Box–Behnken Design-Based Development, Optimization, and Physicochemical Characterization of a Pregabalin-Loaded Self-Nanoemulsifying Drug Delivery System (SNEDDS) for Neuropathic Pain Management

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Abstract

Background: Pregabalin, a first-line agent for neuropathic pain, has physicochemical and pharmacokinetic characteristics — high aqueous solubility combined with variable, dose-dependent absorption and a short elimination half-life — that make conventional oral formulations suboptimal for sustained symptom control. Self-nanoemulsifying drug delivery systems (SNEDDS) offer a lipid-based strategy to improve solubilisation, present the drug in a pre-dissolved nanoemulsion state, and modulate release.

Objective: This study aimed to develop and statistically optimize a pregabalin-loaded liquid SNEDDS (L-SNEDDS) using a Box–Behnken design (BBD) in Design-Expert software and to characterize the optimized formulation.

Methods: Preformulation studies (solubility, melting point, Fourier-transform infrared [FTIR] compatibility, UV λmax and calibration) were performed. Isopropyl myristate, Tween 80, and PEG 400 were selected as oil, surfactant, and co-surfactant, respectively, following solubility and emulsification-efficiency screening, and their proportions were mapped using a pseudo-ternary phase diagram. A three-factor, three-level BBD (17 runs) was used to optimize the amounts of oil, surfactant, and co-surfactant against self-emulsification time, percentage transmittance, and cloud point. The optimized batch was characterized for pH, viscosity, globule size, polydispersity index (PDI), zeta potential, morphology, drug content, entrapment efficiency, *in vitro* release, release kinetics, and thermodynamic/dilution stability.

Results: Quadratic models best described all three responses ($p < 0.05$, non-significant lack-of-fit). The optimized formulation showed a self-emulsification time of 25.2 s, percentage transmittance of 100.06%, and a cloud point of 84.6 °C, closely matching model predictions. The optimized L-SNEDDS exhibited a mean globule size of 28.2 nm, PDI of 0.324, zeta potential of −3.7 mV, drug content of 109.9% w/w, and entrapment efficiency of 89.47%. *in vitro* release under simulated gastric conditions reached 78.4% at 60 min and best fitted the Higuchi and Korsmeyer–Peppas models ($R^2 = 0.716$ and 0.717, respectively; release exponent $n = 0.474$), indicating Fickian diffusion-controlled release. The optimized formulation was thermodynamically stable to heating–cooling cycling, centrifugation, freeze–thaw cycling, and serial aqueous dilution.

Conclusion: Integration of Design-Expert–driven Box–Behnken optimization enabled rational, statistically validated development of a nanoscale, stable pregabalin SNEDDS with favourable *in vitro* release characteristics, providing a robust liquid intermediate for subsequent solidification into an oral solid dosage form.

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1. Introduction

Neuropathic pain arising from somatosensory nervous system lesion or disease affects a substantial proportion of patients with diabetic peripheral neuropathy, postherpetic neuralgia, spinal cord injury, and other conditions, and remains difficult to manage with conventional analgesics [7, 8]. Pregabalin, a γ-aminobutyric acid (GABA) analogue that binds the α2δ subunit of presynaptic

voltage-gated calcium channels and reduces release of excitatory neurotransmitters, is established first-line therapy for neuropathic pain and is also used in fibromyalgia and as adjunctive antiepileptic therapy [1, 2, 3]. Although pregabalin is highly water-soluble and has oral bioavailability generally reported at 90% or greater, its clinical effect depends on maintaining steady plasma concentrations, and its short elimination half-life of approximately 6 hours necessitates multiple daily dosing with conventional immediate-release tablets, which can compromise adherence and produce fluctuating plasma levels linked to dose-dependent central nervous system adverse effects such as dizziness and somnolence [4, 5, 6].

Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, and co-surfactant that spontaneously form oil-in-water nanoemulsions of droplet size typically below 200 nm upon mild agitation in gastrointestinal fluids [9, 10]. By presenting the drug already solubilised within nanoscale oil droplets, SNEDDS increase the effective interfacial surface area available for absorption, can protect labile drugs from luminal degradation, and are increasingly used as platforms to modulate the release and bioavailability of both poorly soluble and highly soluble low-molecular-weight drugs [11, 12, 13]. For a highly water-soluble drug such as pregabalin, the value of a SNEDDS platform lies less in solubility enhancement than in the ability to entrap the drug within a nanostructured lipidic matrix, thereby providing a means of controlling the rate and extent of drug liberation and a versatile liquid intermediate that can subsequently be solidified into a tablet dosage form [14, 15, 16, 17].

Rational SNEDDS development requires simultaneous optimization of multiple, often interacting, formulation variables — the type and quantity of oil, surfactant, and co-surfactant — against several critical quality responses such as self-emulsification time, optical clarity (percentage transmittance), and thermal stability (cloud point). One-variable-at-a-time approaches are inefficient for capturing such interactions, whereas response surface methodology (RSM), and in particular the Box–Behnken design (BBD), enables efficient exploration of the design space with a reduced number of experimental runs while allowing quadratic modelling of main, interaction, and curvature effects [34, 36, 37]. Design-Expert software is widely used to implement BBD, fit response surfaces, and identify optimal formulations via desirability-function-based numerical optimization [35, 56].

Despite extensive literature on SNEDDS for poorly water-soluble drugs, comparatively few studies have applied a systematic quality-by-design (QbD) framework to a highly water-soluble neuropathic pain agent such as pregabalin, or have coupled Box–Behnken optimization with the thorough physicochemical, release-kinetic, and stability characterization that is required before progression to a solid dosage form. The present study addresses this gap. The specific objectives were to (i) conduct preformulation and excipient-screening studies for pregabalin; (ii) construct a pseudo-ternary phase diagram to delineate the self-nanoemulsifying region for the selected oil–surfactant–co-surfactant system; (iii) apply a three-factor, three-level Box–Behnken design in Design-Expert software to optimize the liquid SNEDDS with respect to self-emulsification time, percentage transmittance, and cloud point; and (iv) comprehensively characterize the optimized batch, including its *in vitro* release behaviour and release-kinetic mechanism, as the foundation for a companion solidification and tableting study.

2. Materials and Methods

2.1. Materials

Pregabalin was procured from Yarrow Chem Products (Mumbai, India). Isopropyl myristate (oil phase), Tween 80 (polysorbate 80; surfactant), and polyethylene glycol 400 (PEG 400; co-surfactant) were obtained from Spectrum Reagents and Chemicals (Cochin, India). Oleic acid, olive oil, Tween 20, Tween 40, propylene glycol, and PEG 200 (used for excipient screening) and all other chemicals were of analytical grade. Distilled water was used throughout. Excipients were selected and characterized with reference to standard pharmaceutical excipient specifications [19], and preformulation studies followed established pharmaceutical development practice [20].

2.2. Preformulation Studies

Organoleptic properties (colour, odour, physical state) of pregabalin were assessed visually against British Pharmacopoeia specifications [18]. Aqueous solubility was determined in 0.1 N HCl, phosphate buffer pH 6.8, and distilled water (1 mg/mL) [18, 21, 22]. Melting point was determined by the open capillary method [21]. Drug–excipient compatibility was assessed by FTIR (JASCO FTIR-4600, 4000–400 cm^{-1}, ATR mode) on pregabalin alone and in 1:1 physical mixtures with isopropyl myristate, Tween 80, and PEG 400 [31]. The wavelength of maximum absorbance (λmax) was determined by scanning pregabalin solutions (200–400 nm) in distilled water and in 0.1 N HCl using a Shimadzu UV-1800/160A spectrophotometer, and calibration curves were constructed over 2–10 µg/mL (distilled water) and 1–8 µg/mL (0.1 N HCl) at 210 nm [32, 33].

2.3. Screening of Oil, Surfactant, and Co-Surfactant

Pregabalin solubility in candidate oils (oleic acid, isopropyl myristate, olive oil), surfactants (Tween 20, Tween 40, Tween 80), and co-surfactants (propylene glycol, PEG 200, PEG 400) was determined by equilibrating excess drug with each vehicle (vortex mixing, centrifugation at 10,000 rpm for 15 min, 0.45 µm filtration) followed by UV assay at 210 nm [25, 26]. Emulsification efficiency of surfactants and co-surfactants with the selected oil was assessed by the number of flask inversions required to achieve a clear, non-turbid emulsion upon aqueous dilution and by percentage transmittance at 650 nm [26, 27].

2.4. Pseudo-Ternary Phase Diagram

Using isopropyl myristate as oil, Tween 80 as surfactant, and PEG 400 as co-surfactant at a fixed surfactant:co-surfactant (Smix) ratio of 1:1, oil-to-Smix weight ratios of 1:9, 1:7, 1:5, 1:3, 1:1, and 2:1 were titrated with water in 5% increments at ambient temperature, and phase transitions (transparent to turbid) were recorded visually to delineate the self-nanoemulsifying region [28, 29, 30].

2.5. Experimental Design

A three-factor, three-level Box–Behnken design (17 runs, including 5 centre points) was constructed in Design-Expert software (version 13, Stat-Ease Inc.) [34, 35, 36]. The independent variables were the volumes of isopropyl myristate (X1, oil), Tween 80 (X2, surfactant), and PEG 400

(X3, co-surfactant), each studied at low, medium, and high levels (Table 1). The dependent responses were self-emulsification time (Y1, seconds; minimized), percentage transmittance (Y2, %; maximized), and cloud point (Y3, °C; maximized). Data were fitted to the second-order polynomial $Y = \alpha0 + \alpha1X1 + \alpha2X2 + \alpha3X3 + \alpha4X1X2 + \alpha5X2X3 + \alpha6X1X3 + \alpha7X1^2 + \alpha8X2^2 + \alpha9X3^2$, and model adequacy was assessed by sequential p-value, lack-of-fit p-value, and adjusted/predicted R^2 [37]. Analysis of variance (ANOVA), residual diagnostics, and response-surface/contour plots were used to interpret main, interaction, and quadratic effects, and the desirability function was used to numerically identify the optimum factor combination [54, 55, 56].

Table 1: Independent variables and levels used in the Box–Behnken design.

Factor	Unit	Type	Low (−1)	Medium (0)	High (+1)
X1 – Isopropyl myristate (oil)	mL	Numeric	0.2	0.4	0.5
X2 – Tween 80 (surfactant)	mL	Numeric	2	3	4
X3 – PEG 400 (co-surfactant)	mL	Numeric	2	3	4

2.6. Formulation of Pregabalin L-SNEDDS

Tween 80 and isopropyl myristate were combined and stirred magnetically (500 rpm) to homogeneity, PEG 400 was added gradually with continued stirring, and pregabalin (25 mg/mL of the oil–surfactant–co-surfactant blend) was dissolved into this mixture. Distilled water was then added dropwise (500 rpm) to form a pre-emulsion, which was probe-sonicated to yield a clear, transparent nanoemulsion [25]. Nine BBD-derived formulations (F1–F9) were prepared varying the oil, surfactant, and co-surfactant volumes according to the design matrix.

2.7. Characterization of Liquid SNEDDS

Self-emulsification efficiency was assessed by diluting 1 mL of each formulation in 500 mL water under gentle magnetic stirring (37 °C, 50 rpm) and grading the resulting dispersion (Grades A–E) and time to clear emulsion formation [38, 39]. Percentage transmittance was measured at 630 nm after 1:100 aqueous dilution [40, 41]. Cloud point was determined by heating a 1:100 aqueous dilution at 10 °C/min and noting the onset of turbidity [42]. The optimized batch was further evaluated for pH (calibrated digital pH meter, 25 °C, triplicate), viscosity (Brookfield DV-II Pro viscometer, spindle 62, 100 rpm, 25 °C), mean globule size and PDI (dynamic light scattering; Horiba nanoPartica SZ-100V2), zeta potential (electrophoretic light scattering; same instrument), and surface morphology (scanning electron microscopy; TESCAN MIRA3 XMU, 15 kV) [43, 44, 45, 46, 47]. Drug content was determined by UV assay at 210 nm after appropriate dilution, and entrapment efficiency was determined indirectly by centrifuging the formulation (10,000 rpm, 20 min), assaying unbound drug in the supernatant, and calculating $\%EE = (1 - Cfree/Ctotal) \times 100$ [47, 48].

2.8. *in vitro* Drug Release and Release Kinetics

In vitro release from the optimized L-SNEDDS was studied using a modified dialysis-bag method: dialysis membranes pre-hydrated in 0.1 N HCl for 12 h were loaded with 2.5 mL of formulation and immersed in 200 mL of 0.1 N HCl (37 °C, 50 rpm), with 5 mL aliquots withdrawn at intervals and replaced with fresh medium; released drug was quantified by UV assay at 210 nm [48, 50, 51]. Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, and the best-fit model was identified by the coefficient of determination (R^2) [49].

2.9. Stability Studies

Dilution/acidic-pH stability was assessed by diluting the optimized formulation 10-, 100-, and 1000-fold in Milli-Q water, distilled water, and 0.1 N HCl and visually inspecting for precipitation, cloudiness, or phase separation after 2 h and 24 h [50, 52]. Thermodynamic stability was assessed by (i) six heating–cooling cycles between 4 °C and 45 °C (≥48 h per temperature); (ii) centrifugation at 3500 rpm for 30 min; and (iii) freeze–thaw cycling between −21 °C and 25 °C (≥48 h per temperature) [52, 53].

2.10. Statistical Analysis

All formulation and characterization measurements were performed in triplicate unless stated otherwise and are reported as mean ± standard deviation. Design-Expert 13 was used for design generation, ANOVA, regression modelling, and desirability-based numerical optimization.

3. Results and Discussion

3.1. Preformulation Studies

Pregabalin appeared as a white to off-white crystalline powder without odour, complying with British Pharmacopoeia specifications [18]. The drug was freely soluble in 0.1 N HCl, phosphate buffer pH 6.8, and distilled water, confirming suitability across simulated gastric, intestinal, and aqueous media. The experimental melting point (178.4 °C) fell within the literature range of 176–178 °C, confirming drug identity and purity [21]. FTIR spectra of pregabalin in physical mixtures with isopropyl myristate, Tween 80, and PEG 400 showed retention of all characteristic drug bands (N–H bending at 3628 cm^{-1}, C=O stretching at 1738.51 cm^{-1}, C–N stretching at 1064.51 cm^{-1}, and $–COO^-$ stretching at 1646.91 cm^{-1}) without new peaks or significant shifts, indicating the absence of chemical interaction between pregabalin and the selected excipients [31]. UV scanning identified λmax at 210 nm in both distilled water and 0.1 N HCl; calibration curves were linear over 2–10 µg/mL ($y = 0.0047x + 0.3543$, $r^2 = 0.9986$) and 1–8 µg/mL ($y = 0.013x + 0.0002$, $r^2 = 0.9983$), respectively, confirming the analytical method was suitable for formulation quantification and consistent with reported chromatographic and spectrophotometric assay approaches for pregabalin in bulk and dosage-form matrices [32, 33, 23], and in line with conventional pregabalin solid-dosage development approaches [24].

3.2. Excipient Screening

Pregabalin solubility was highest in isopropyl myristate (11.65 mg/mL) among the oils tested, in Tween 80 (12.54 mg/mL) among surfactants, and in PEG 400 (7.50 mg/mL) among co-surfactants. Emulsification-efficiency screening corroborated this selection: Tween 80 produced the highest percentage transmittance (98.17%) with the fewest

inversions (7) among surfactants, and PEG 400 gave the highest transmittance (95.53%) with the fewest inversions (8) among co-surfactants. Isopropyl myristate, Tween 80, and PEG 400 were therefore carried forward as the oil, surfactant, and co-surfactant, respectively, for phase-diagram construction and Box–Behnken optimization.

3.3. Pseudo-Ternary Phase Diagram

Water titration of isopropyl myristate–Tween 80–PEG 400 mixtures (Smix 1:1) revealed the largest self-nanoemulsifying region at oil-to-Smix ratios between 1:9 and 1:3, consistent with reduced interfacial tension and enhanced droplet formation at equal surfactant:co-surfactant proportions. This region guided selection of the oil, surfactant, and co-surfactant ranges used in the Box–Behnken design.

3.4. Box–Behnken Design: Formulation Matrix and Responses

Nine BBD-derived formulations (F1–F9; Table 2) were evaluated for self-emulsification time, percentage transmittance, and cloud point.

Table 2: Box–Behnken formulation matrix and observed responses. SET = self-emulsification time; %T = percentage transmittance.

Code	Oil (mL)	Surfactant (mL)	Co-surfactant (mL)	SET (s)	%T	Cloud point (°C)
F1	0.75	5.0	7.5	27.62	99.2	72
F2	0.75	7.5	5.0	28.2	94.6	72
F3	1.0	5.0	10.0	33.6	99.9	80
F4	1.0	7.5	7.5	23.29	100.9	88
F5	1.0	5.0	5.0	23.78	90.54	74
F6	1.0	7.5	7.5	24.45	100.6	83
F7	1.0	10.0	5.0	32.12	97.6	82
F8	1.25	5.0	7.5	31.03	90.61	70
F9	1.25	7.5	5.0	30.22	92.3	82

Self-emulsification time ranged from 21.05 to 33.60 s, percentage transmittance from 90.54% to 100.9%, and cloud point from 66 °C to 88 °C across the design space, indicating that all formulations formed rapid, optically clear, and thermally stable nanoemulsions, with formulation F4 (0.4 mL oil, 3 mL surfactant, 3 mL co-surfactant on the coded scale) performing best across all three responses.

3.5. Model Fitting and ANOVA

For all three responses, the quadratic model gave the best sequential fit (significant sequential p-value, non-significant lack-of-fit) and was recommended over linear, two-factor-interaction (2FI), and cubic (aliased) alternatives. Self-emulsification time was best described by a quadratic model ($F = 18.84$, $p = 0.0004$; adjusted $R^2 = 0.9094$; predicted $R^2 = 0.7989$; adequate precision = 13.40), with isopropyl myristate (A), Tween 80 (B), the AB, AC, and BC interactions, and the A^2 and C^2 quadratic terms being significant contributors ($p < 0.05$). Percentage transmittance showed an excellent quadratic fit ($F = 105.30$, $p < 0.0001$; adjusted $R^2 = 0.9832$; predicted $R^2 = 0.9247$; adequate precision = 27.18), with all linear, interaction, and quadratic terms statistically significant. Cloud point was adequately described by a quadratic model ($F = 5.48$, $p = 0.0177$; adjusted $R^2 = 0.7161$; predicted $R^2 = 0.5613$; adequate precision = 7.11), with isopropyl myristate and its quadratic term, together with the Tween 80 quadratic term, being the dominant significant factors. In all three models, the non-significant lack-of-fit ($p > 0.05$) and the close agreement between adjusted and predicted R^2 (difference < 0.2) supported model adequacy and predictive reliability.

The fitted second-order polynomial equations in coded terms were:

$$Y1 = 92.68 - 218.81X1 - 18.26X2 - 1.08X3 + 7.59X1^2 + 29.03X1X2 + 52.80X1X3 + 3.69X2^2 - 5.39X2X3 - 0.66X3^2$$

$$Y2 = 47.58 + 75.23X1 + 5.09X2 + 16.88X3 - 276.12X1^2 + 36.62X1X2 + 15.69X1X3 - 2.05X2^2 - 2.09X2X3 - 2.73X3^2$$

$$Y3 = -81.81 + 544.20X1 + 18.12X2 + 15.41X3 - 814.58X1^2 + 42.22X1X2 - 2.76X1X3 - 4.33X2^2 - 2.76X2X3 - 0.60X3^2$$

Regression analysis indicated that increasing Tween 80 and PEG 400 shortened self-emulsification time and increased percentage transmittance, consistent with enhanced interfacial activity and reduced droplet-formation energy at higher surfactant/co-surfactant proportions, while higher isopropyl myristate levels, balanced against surfactant and co-surfactant, maximized cloud point and hence thermal stability. Response-surface and contour plots showed that intermediate-to-high Tween 80 and PEG 400 concentrations, combined with a moderate oil volume, jointly optimized all three responses, reflecting synergistic rather than purely additive excipient interactions.

3.6 Numerical Optimization and Validation

Simultaneous optimization for minimum self-emulsification time and maximum percentage transmittance and cloud point, using the Design-Expert desirability function, identified an optimal factor combination that was prepared and evaluated in triplicate to verify model predictions (Table 3).

Table 3: Comparison of Design-Expert-predicted and experimentally observed responses for the optimized L-SNEDDS batch.

Response	Predicted mean	Observed (experimental) mean	95% CI (low–high)
Self-emulsification time (s)	25.2	25.2	23.91–26.49
Percentage transmittance (%)	100.06	100.06	99.58–100.54
Cloud point (°C)	84.6	84.6	80.97–88.23

The close agreement between predicted and experimentally observed values for all three responses confirmed the accuracy and predictive validity of the Box–Behnken model, and supports its use for the rational, statistically grounded selection of the pregabalin SNEDDS composition.

3.7. Characterization of the Optimized L-SNEDDS

The optimized formulation was clear, transparent, and free of phase separation, forming a fine oil-in-water nanoemulsion within seconds of gentle aqueous dilution, with consistent behaviour across three independently prepared batches. Table 4 summarizes its physicochemical properties.

Table 4: Physicochemical characterization of the optimized pregabalin L-SNEDDS.

Parameter	Result
pH (n = 3)	5.6 ± 0.04
Viscosity (cP, n = 3)	42 ± 2
Mean globule size (nm, n = 3)	28.2 ± 1.1
Polydispersity index (PDI)	0.324
Zeta potential (mV, n = 3)	−3.7 ± 0.1
Morphology (SEM)	Nanoparticulate, amorphous domains; no visible crystals
Drug content (% w/w)	109.9
Entrapment efficiency (%)	89.47

The mildly acidic pH (5.6) falls within the range considered favourable for minimizing pregabalin degradation. The measured viscosity (42 cP) is below the range typically reported for SNEDDS (100–1000 cP) but is consistent with a low-viscosity system that favours rapid self-emulsification. The mean globule size (28.2 nm) confirms formation of a true nanoemulsion; the PDI (0.324), although marginally above the conventional ≤0.3 threshold for an ideal self-nanoemulsifying system, still indicates a near-monodisperse, reasonably homogeneous droplet population. The low absolute zeta potential (−3.7 mV) indicates that the optimized SNEDDS is stabilized predominantly through steric rather than electrostatic mechanisms, consistent with its formulation using non-ionic surfactants (Tween 80, PEG 400); such systems can remain kinetically stable despite low zeta potential magnitude provided steric stabilization is sufficient, as supported by the thermodynamic stability data below. SEM confirmed nanoparticulate, amorphous domains without discernible drug crystals, supporting effective molecular-level entrapment of pregabalin within the oily matrix. Drug content (109.9% w/w) and entrapment efficiency (89.47%) together confirm efficient, reproducible drug loading into the SNEDDS system.

3.8. *in vitro* Drug Release and Release Kinetics

Under simulated gastric conditions (0.1 N HCl, modified dialysis method), pregabalin release from the optimized L-SNEDDS was 31.74%, 45.28%, 48.97%, and 78.40% at 15, 30, 45, and 60 min, respectively, indicating a sustained, progressively increasing release profile rather than an immediate burst. Kinetic modelling showed poor fit to the zero-order model (R^2 = 0.209) and moderate fit to the first-order model (R^2 = 0.648), whereas the Higuchi (R^2 = 0.716) and Korsmeyer–Peppas (R^2 = 0.717) models best described the data. The Korsmeyer–Peppas release exponent (n = 0.474, < 0.45 threshold region for spherical/near-Fickian systems) indicated that Fickian diffusion through the self-emulsified oil-in-water matrix was the dominant release mechanism, consistent with drug transport governed by concentration-gradient-driven diffusion out of the nanoemulsion droplets rather than by matrix erosion or polymer relaxation.

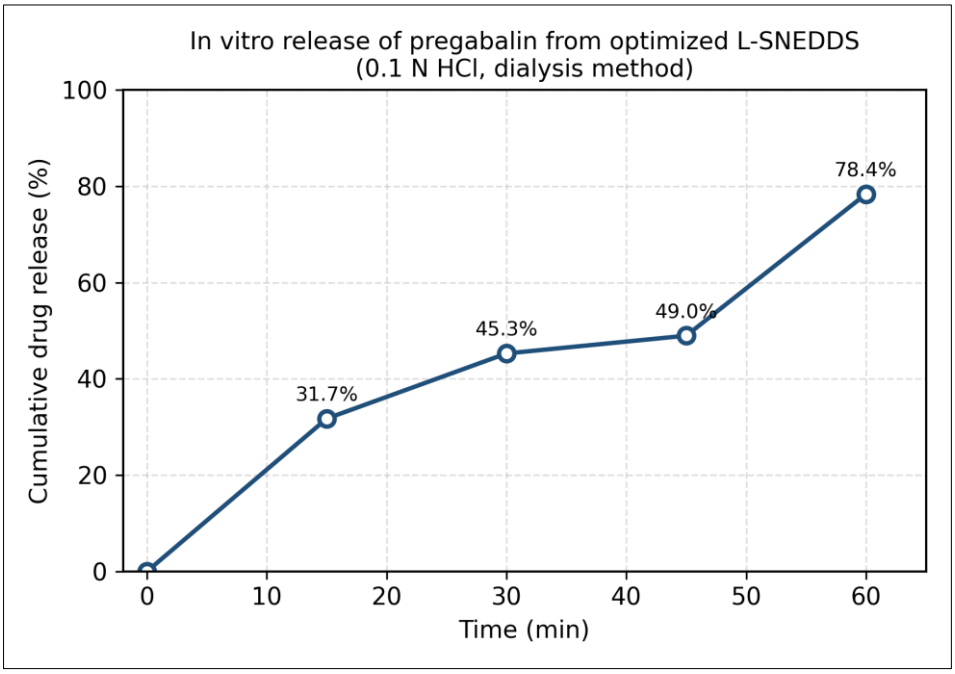

Fig 1: ***in vitro*** cumulative release profile of pregabalin from the optimized L-SNEDDS formulation in 0.1 N HCl (modified dialysis-bag method, 37 ± 0.5 °C, 50 rpm; mean, n = 3).

3.9. Stability Studies

The optimized formulation remained visually clear, without precipitation, turbidity, or phase separation, following 10-, 100-, and 1000-fold dilution in Milli-Q water, distilled water, and 0.1 N HCl, both immediately and after 24 h, supporting robustness of the nanoemulsion to the dilution encountered upon oral administration and gastrointestinal transit. The formulation also withstood six heating–cooling cycles (4–45 °C), centrifugation (3500 rpm, 30 min), and freeze–thaw cycling (−21 to 25 °C) without cracking, creaming, or phase separation, confirming thermodynamic stability and supporting an adequate shelf-life for the liquid preconcentrate and its suitability as an intermediate for solidification.

4. Conclusion

A pregabalin-loaded liquid SNEDDS was successfully developed and optimized using a Box–Behnken design implemented in Design-Expert software. Isopropyl myristate, Tween 80, and PEG 400 were identified as an optimal oil–surfactant–co-surfactant combination through systematic solubility and emulsification-efficiency screening. Quadratic response-surface models accurately predicted self-emulsification time, percentage transmittance, and cloud point, and the desirability-optimized formulation was validated experimentally with close agreement between predicted and observed values. The optimized L-SNEDDS exhibited nanoscale droplet size, high drug loading and entrapment efficiency, sustained diffusion-controlled release, and robust thermodynamic and dilution stability. These findings establish the optimized liquid SNEDDS as a well-characterized platform suitable for conversion into a solid oral dosage form, which is addressed in a companion study describing solid-carrier adsorption, MINITAB-based factorial optimization, and tablet-level evaluation of pregabalin self-nanoemulsifying solid dispersions for neuropathic pain management. This approach is consistent with the broader body of evidence supporting SNEDDS-based delivery of neuroactive and neuroprotective agents in preclinical neuropathic pain models [57, 58].

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Conflict of Interest

The authors declare no conflict of interest.

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