RESEARCH PAPER

Advancements in Self-Nanoemulsifying Drug Delivery Systems: A Comprehensive Study on Curcumin Solubility Enhancement

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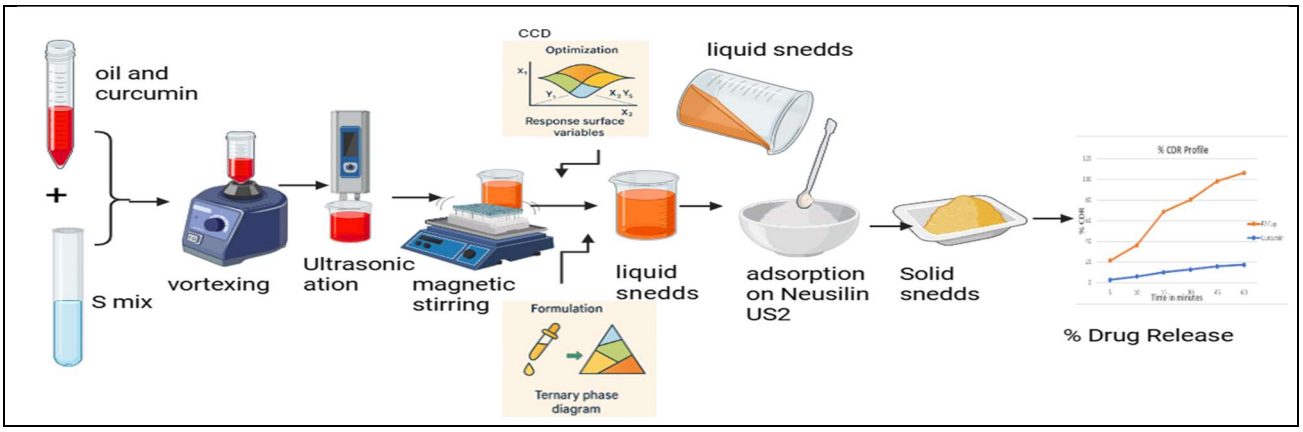
Graphical Abstract:



S mix: surfactant and co-surfactant mixture; CCD: Central composite Design

Abstract:

Background

Curcumin is a natural compound with significant therapeutic potential but suffers from poor water solubility, which limits its bioavailability. To overcome this limitation, self-nanoemulsifying drug delivery systems (SNEDDS) have been explored as a promising approach for enhancing solubility and drug release.

Methodologies

Different curcumin-loaded SNEDDS formulations were developed using the aqueous phase titration method, and the nanoemulsion regions were determined through ternary phase diagrams. Transcutol P (co-surfactant), Brij-35 (surfactant), and cinnamon oil (oil phase) were selected based on their maximum nanoemulsion region and solubility profile. Optimization was carried out using a Response Surface Methodology–Central Composite Design (RSM-CCD), with oil quantity (X1) and S-mix (X2) as independent variables, and zeta potential (Y1), globule size (Y2), PDI (Y3), transmittance (Y4), and drug content (Y5) as response variables. The optimized liquid formulation (Cur-SNEDDS F3) was further solidified into S-SNEDDS by adsorption on Neusilin US2.

Discussion

The optimized S-SNEDDS exhibited favorable physicochemical properties, with drug loading of 82% ± 0.8%, zeta potential of -19.2 ± 2.54 mV, and particle size of 101.3 ± 2.0 nm. In vitro drug release studies revealed that S-SNEDDS

achieved 88.93% ± 0.03% drug release compared to only 17.20% ± 1.15% from raw curcumin. Additionally, solubility studies confirmed the significantly enhanced performance of S-SNEDDS over pure curcumin.

Conclusion

This study successfully demonstrated that curcumin-loaded SNEDDS, optimized and converted into solid form, can markedly enhance solubility and drug release compared to raw curcumin. The findings support the potential of SNEDDS as an effective delivery system for improving curcumin bioavailability.

Keywords: Curcumin, solid SNEDDS, solubility, central composite design, ternary phase diagram

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1. Introduction:

The isotropic combination of oil, surfactants, and co-surfactants known as self-nano-emulsifying drug delivery systems (SNEDDS) is commonly used to improve the oral bioavailability of lipophilic compounds [1]. When these formulations come into contact with the gastrointestinal fluids, they emulsify spontaneously to produce nanosized globules. SNEDDS improve oral bioavailability by reducing droplet size, solubilizing, protecting against enzymatic and chemical degradation, and increasing permeation through tight junction opening and surfactant-induced membrane fluidity [2,3]. This technology seems to be a good option in terms of improved bioavailability and manufacturability, even though a number of different methods are being used to boost curcumin's bioavailability when taken orally. The main active polyphenolic pigment in curry spice turmeric, curcumin, a nutraceutical that is derived from Curcuma longa's rhizome, exhibits potential for a number of ailments. That belongs to the ginger (Zingiberaceae) family [4,5,6]. Curcumin possesses hepatoprotective, anti-asthmatic, anti-inflammatory, anti-diarrheal [7], anti-diabetic, hypolipidemic, and anti-cancer qualities [8]. In addition to its many other uses in cosmetics, curcumin's pharmacological activities were demonstrated in the Figure-1

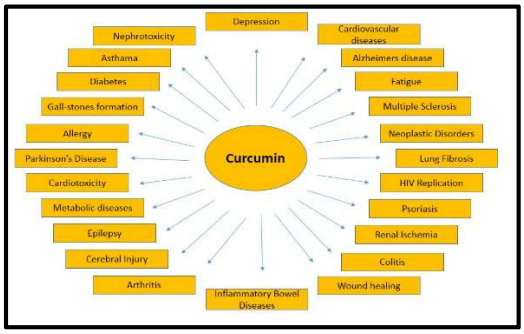

Figure-1: Pharmacological activities of Curcumin

More than 40% of novel chemical compounds developed by the pharmaceutical industry are nearly insoluble in water [9,10]. Despite the fact that oral delivery is generally favored due to its low cost, comfort, and safety, curcumin is a challenging molecule for this delivery route. Curcumin can be categorized as a BCS class IV due to its limited intestinal permeability and poor solubility in aqueous solutions. Researchers studying curcumin have been troubled by its poor bioavailability and low water solubility. Numerous investigations have been conducted to evaluate CRM's pharmacokinetic characteristics and bioavailability in humans [11] and rodents [12]. Its poor systemic bioavailability is caused by a number of issues, including its extensive metabolism and poor water solubility [13]. Because of its limited water solubility, curcumin has been discovered to have very poor absorption [4]. Even after a daily intake of up to 4 g, very low quantities of curcumin were found in the plasma of healthy human volunteers in clinical trials [14]. Twelve patients with hepatic metastases who received oral curcumin demonstrated that the parent chemical was not readily available and that very little of it was present in the portal or peripheral circulation [15]. During intestinal absorption, curcumin experiences a significant amount of metabolic biotransformation, a very high first-pass metabolism, and maybe enterohepatic recirculation [16,17,18]. Furthermore, it has been demonstrated that curcumin breaks down at neutral and alkaline pH levels as well as in aqueous solution [2,13]. Numerous techniques have been employed to increase bioavailability and solubility. This includes methods like solid dispersion, nanosuspension, particle size reduction, inclusion complex formation-based processes, hydro trophy, crystal engineering, micellar solubilization, and cryogenic techniques [19].

2. Materials and Methods

2.1. Materials:

Research-Lab Fine Chemical Industries was the supplier of curcumin, kolliphor RH40, polyethylene glycol 400, Tween 80, polyethylene glycol 600, polyethylene glycol 200, brij 35, propylene glycol, transcutol P, liquid paraffin, and cinnamon oil. We bought from Modern Industries ethyl oleate, castor oil, oleic acid, olive oil, isopropyl myristate, eucalyptus oil, and labrasol. We bought Tween 20 from Loba Chemie. A complimentary

sample of Neusilin US2 was sent by Fuji Chemicals of Japan.

2.2. Experimental:

2.2.1. Curcumin Solubility Studies in Different Oils, Cosurfactants, and Surfactants:

The solubility tests for raw curcumin [20] have been conducted in order to determine the optimal oil, surfactant, and co-surfactant for the formulation of SNEDDS. Curcumin's solubility in a variety of oils (oleic acid, isopropyl myristate, cinnamon oil, ethyl oleate liquid paraffin, olive oil, castor oil, and eucalyptus oil), cosurfactants (PEG 200, PEG 400, PEG 600, propylene glycol, and transcutol P), and surfactants (labrasol, cremophor RH 40, tween 20, tween 80, Brij 35) were tested using the shake flask method [21]**.** The amount of medication dissolved was measured using UV spectroscopy. Excess curcumin (50mg) was put to 2 ml tiny vials that contained various oils, surfactants, and co-surfactants. The vials were sealed tightly, vortexed for two minutes (CM 101 CYCLO MIXER, REMI, India) to ensure that the curcumin and vehicle were properly mixed, and then continuously swirled for seventy-two hours at 37±5°C in a shaking water bath. The mixtures were centrifuged for 20 minutes at 5,000 rpm after reaching equilibrium. Following separation and filtering, the drug that had not dissolved was appropriately diluted with methanol. The amount of drug present in the solution was measured using a UV spectrophotometer [22,23] (UV-1800, Shimadzu, Japan).

2.2.2. Drug Excipients Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FT-IR):

A Shimadzu FTIR-spectrophotometer (Shimdzu, IR Spirit) was used to record Fourier transform infrared (FTIR) spectroscopy in order to determine whether curcumin was compatible with the excipients. The test was conducted using a frequency range of 4000–400 cm^{-1} and a resolution of 4 cm^{-1}. Curcumin, oils, surfactants, and co-surfactants were combined physically. The crystal was directly covered with the samples. To find any chemical or physical interactions between medications and excipients, the ATR used [24]**.**

2.2.3. Construction of pseudo ternary phase diagrams:

Transcutol P was chosen as a co-surfactant, Brij-35 was selected as surfactant, and the oil phase was cinnamon oil based on the outcomes of solubility studies. The aqueous phase was water. Using an aqueous phase titration method for the creation of the SNEDDS of curcumin, pseudo-ternary phase diagrams were produced in order to ascertain the concentration range of components for the current weight ratios of nanoemulsion components. Water was gradually added to the transparent combination of oil, surfactant, and co-surfactant to form the pseudo-ternary phase diagram. Five surfactant and co-surfactant weight ratios (s-mix) were chosen: 1:1, 1:2, 2:1, 1:3, and 3:1. The oil to s-mixture ratios for each phase diagram were modified to 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 for a specific weight ratio of surfactant to co-surfactant. In order to dilute the oil, surfactant, and co-surfactant solutions at particular weight ratios with water dropwise from the burette, continuous magnetic stirring was applied. The mixes were visually evaluated after equilibration and identified as nanoemulsions. When the transparent solution became opaque, it was observed [25]**.** A pseudo-ternary phase diagram was created with Ternary Plot.com software. A distinct phase diagram was made for each Smix ratio, with oil represented as point A, Smix as point B, and water as point C in the diagrams. To differentiate them from other phases, the nanoemulsion zones were darkened.

2.2.4. Design of experiments:

The two independent variables in RSM-CCD (Response Surface Methodology-Central Composite Design) design were selected to be X1 and X2. It enables optimization through the study of the 2FI response surfaces and the construction of a second-order polynomial model. All other formulation and processing characteristics did not change during the study. L-SNEDDS optimization was performed using Design Expert 7.0. Each and every one of the previously stated formulations was created and evaluated based on a variety of standards. The design expert program generated a polynomial equation when the data was entered. The responses (dependent variables) that were being examined were Y1, Y2, Y3, Y4, and Y5. Because it enables the assessment of the factors influencing L-SNEDDS with the fewest number of experiments, the RSM-CCD design was selected for optimization. Independent variables were oil quantity (X1) and S mix (X2). Zeta potential (Y1), globule size (nm) (Y2), PDI (Y3), transmittance (Y4), and drug content (Y5) were the response variables. Eight formulations were created using a factorial design. F1 through F8 were the formulas. Design Expert 7.0 statistics software was used to statistically analyze the replies derived from the design matrix [26]. Formulations Batches as per RSM-CCD design mentioned in Table 1.

Table 1: Formulations Batches as per RSM-CCD design

Formulation Code	OIL	S MIX (2:1)
F1	5	45
F2	24	45
F3	5	57
F4	24	57
F5	1.1	51
F6	27.9	51
F7	14.5	42.5

F8	14.5	59.5

2.2.5. Formulation of L-SNEDDS:

Selected quantity of oil and smix as per compositions obtained from central composite design for preparation of F1 to F8 formulations. The curcumin was measured, added gradually to the oil in a beaker, and vortexed for 10 minutes. Dropwise, a 2:1 Smix was added to the solution, creating an isotropic mixture that was continuously stirred for 30 minutes. After 10 minutes of vortexing, sonication by using ultrasonicator for 5 minutes then the mixture was agitated at 2000 rpm using a magnetic stirrer until a homogenous solution was obtained. After 48 hours of equilibration at room temperature, any phase separation was not observed in the mixture.

2.2.6. Characterization of L-SNEDDS:

A) Fourier Transform Infrared Spectroscopy (FT-IR):

Using a Shimadzu FTIR-spectrophotometer (Shimdzu, IR Spirit), Fourier transform infrared (FTIR) spectroscopy was recorded to determine whether curcumin was compatible with the excipients. The test was carried out with a resolution of 4 cm^{-1} and a frequency range of 4000–400 cm^{-1}. Samples of L-SNEDDS were put directly onto the crystal. Any chemical or physical interactions between medications and excipients were found using the ATR.

B) Measurement of zeta potential and droplet size:

Using the Malvern zeta sizer, Photon Correlation Spectroscopy (PCS) was used to evaluate the PDI and zeta potential droplet size, of SNEDDS (Microtarc MRB Version 12.0.1). 50 mV lasers were used to record in disposable polystyrene cells at a fixed 90° angle and 25°C. 100 mL of double-distilled water was used to dilute the 100 µL L-SNEDDS/S-SNEDDS sample. Eight sub-runs were performed throughout each run, each lasting two minutes. Every study was conducted three times, and the mean outcomes were noted [20]**.**

C) Spectroscopic characterization of optical clarity (% Transmittance):

The optical clarity of curcumin SNEDDS was investigated by measuring % transmittance after dilution with double distilled water. One milliliter of SNEDD was dispersed in 100 ml of deionized water and % transmittance of resulted nanoemulsion was measured at 425 nm against deionized water as blank by using UV Visible spectrophotometer. Since nanoemulsion is an optically isotropic and thermodynamically stable solution, the optical clarity of the diluted formulations was assessed by measuring the transmittance percentage. Additionally, a smaller globule size range is reflected in a larger percentage of transmittance values, which improves drug release and oral bioavailability [27]**.**

D) Drug content:

Curcumin SNEDDS formulations containing 100 mg of curcumin was dissolved in an appropriate amount of methanol. The curcumin was dissolved in methanol by continuous agitation. After 15 minutes of ultrasonication, the samples were examined at 425 nm using a Shimadzu 1700 A UV visible spectrophotometer.

E) Thermodynamic stability:

It appears that the L-SNEDDS will exhibit both thermodynamic and kinetic stability. To evaluate their thermodynamic stability, formulations were stored for 48 hours, subjected to cooling-heating cycles (4°C and 40°C) and freeze-thaw cycles (-21°C and +25°C), and their cloud point was determined. The kinetic stability of the formulations was determined by centrifuging the diluted SNEDDS formulations at 10,000 g for 15 minutes whereas maintaining focus on drug precipitation, creaming, and cracking [28]**.** After manufactured formulations (1 mL) were diluted in 500 mL of water and heated gradually on a temperature-regulated digital water bath, the temperature at which cloudiness emerges was measured using a thermometer.

The L-SNEDDS expected to be both kinetically and thermodynamically stable. Formulations were subjected to cooling-heating cycles (4°C and 40°C) and freeze-thaw cycles (-21°C and +25°C) with storage for 48 hours and cloud point determination in order to assess their thermodynamic stability. By centrifuging the diluted SNEDDS formulations at 10,000 g for 15 minutes and monitoring creaming, cracking, and drug precipitation, the kinetic stability of the formulations was ascertained [28].

A thermometer was used to measure the temperature at which cloudiness appears after prepared formulations (1 mL) were diluted in 500 mL of water and heated gradually on a temperature-regulated digital water bath [20,28]. The temperature at which the transparent emulsion began to exhibit milky opalescence was used to visually observe the appearance of cloudiness [29]**.** These investigations involved subjecting the created nanoemulsion to mechanical and thermal stress, both high and low, and monitoring the impact on the nanoemulsion's homogeneity.

The test was conducted in three stages: alternating heating at 45°C and cooling at 5°C. The formulation was stored at each temperature alternately for at least 48 hours, for six cycles. Formulations that were clear under these circumstances were chosen for the centrifugation test that followed. The test involved centrifuging the formulations for 30 minutes at 3500 rpm. Freeze-thaw cycles comprised formulations that were still clear and did not exhibit any phase separation. Freeze-thaw cycles: This involved storing produced formulations for at least 48 hours at alternating temperatures of -21°C and 25°C [29].

F) Dispersibility test /self-emulsification time:

To verify the self-nanoemulsification, a phase separation or precipitation test was conducted using

water, phosphate buffer (pH 7.40), and acid buffer (0.1 N HCl). Water, 0.1 N HCl, and phosphate buffer (pH 7.40) were used to dilute 1.0 mg per milliliter of each Cur-loaded SNEDDS (F1 to F8) in a 1:500 dilution ratio for this test. The self-Nano emulsification efficiency of each formulation was assessed visually using grade systems:

Grade A: Grade A transparent nanoemulsion produces spontaneously and rapidly.
Grade B: bluish, slightly less transparent nanoemulsion that forms quickly or spontaneously.
Grade C: turbid emulsion that forms gradually.
Grade D: a grayish, drab, turbid emulsion that forms gradually.
Grade E: a muddy mixture with oil globules that are visible on the surface [26].

G) Physicochemical characterization of the Cur-SNEDDS:

Using spindle C 50-1 at 25 ± 0.5 °C, the viscosity of the produced Cur-SNEDDS was determined both before and after dilution using a Brookfield viscometer R/S CPS Plus (Brookfield Engineering Laboratories Inc., Middleboro, MA, USA). At 70 rpm, 413 shear stress per minute, and a 15-minute wait time, spindle number 50 is operated. Finally, the shear rate in centipoises was measured as a viscosity parameter. The Abbes-type refractometer was used to determine the Cur-SNEDDSs (F1 to F8) refractive indices. (Precision Testing Instruments Laboratory, Germany) [26].

2.2.7. Preparation of Solid self-nanoemulsifying drug delivery system of Curcumin by adsorption technique:

To load the liquid SNEDDS, Neusilin®gradeUS2, (aluminum metasilicate, inorganic material) was employed as a microporous inorganic adsorbent. Curcumin's modified liquid SNEDDS formulation was physically mixed in a mortar and pestle to adsorb it onto the Neusilin US2 carrier at a 1:1 w/w ratio. In order to ensure that the mixture was evenly dispersed, the resultant Solid SNEDDS were homogenized uniformly. The moist substance was drying at room temperature after passing over sieve number 120. After that, a free-flowing powder was put through dissolution tests, solid state characterization, and another parameter. For later use, the created solidified SNEDDS were kept in airtight glass vials [30].

A) Drug-excipient compatibility studies:

a) Differential scanning calorimetry analysis:

To characterize the physical state of curcumin in solid SNEDDS Differential scanning calorimetry was used. In a closed, perforated aluminum pan, all of the samples were heated to between 30 and 300°C at a scanning rate of 10°C/min. DSC was carried out utilizing the DSC-60 (Shimadzu, Japan) to develop an optimal formulation and investigate the thermal behavior of the drug alone and drug plus polymer mixtures.

b) Infrared spectroscopy using the Fourier transform (FTIR):

Using a Shimadzu FTIR-spectrophotometer (Shimdzu, IRSpirit), infrared spectroscopy was performed. The test was carried out with a resolution of 4 cm^{-1} and a frequency range of 4000–400 cm^{-1}. The crystal was directly covered with the samples. To find any chemical or physical interactions between medications and excipients, the ATR was employed [24].

B) Shape and surface morphological analysis by SEM and TEM:

The prepared Cur-NE's surface morphology was evaluated using a TEM (Morgagni268D; FEI Company, Hillsboro, OR). To stick Cur NE, a drop of NE was briefly put on a paraffin sheet (1 minute). After that, a copper grid was placed over it, and the grid was then submerged in a drop of phosphotungstate for more than five seconds. After the sample was allowed to air dry, any remaining solution was removed with filter paper. Using TEM, the material was examined once more. Utilizing a Zeiss EVO40 SEM (Carl Zeiss, Cambridge, UK), the surface texture of the improved Cur-NE was ascertained. To put it briefly, sample dissemination was done using double-sided conductive tape. Next, under high vacuum, gold was coated to the surface using a SCD020 Blazers sputter coater unit (BAL-TEC GmbH, Witten, Germany). Argon gas was used to pre-maintain the sputter unit for 100 seconds at 50 mA [26].

C) Flow properties of S-SNEDDS [24]:

Flow properties of solid SNEDDS viz. angle of repose, bulk density, tapped density, true density, Carr's index, Hausner ratio.

a) Angle of Repose:

The angle of repose was determined by funnel method. The height of funnel was adjusted from the surface of graph paper. The powder was allowed to flow through the funnel on to a graph paper in such way that the tip of funnel just touches the heap of powder. By measuring the powder cone's diameter and applying the following formula, the angle of repose was determined;

$$\tan \theta = 2h/D$$

In this case, ɵ is the angle of repose,

h is the pile's height,
D is the heap's diameter.

Relationship between flowability and angle of repose shown in Table 2:

Table 2: Relationship between flowability and angle of repose.

Type of Flow	Value for angle of repose
Excellent	<25
Good	25-30
Passable	30-40
Poor	>40

b) Bulk density:

A glass funnel was used to carefully distribute 10 grams of powder into a 50-milliliter graduated cylinder in order to measure the bulk density of solid SNEDDS.
The volume occupied by sample was recorded. The bulk density was calculated as follows:

Bulk density (ρb) = weight/Bulk volume

c) Tapped density:

A glass funnel was used to carefully pour 10 grams of the sample into a graduated cylinder that held 50 milliliters. A consistent volume was achieved by tapping the cylinder from a height of two inches. Volume occupied by sample after tapping were recorded and tapped density was calculated as follow

Tapped density (ρt)=weight/Tapped volume

d) Carr's index:

The compressibility index of the powder blend was determined using Carr's index.
Carr's index $=(p_t - p_b)/p_t \times 100$

e) Hausner Ratio:
he Hausner ratio was calculated to characterize the flow powder blend.ratio greater than 1.25 is considered to be indication of poor flow ability. Formula used as follows;
Hausner ratio $= p_t / p_b$

Relationship between Compressibility index and Hausner ratio included in table Table 3.

Table 3: Relationship between Compressibility index and Hausner ratio.

Compressibility index (%)	Flow character	Hausner ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

D) Drug content estimation:
An appropriate amount of methanol was used to disperse SNEDDS equal to 10 mg of curcumin. The medication was dissolved in methanol by vigorously mixing the samples. To separate the Neusilin particles, the samples were sonicated in an ultrasonicator and centrifuged for 15 minutes at 3000 rpm using a 12C micro-centrifuge (Remi motors, Mumbai, India). After being appropriately diluted, the supernatant was examined at 425 nm using a Shimadzu 1700A UV visible spectrophotometer [26]. The following formula was used to determine the drug content:

$$\text{Sample concentration} = \frac{\text{sample absorbance} \times \text{standard concentration}}{\text{standard absorbance}}$$

E) In - vitro drug release study:
Basket type (USP I) dissolution test apparatus (Electrolab) was used for in vitro drug release studies. Separate dissolution tests were conducted for developed SNEDDS and pure drugs. Five milligrams of pure curcumin and SNEDDS equivalent to five milligrams were placed in capsules for dissolution tests. The dissolution process, which involved 900 ml of SGF (pH 1.2), was run at 37 ± 0.2°C for 60 minutes at 100 ± 4 rpm. At predetermined intervals, sample aliquots (10 ml) are removed and replaced with new media. Absorbance at 425 nm was measured using a UV spectrophotometer (UV spectrophotometer 1700 Shimandu) to determine the amount of drug released [29].

F) in vivo pharmacokinetic study
The in vivo pharmacokinetic study protocol was approved by IAEC having IAEC approval no 27/IAEC-II/SLSRPL/2024. An in vivo pharmacokinetic study was conducted in male Wistar rats to compare the oral bioavailability of optimized solid SNEDDS of curcumin with pure curcumin and liquid SNEDDS, in accordance with CPCSEA guidelines and approved protocols. Rats (250–300 g) were randomly assigned to four groups (n = 6) and fasted overnight prior to dosing. Group I received curcumin suspension in 1% w/v sodium carboxymethyl cellulose (100 mg/kg, oral), Group II received optimized liquid SNEDDS (100 mg/kg, oral), Group III received solid SNEDDS equivalent to 100 mg/kg curcumin (oral), and Group IV received curcumin solution in PEG 400: saline (30:70, v/v) at 20 mg/kg via tail vein for absolute bioavailability determination [49] Blood samples were collected at predefined intervals up to 24 h post-administration, and plasma curcumin concentrations were quantified using an HPLC method with a C18 column (4.6 × 250 mm, 5 µm), acetonitrile:water (80:20, v/v) as mobile phase, a flow rate of 1.0 mL/min, and UV

detection at 425 nm. Pharmacokinetic parameters (Cmax, Tmax, $AUC_{0-\infty}$) were calculated using non-compartmental analysis (PK Solver). Statistical analysis was performed using one-way ANOVA in GraphPad Prism 8.0, with $P < 0.01$ considered statistically significant.[33]

F) Stability studies

In a stability chamber with an ambient temperature of 40°C ±2°C and a relative humidity of 75% ± 5%, the stability of a capsule containing snedds was observed for up to 90 days. Samples were taken out on a regular basis and evaluated for physical appearance, drug content, and dissolution [29].

3. Results and Discussion:

3.1. Solubility Study

Curcumin's λ max was found to be 425 nm when it was evaluated using a spectrophotometric method in methanol. Figure 3 shows the solubility of curcumin in different carriers. It was found that there was no change in curcumin's λ max when the λ max was scanned in the presence of different vehicles. It can be concluded that the chosen vehicles won't hinder the drug's developed analysis procedure. Additionally, the outcomes verify that the drug and the vehicle employed in this investigation are compatible. Cinnamon oil had the highest solubility of curcumin among the several oils that were examined; as a result, Brij-35 and Transcutol-P were chosen as surfactants and cosurfactants, respectively. In Figure 2, the solubility profile of curcumin in different oils, surfactants, and co-surfactants was discussed.

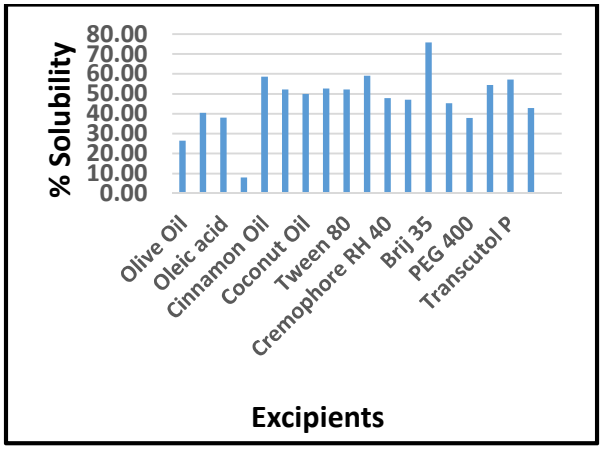

Figure-2: Solubility profile of curcumin in various oils, surfactants, co-surfactants

3.2 Drug Excipients Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FT-IR):

FTIR spectroscopy was used to analyze a drug-excipient compatibility study. The principal absorption peaks at 1652, 1585, 1512, 1498, 1424, 1270, 1157,1131, 1031, 956, 852, 809, and 776 cm−1 in the FTIR spectra of pure curcumin powder. (Figure 3) and the IR spectra of a physical mixture of drug and excipients (Figure 7) showed no significant shift when compared; the FTIR spectra of the pure drug demonstrate that there is no interaction between the drug and excipient [24]. FTIR spectra of oil given in Figure 4, surfactant given in Figure 5 and co-surfactant in Figure 6.

Fourier Transform Infrared Spectroscopy (FT-IR)

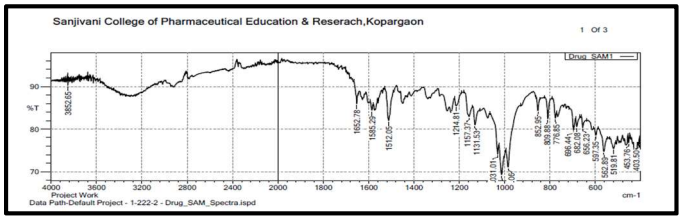

Figure-3: FTIR spectra of drug

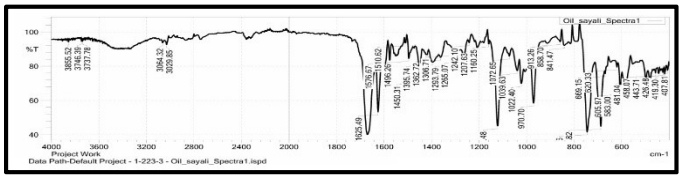

Figure-4: FTIR spectra of oil

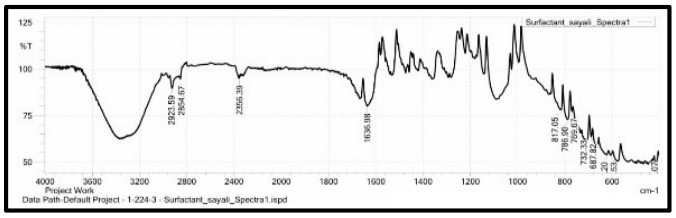

Figure 5: FTIR spectra of surfactant

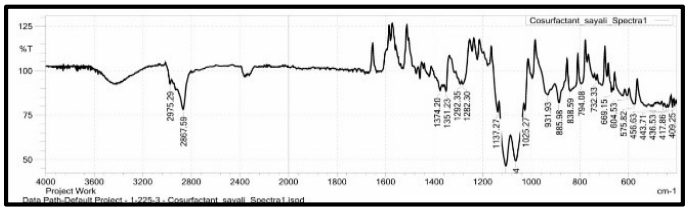

Figure 6: FTIR spectra of co-surfactant

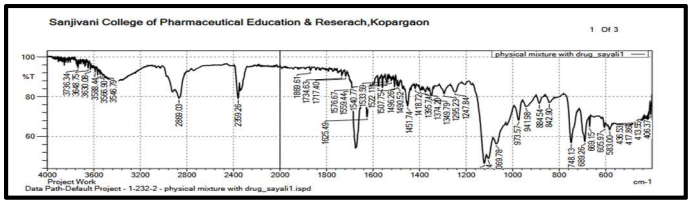

Figure-7: FTIR spectra of physical mixture

3.3 Construction of pseudo-ternary phase diagram:

2:1 Smix ratio phase diagram showed a wide emulsification domain, making it the best configuration

for creating the formulation of curcumin L-SNEDDS. In order to ensure stable nanoemulsion formation, the Smix (Brij-35: Transcutol-P) concentration ranges from 45 to 60%, whereas the oil (cinnamon Oil) content in the curcumin SNEDDS formulation normally ranges from 5 to 30%. The ternary phase diagram (Figure 8) and formulation stability should be used to adjust these concentrations in order to ensure efficient drug release and system performance as a whole.

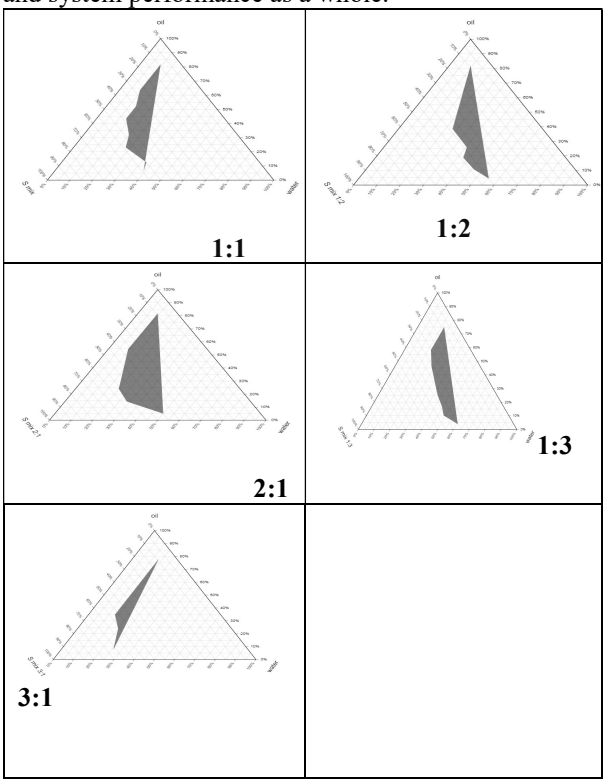

Figure-8: Pseudoternary phase diagrams

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3.4 Systematic development using CCD for L-SNEDDS:

As advised by CCD, a total of eight randomized formulations were tested. (Table 4) Table 1 provides a summary of the experimental values for the dependent variables. Zeta potential values of the emulsions formed upon dilution with HPLC water were found to be between -25.2 and -7.19 mV, while globule diameters were determined to be between 69.8 and 517.3 nm. The co-surfactant (Transcutol-P) and surfactant (Brij-35) utilized in this investigation are both non-ionic. PDI results ranged from 0.5 to 0.97. Transmittance has been determined to be between 91.85 to 100.02%. Values regarding the drug content vary between 83.40 to 107.61%. Given that F3's particle size was 84.46 nm, globules were found to be within the nanometric size range. A narrow globule size distribution that forms more homogenous emulsions is indicated by a zeta potential of -19 mV, a transmittance percentage of 99.37%, and a PDI value of 0.53. % With a drug content of 101.11%, the emulsion created showed good physical stability and was chosen as an optimal batch.

For each of the five dependent variables, the optimization software suggested a linear relationship ($p = 0.0101$ for Y1, 0.0015 for Y2, 0.0044 for Y3, 0.0003 for Y4, and 0.0057 for Y5), when it was presented with the dependent variables' observed data.

Table 5 summarizes the mean, standard deviation, and coefficient of variation (%) for each of the five dependent variables. The adjusted R2 values and the projected R2 values for each of the five dependent variables agreed by a difference of less than 0.2. Figure 10. The effects of the oil concentration (A) and Smix concentration (B) on the formulation's zeta potential (I), globule size (II), PDI (III), percentage of transmission (IV), and percentage of drug loading (V) were displayed in the 3D surface plots (Figure I to V).

Table-4: CCD-observed curcumin formulation experimental runs along with experimental values for dependent variables.

	Independent Variables		**Dependent Variables**				
Batch	**Factor 1: OIL**	**Factor 2: SMIX (2:1)**	**Response 1: Zeta potential (Y1) mV**	**Response 2: Globule size (Y2) nm**	**Response 3: PDI (Y3)**	**Response 4: % Transmittance (Y4)**	**Response 5: % drug content (Y5)**
F1	5	45	-21.1	142	0.57	99.32	100.19
F2	24	45	-16	389.9	0.97	92.72	91.84
F3	**5**	**57**	**-19**	**84.46**	**0.53**	**99.37**	**101.11**
F4	24	57	-12	362.2	0.8	92.25	92.58
F5	1.1	51	-25.2	120.20	0.55	99.10	99.89
F6	27.9	51	-7.19	517.3	0.85	91.85	83.40
F7	14.5	42.5	-15.4	420.5	0.91	95.96	92.76

F 8	14.5	59.5	-12.7	193.8	0.5	97.88	94.62

Table-5. Summarized regression analysis data for selected dependent variables.

Model	R^2 Value (Coefficient of Correlation)	Adjusted R^2	Predicted R^2	Adeq. Precision	Standard Deviation	Mean	Coefficient of Variation (C.V.%)
Y1	0.8408	0.7771	0.5924	8.113	2.67	-16.07	16.63
Y2	0.9265	0.8970	0.8117	12.229	54.68	272.55	20.06
Y3	0.8858	0.8401	0.7077	10.040	0.077	0.7196	10.79
Y4	0.9597	0.9436	0.8969	17.75	0.82	.17	0.85
Y5	0.8731	0.8224	0.6752	9.545	3.09	95.51	3.24

In Figure I, the zeta potential was positively impacted by the oil and negatively by the Smix. This indicates that when the concentration of oil in the formulation increases, the zeta potential will rise, while the concentration of Smix will fall. Figure II shows that the oil had a positive effect on the globule size while the Smix had a negative effect. This indicates that the globule size will increase as the oil concentration in the formulation rises and will decrease as the Smix concentration rises. Figure III shows that the oil had a positive effect on the PDI while the Smix had a negative effect. This indicates that the PDI will rise as the oil content in the formulation increases while the Smix concentration will fall. In Figure IV, the oil had a negative effect on the transmittance percentage while the Smix had a positive effect. This indicates that when the oil concentration in the formulation decreases, the transmittance percentage will rise, while when the Smix concentration increases, it will rise. Figure V shows that the oil had a negative effect on the percentage of drug content while the S-mix had a positive effect. This indicates that the drug content will rise as the formulation's oil concentration decreases and rise as the S-mix concentration increases.

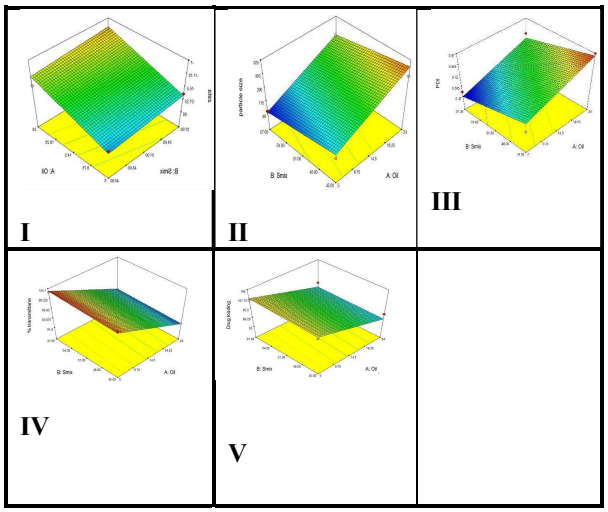


Figure-9: Three-dimensional surface plots depicting the interaction effects of independent variables on zeta potential (I), Globule size (II), PDI (III), % Transmission (IV), and % Drug loading (V)

3.5 Characterization of L-SNEDDS:

A) Fourier Transform Infrared Spectroscopy (FT-IR):

The principal absorption peaks at 1670, 1626, 1507, 1454, 1418, 1288, 1247,1101, 1058, 976, and 749 cm^{-1} in the FTIR spectra of pure curcumin powder and the IR spectra of curcumin L-SNEDDS and excipients showed no significant shift when compared; the FTIR spectra of the pure drug demonstrate that there is no interaction between the drug and excipient [24] (Figure 10).

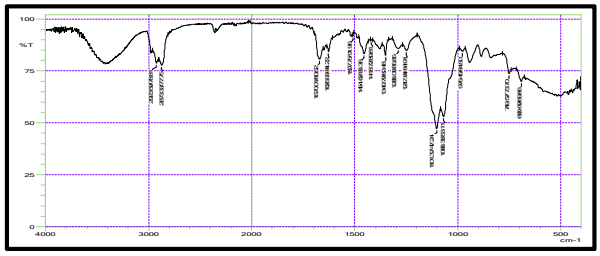


Figure-10: FT-IR spectra of L-snedds

B) Measurement of zeta potential and droplet size:
The globules were in the nanometric size range, as indicated by the liquid snedds F3 formulation's particle size of 84.46 nm. zeta potential -19 mV and PDI value 0.53, shown in Figure 11, indicated that more homogeneous emulsions are formed by a narrow globule size distribution chosen as an optimal batch as a result.

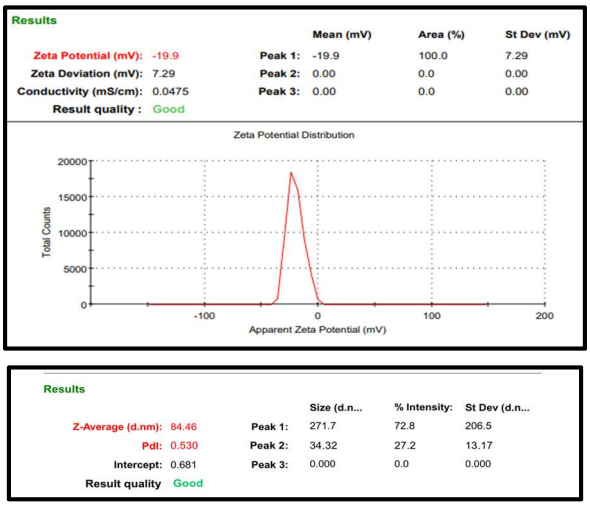


Figure-11: Zeta potential and droplet size measurement

C) Determination of thermodynamic stability and self-emulsification classes for L-SNEDDS:

To optimize the formulation, the F1–F8 formulations were tested for centrifugation, heating/cooling cycles, and subsequent freeze/thaw cycles, respectively. The lack of phase separation or drug precipitation throughout centrifugation, heating/cooling cycles, and freeze/thaw cycles proved the stability of these formulations [29]. Determining the cloud point of a nanoemulsion system is crucial to ensuring formulation stability at physiological temperature. (37ºC). formulations should be at above 37ºC as suggested by different researchers previously. According to the chart, the cloud point of a few drug-loaded SNEDDS formulations was discovered to be significantly higher than the temperature at which phase separation and cloudiness occur in a nanoemulsion system is known as the cloud point. This could lead to a decrease in the loaded drug's bioavailability and absorption. The physiological temperature cloud point for SNEDDS (37ºC) [20]. Table 6 shows the results of each physicochemical analysis for Cur SNEDDS (F1–F8).

Table-6: Thermodynamic stability and self emulsification classes for L-SNEDDS (F1-F8)

Batch	Grades (for Self nanoemulsification test)	Thermodynamic stability test			
		Centrifugation	Heating and cooling cycles	Freeze pump – thaw cycles	Cloud point (˚C)
F1	**A**	√	√	√	62 ± 0.5 ˚C
F2	**B**	×	×	×	40 ± 0.3 ˚C
F3	**A**	√	√	√	64 ± 0.8 ˚C
F4	**B**	×	×	×	47 ± 1.0 ˚C
F5	**A**	√	√	√	58 ± 0.2 ˚C
F6	**B**	×	×	×	49 ± 0.3 ˚C
F7	**B**	√	√	√	61 ± 0.4 ˚C
F8	**B**	√	√	√	56 ± 0.5 ˚C

√ = Passed the proposed tests ×= Fails the proposed tests

D) Physicochemical characterization of the Cur-SNEDDS:

Viscosity and Refractive index for Cur SNEDDS (F1-F8) were mentioned in Table **7.**

Batch	Viscosity	Refractive Index
F1	98 ± 1.12	1.433 ± 0.07
F2	112 ± 1.35	1.490 ± 0.09
F3	**152 ± 1.40**	**1.752 ± 0.13**
F4	115 ± 1.20	1.505 ± 0.10
F5	109 ± 1.30	1.471 ± 0.11
F6	130 ± 1.44	1.620 ± 0.09
F7	103 ± 1.15	1.460 ± 0.08
F8	118 ± 1.27	1.499 ± 0.07

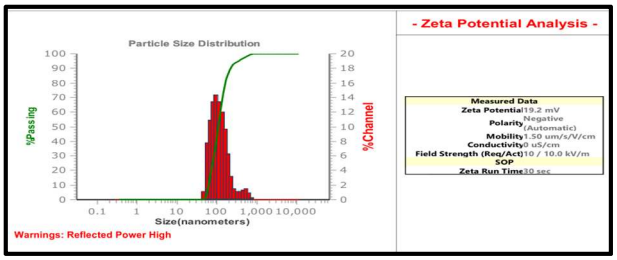
Table-7: Viscosity and Refractive index for Cur SNEDDS (F1-F8)

3.6 Characterization of S-SNEDDS:

A) Drug-excipient compatibility studies:

a) Differential scanning calorimetry analysis:

The crystalline nature of pure curcumin was demonstrated by a strong endothermic peak at roughly 180.56°C [31]. Because Neusilin US2 is amorphous, it displayed a flat line without a melting endotherm. It is noteworthy that in their S-SNEDDS made with Neusilin US2 as a carrier, the endothermic peaks of curcumin disappeared. (Figure 12) This demonstrated that the SNEDDS formulation contained the CRM in its fully dissolved form. Furthermore, it has been demonstrated that the oil-surfactant-co-surfactant combination adequately stabilizes the drug [20].



DSC for A: Curcumin; B: Curcumin SNEDDS; C: Neusilin

A

Figure-12: DSC overlay

b) Infrared spectroscopy using the Fourier transform (FTIR):

FTIR spectroscopy was used to analyze a drug-excipient

B

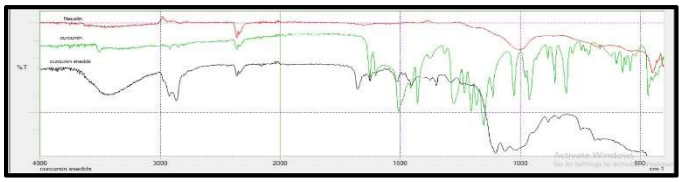
compatibility study. When comparing the FTIR spectra of pure curcumin powder with the IR spectra of a physical mixture of drug and excipients, there was not a significant shift in the principal absorption peaks at

C

1652, 1585, 1512, 1498, 1424, 1270, 1157,1131, 1031, 956, 852, 809, and 776 cm−1. The FTIR spectra of the pure drug show that there is no interaction between the drug and excipient [24]. Figure 13 showed the FT-IR overlay.

B

C



FT-IR spectra for A: Neusilin; B: Curcumin; C: Curcumin SNEDDS

Figure-13: overlay of FT-IR

B) Zeta potential, PDI and particle size of solid snedds

Solids snedds have particle size 101.3 nm, which indicated that globules are in nano-metric size range. zeta potential -19.2 mV, PDI value 0.13, (Figure 14) indicating narrow globule size distribution forming more uniform emulsions [29]**.**

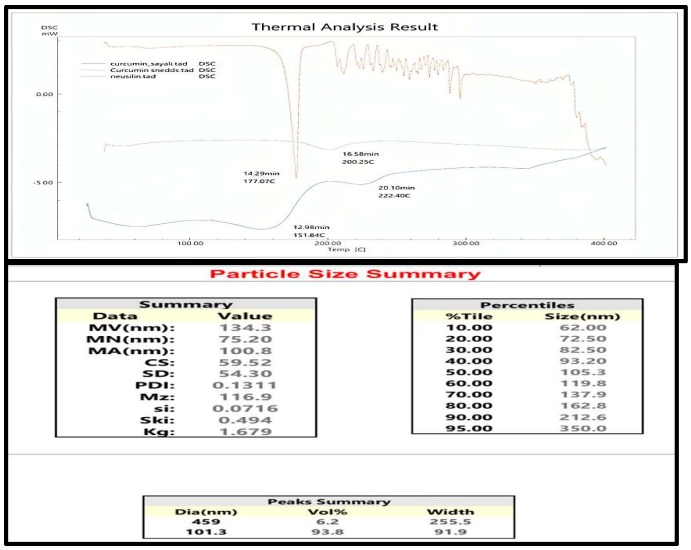


Figure-14: Zeta potential, PDI and particle size of solid snedds

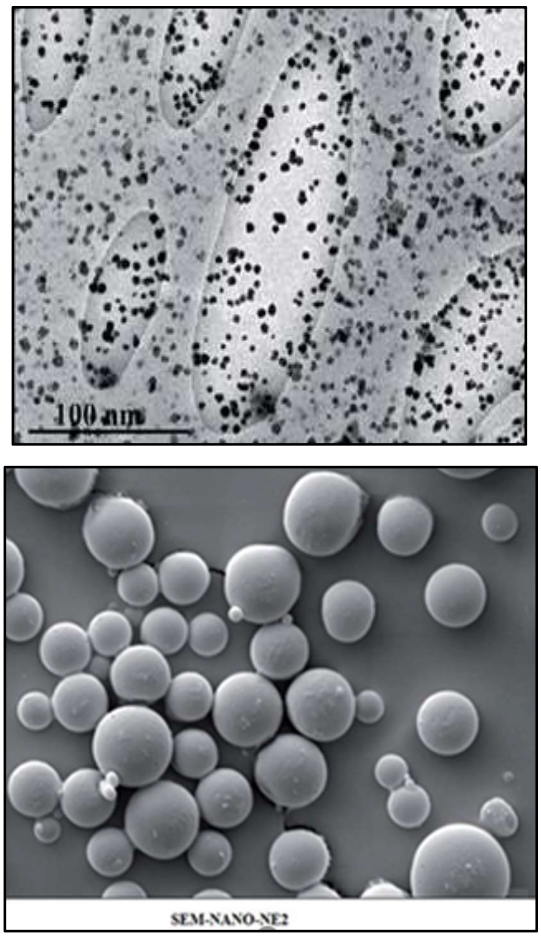
C) Shape and surface morphological analysis by SEM and TEM:

Cur-NE's surface texture and form were assessed using TEM and SEM (Figure 15) SEM revealed Cur NE's spherical, smooth surface (Figure.15A). The TEM showed a spherical particle form with a diameter of less than 100 nm, or a globule size of 93.64 nm (Figure15B).

A

Most significantly, there were no traces of any remaining oily excipients and CUR SNEDDS were fully solidified.

This conclusion was further reinforced by the solidified sample's texture and appearance.



A

B

Figure-15: SEM and TEM image of F3 Formulation

D) Flow properties S-SNEDDS:

To ascertain the appropriateness for S-SNEDDS formulation, flow characteristics including compressibility index, bulk density, tapped density, and angle of repose were assessed. The F3 optimized batch shows good flow qualities, as shown in Table 8.

Table-8: Flow properties of F3 formulation.

Batch Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner Ratio	Angle of Repose
F3	0.49 ± 0.02	0.53 ± 0.02	7.54 ± 0.02	1.08 ± 0.02	22.95 ± 0.12

E) In - vitro drug release study:

Early dissolving might be viewed as beneficial since it is thought to be crucial to enhance the oral bioavailability of poorly soluble medications by ensuring both a better and a quick dissolution. Table 9 shows comparison between In-vitro release of curcumin drug and F3 capsule solid snedds formulation. Figure 16 gives its graphical presentation[32].

Table-9: *In-vitro* release profile of curcumin solid snedds

Sr. No.	Time (Mins)	Curcumin	F3 Cap
1	5	2.68±0.02	18.61±0.05
2	10	5.83±0.04	30.29±0.09
3	15	9.85±0.07	58.62±0.03
4	30	12.72±0.05	67.47±0.04
5	45	15.73±0.03	82.38±0.06
6	60	17.20±0.06	88.93±0.03

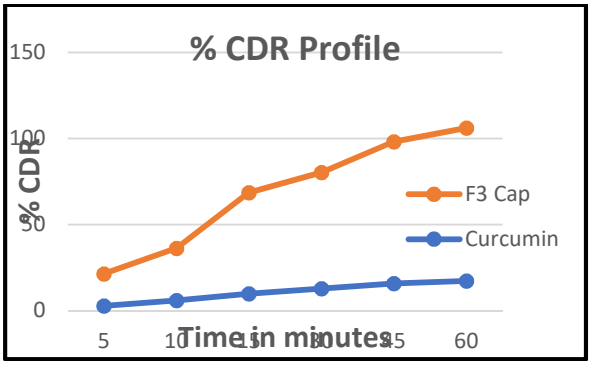


Figure-16: *In-vitro* drug release study of curcumin solid snedds

F) In vivo pharmacokinetic study

The in vivo pharmacokinetic profiles of curcumin following oral administration of pure curcumin, liquid SNEDDS, and solid SNEDDS, as well as intravenous administration of curcumin solution, are shown in Figure 13. Pure curcumin exhibited a low Cmax of 0.526 ± 0.34 µg/mL at 1.5 h. In contrast, liquid SNEDDS and solid SNEDDS resulted in significantly higher Cmax values of 2.256 ± 0.52 µg/mL at 0.58 h and 2.091 ± 0.38 µg/mL at 0.80 h, respectively ($p < 0.01$). The $AUC_{0–t}$ for liquid SNEDDS (18.63 ± 1.07 µg·h/mL) and solid SNEDDS (16.35 ± 1.39 µg·h/mL) was markedly greater than that of pure curcumin (4.63 ± 1.42 µg·h/mL). Similarly, the $AUC_{0–\infty}$ values increased from 7.06 ± 4.12 µg·h/mL for pure curcumin to 23.39 ± 6.26 µg·h/mL and 19.05 ± 5.42 µg·h/mL for liquid and solid SNEDDS, respectively. Liquid SNEDDS produced a 4.28-fold increase in Cmax and a 3.31-fold increase in $AUC_{0–\infty}$ compared with pure curcumin. The intravenous formulation showed the highest systemic exposure, with a Cmax of 4.383 ± 0.41 µg/mL and $AUC_{0–\infty}$ of 29.51 ± 4.32 µg·h/mL [33].

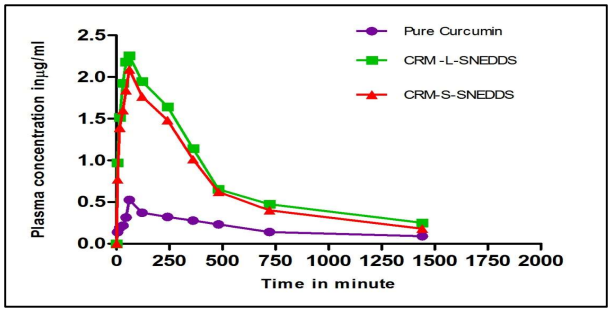


Figure 17: Plasma concentration profile of Pure Curcumin, Curcumin liquid SNEDDS, Curcumin solid SNEDDS

G) Stability Study:

Stability tests were performed on the optimized capsules, and Table 10 presents the findings. These findings indicate that the capsule (Formulation batch F3) had a stable formulation under the specified humidity and temperature conditions.

Table-10: Stability study of parameters of the optimized formulation (F3)

Parameters	Initial Month	1st Month	2nd Month	3rd Month
Physical Appearance	No Change			
Drug Content	101.11± 0.22	100.02± 0.18	101.56± 0.22	99.93± 0.31
Dissolution (%)	88.93±0 .05	87.48±0 .19	88.04±0 .35	89.43± 0.24

Discussion:

The present study aimed to overcome curcumin's poor aqueous solubility and limited oral bioavailability by developing and optimizing a self-nanoemulsifying drug delivery system (SNEDDS). A systematic approach involving solubility studies, pseudo-ternary phase diagram construction, physicochemical evaluation, and RSM-CCD optimization was employed to obtain a stable and efficient formulation.

Solubility screening identified cinnamon oil as the optimal oil, with Brij-35 and Transcutol-P selected as surfactant and co-surfactant, respectively. No shift in the λmax of curcumin (425 nm) and the absence of significant FTIR peak changes confirmed drug–excipient compatibility. DSC analysis indicated complete amorphization and molecular dispersion of curcumin within the SNEDDS matrix.

Pseudo-ternary phase diagrams revealed a broad nanoemulsion region at a 2:1 Smix ratio. RSM-CCD optimization demonstrated that oil concentration and Smix ratio significantly influenced globule size, PDI, zeta potential, transmittance, and drug content. The optimized formulation (F3) exhibited a small droplet size (84.46 nm), narrow PDI, negative zeta potential, high transmittance, and excellent drug loading, indicating good stability and dispersion.

Optimized SNEDDS showed rapid self-emulsification (Grade A), high thermodynamic stability, and cloud points above body temperature. Liquid SNEDDS were successfully converted into solid SNEDDS (S-SNEDDS) using Neusilin US2, yielding free-flowing powders with suitable micromeritic properties. SEM and TEM confirmed spherical particles with nanoscale distribution and uniform morphology.

In vitro dissolution studies demonstrated significantly enhanced drug release from S-SNEDDS compared to pure curcumin. Pharmacokinetic studies revealed markedly higher Cmax, AUC, and faster absorption for both liquid and solid SNEDDS, confirming improved oral bioavailability. Accelerated stability studies showed no significant changes over 90 days.

Overall, the optimized curcumin-loaded SNEDDS, particularly formulation F3, effectively improved solubility, stability, and oral bioavailability, highlighting its potential for enhanced therapeutic application of curcumin.

Conclusion:

Using the components of cinnamon oil Brij-35 and Transcutol-P, S-SNEDDS of curcumin was successfully created. CCD was utilized to maximize the amount of solubilizers. Neusilin US2 was used for adsorption in order to solidify the liquid formulation. SEM, and DSC analyses further confirmed that the drug was in a molecularly dispersed state and that it underwent a change from crystalline to amorphous form. The FTIR study confirms that there is no incompatibility between the Curcumin and the carriers used in the formulation of SNEDDS. From the results of the in vitro dissolution study, it was revealed that the SNEDDS had a noticeably higher level of dissolution 88.93% ± 0.03% drug release compared to only 17.20% ± 1.15% from raw curcumin within 60 mins. SNEDDS drug release depends on how fast the drug partitions from the nanoemulsion droplets into the dissolution medium. Higher solubilization capacity inside droplets leads to concentration-dependent release. In comparison to their naive forms, the prepared formulations were found to have a greater dissolving rate, good flow characteristics, a zeta potential of -19.2 mV, a PDI value of 0.13, and a droplet size of 101.3 nm. The absence of drug precipitation and phase separation demonstrated that the suggested formulation remained stable when temperature, dilution, and pH varied throughout time and freeze-thaw cycles. As a result, the creation of SNEDDS using hydrophilic carriers (Neusilin) by adsorption method seemed to be a novel method that enhanced Curcumin solubility and dissolution. The present study successfully demonstrated that self-nanoemulsifying

drug delivery systems (SNEDDS) are an effective approach for overcoming the poor solubility and low oral bioavailability of curcumin. Both liquid and solid SNEDDS significantly enhanced solubility, dissolution rate, and in-vivo pharmacokinetic performance compared to pure curcumin. Among the formulations, liquid SNEDDS showed superior absorption, higher peak plasma concentration, and greater systemic exposure, while solid SNEDDS provided additional advantages of improved stability and handling. Overall, SNEDDS represent a promising oral delivery platform for enhancing the therapeutic efficacy of curcumin.

Conflict of Interest Statement

The authors declare that they have no known competing financial interest

Ethical Declarations

All animal experiments were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) having approval no.: [27/IAEC-II/SLSRPL/2024]

Acknowledgment:

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