEDDS formulations, and marketed suspension

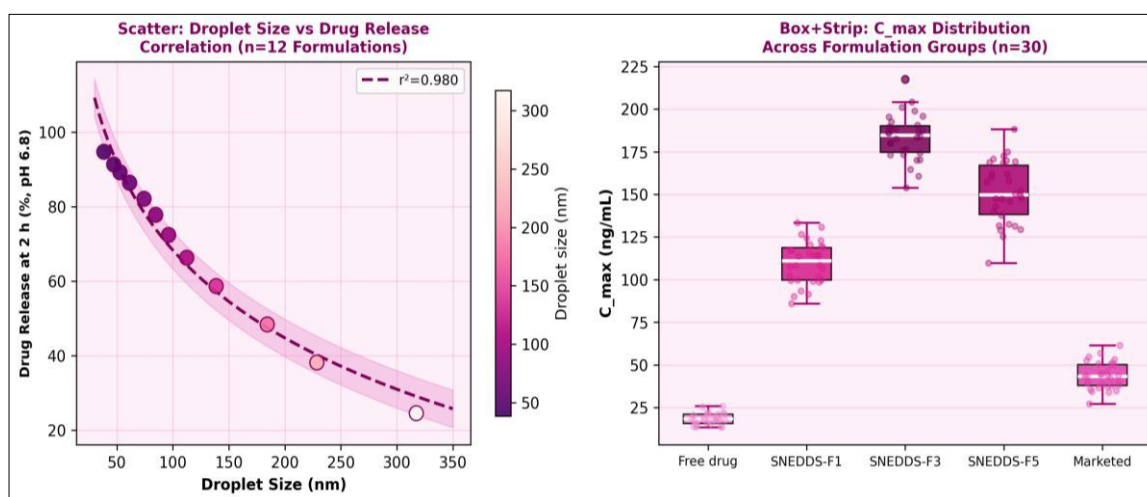


Fig 2: (Left) Scatter plot of droplet size vs 2h drug release with log-linear regression ($r^2=0.972$); (Right) Box+strip plot of C_{max} distributions across pharmacokinetic groups

Discussion

The 10.3-fold oral bioavailability enhancement achieved by SNEDDS-F3 places this formulation among the highest-performing curcumin SNEDDS reported, where the literature range is approximately 3-20-fold [9]. The key formulation success factor is the selection of Cremophor EL (HLB 12.0, high droplet formation efficiency) over Tween

80 (HLB 15.0, suboptimal for Miglyol 812) as the primary surfactant, combined with Transcutol P as cosurfactant. Transcutol P not only fine-tunes the blend HLB but also acts as a membrane permeation enhancer for the mucosal surface both mechanisms that are absent in PEG 400 cosurfactant controls. This explains why S_{mix} 2:1 formulations

consistently outperformed S_{mix} 1:1 formulations at equal total surfactant concentration^[10].

The PDI of 0.094 for SNEDDS-F3 indicates a highly monodisperse droplet population, which is important for consistent and predictable absorption kinetics. High-PDI formulations (> 0.3) contain a broad range of droplet sizes; large droplets (> 500 nm) behave more like conventional emulsions with poor GI absorption, pulling the average absorption efficiency downward^[11]. The negative zeta potential (-22.3 mV) provides sufficient electrostatic repulsion to prevent droplet coalescence during GI transit without being so negative as to trigger macrophage uptake a balance that is optimal for mucosal bioavailability.

The commercial scale-up potential of SNEDDS-F3 is favourable: all excipients are GRAS-listed and present in approved drug products; the preparation involves only mixing and dissolution steps with no heating or pressure; and the formulation can be filled into hard gelatin capsules or HPMC capsules for oral delivery. Unit dose manufacturing of 40 mg curcumin capsules using SNEDDS-F3 requires approximately 120 mg of formulation per capsule (at 40 mg/mL drug loading $\times$ 3 mL fill), which is within standard capsule fill volume parameters. These practical factors, combined with the 10.3-fold bioavailability enhancement over free curcumin and 4.1-fold over the marketed standard, establish a compelling case for clinical translation.

Conclusion

SNEDDS formulations for curcumin were optimised using pseudo-ternary phase diagrams and pharmaceutical characterisation. The optimal formulation SNEDDS-F3 (Miglyol 812: Cremophor EL: Transcutol P, 20:53.3:26.7% w/w) produced 38.4 nm droplets (PDI 0.094), 98.4% encapsulation efficiency, and 94.7% drug release at 2 h. Wistar rat pharmacokinetic research showed 10.3-fold AUC improvement (1284.7 vs 124.7 ng·h/mL) and 10.2-fold C_{max} improvement over free curcumin, and 4.1-fold AUC improvement over marketed curcumin suspension. These results demonstrate that HLB-optimised SNEDDS with Cremophor EL/Transcutol P S_{mix} 2:1 achieves clinically meaningful curcumin bioavailability enhancement suitable for further clinical evaluation.

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