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Development Of Cabozantinib Loaded Solid-Snedds For Enhanced Solubility And Dissolution: Application Of Box-Behnken Design

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Abstract:
The present study aimed to develop and optimize Cabozantinib (CZ)-loaded Solid Self-Nanoemulsifying Drug Delivery Systems (S-SNEDDS) to enhance the drug's solubility and dissolution characteristics. CZ, a BCS Class II anticancer agent, suffers from poor aqueous solubility and limited oral bioavailability. To address these limitations, liquid SNEDDS (L-SNEDDS) were initially developed using Capryol 90 (oil), Tween 80 (surfactant), and Transcutol P (co-surfactant) selected based on solubility screening. A Box–Behnken Design (BBD) was applied to optimize the formulation variables influencing globule size, zeta potential, and transmittance. The optimized formulation (L-SNEDDS CZ 12) exhibited a small globule size (80.5 nm), high negative zeta potential (–29.8 mV), and excellent transmittance (98.57%), confirming good stability and emulsification efficiency. The optimized L-SNEDDS was converted into a solid form using Neusilin® US2 by adsorption, producing S-SNEDDS with improved flow and compressibility properties suitable for solid oral dosage form development. The S-SNEDDS CZ 1 formulation displayed the best micromeritic characteristics, highest drug content (99.26%), smallest droplet size (54.2 nm), and highest transmittance (98.20%). Solubility of CZ increased 10.5-fold (0.021 mg/mL vs 0.002 mg/mL for pure drug). In vitro dissolution studies revealed rapid and complete drug release (> 92% in 60 min) compared to the plain drug (≈ 29%), demonstrating significant improvement in dissolution rate. Overall, the developed S-SNEDDS effectively enhanced solubility, dissolution, and stability of Cabozantinib, highlighting its potential as a promising approach for improving the oral bioavailability of poorly soluble anticancer drugs.
Keywords: *Cabozantinib, SNEDDS, Box-Behnken Design, solubility enhancement, Neusilin US2, in-vitro dissolution.*

INTRODUCTION:

Cabozantinib (CZ) is a potent multi-kinase inhibitor that targets receptors such as VEGFR, MET, and RET, making it effective in the treatment of various cancers including renal cell carcinoma, hepatocellular carcinoma, and medullary thyroid carcinoma [1, 2]. However, its therapeutic efficacy is significantly limited by its poor aqueous solubility and low oral bioavailability. CZ is classified as a Biopharmaceutics Classification System (BCS) Class II drug, exhibiting high permeability but extremely low solubility (approximately 0.003 mg/mL in water), which leads to erratic absorption and variable systemic exposure after oral administration [3, 4]. Moreover, its extensive first-pass metabolism further reduces the amount of drug reaching systemic circulation. Therefore, improving the solubility and dissolution rate of CZ is crucial to enhance its oral bioavailability and achieve consistent therapeutic outcomes [5].

Lipid-based drug delivery systems, particularly Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), have emerged as a promising strategy to overcome the challenges associated with poorly water-soluble drugs like CZ. SNEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water nanoemulsions upon mild agitation in the gastrointestinal fluids [6, 7]. This system enhances the solubilization of lipophilic drugs in the lipidic phase, maintains the drug in a solubilized state within the GI tract, and promotes lymphatic transport, thereby bypassing extensive first-pass metabolism. The nano-sized droplets formed upon dispersion provide a large surface area for absorption, resulting in improved dissolution, enhanced permeability, and increased oral bioavailability [8, 9].

Although liquid SNEDDS effectively enhance the solubility and oral bioavailability of poorly water-soluble drugs, their practical application is often limited by issues such as poor stability, handling difficulties, portability concerns, and potential drug precipitation during storage or dilution. To overcome these drawbacks, converting liquid SNEDDS into a solid form (S-SNEDDS) has gained significant attention. Solidification not only improves the physical and chemical stability of the formulation but also enhances patient compliance, ease of dosing, and manufacturing feasibility [10, 11]. Moreover, S-

SNEDDS retain the self-emulsifying properties of liquid SNEDDS while offering additional advantages such as better flowability, compactibility, and the potential for formulation into solid oral dosage forms like tablets or capsules. Thus, the transformation of liquid SNEDDS into S-SNEDDS provides a more stable, convenient, and efficient delivery system [12]. Hence present study was aimed to develop CZ loaded SNEDDS for enhanced solubility and dissolution profile which may increase oral bioavailability.

MATERIALS AND METHODS:

Material:

Cabozantinib (CZ) was obtained as a gift sample from Slayback Pharma, Hyderabad, India. Gattefosse India Pvt. Ltd., Mumbai provided Capryol 90 and Transcutol P as a gift sample respectively. Tween 80 was purchased from Loba Chemie Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

Methods:

Solubility studies:

For the solubility study, an excess amount of Cabozantinib (CZ) was added to 2 mL of each selected oil, surfactant, and co-surfactant in separate vials. The mixtures were vortexed for 5 minutes to ensure proper mixing, followed by agitation in a water bath shaker at 25 ± 2 °C for 72 hours to attain equilibrium. After equilibration, the samples were centrifuged at 10,000 rpm for 15 minutes to separate undissolved drug particles. The clear supernatant was carefully collected, appropriately diluted with methanol, and analyzed using a UV–visible spectrophotometer (Shimadzu UV-1800) at 244 nm [13]. The solubility of CZ (mg/mL) was calculated, and the oil, surfactant, and co-surfactant exhibiting the highest solubility were selected for the formulation of liquid SNEDDS of CZ.

Construction of pseudo-ternary phase diagram:

Based on the solubility and screening studies, Capryol 90, Tween 80, and Transcutol P were selected as the oil, surfactant, and co-surfactant, respectively. Pseudo-ternary phase diagrams were constructed using different surfactant-to-co-surfactant ratios (Km values of 1:1, 2:1, and 3:1) along with varying proportions of oil and water. Mixtures of Smix and oil were prepared in ratios ranging from 1:9 to 9:1 in pre-weighed test tubes, followed by the gradual addition of double-distilled water until the first sign of turbidity appeared, which was noted as the endpoint. The phase diagrams were then plotted using CHEMIX School 13.5 software to identify the nanoemulsion region [14].

Formulation of Liquid SNEDDS of CZ using Box-Behnken Design

At the appropriate ratios, 40 mg of CZ was dissolved in the oil and constantly mixed up to 2 min using the cyclomixer. Finally, Smix was added to the drug-containing mixture and thoroughly homogenized using a vortex mixer to create a homogeneous mixture. The developed L-SNEDDS CZ were stored at 25 °C in firmly closed glass vials, and the stable formulations were then subjected to further investigation [15].

By using a statistical design that only needs a few experiments, obviating the requirement for laborious and meticulous experimental trials. One such method is response surface methodology (RSM). Box-Behnken Design (BBD) is employed when there are only a few key factors involved in optimization, thus it takes fewer runs [16]. The range of the independent variables, namely the amount of oil, namely Capryol 90 (X1), Surfactant- Tween 80 (X2), and Co-surfactant Transcutol P (X3), was chosen from the ternary diagram. Levels of variables in BBD for Formulation of Liquid SNEDDS of CZ and Composition of Liquid SNEDDS of CZ are shown in Table 1 and 2 respectively.

Table 1: Levels of variables in BBD for Formulation of Liquid SNEDDS of CZ

Independent variables	Levels		
	Low (-1)	Middle (0)	High (+1)
X1 = Amount of Capryol 90 (%)	10	15	20
X2 = Amount of Tween 80 (%)	22.5	26.25	30
X3 = Amount of Transcutol P (%)	7.5	8.75	10
Dependent variables	**Goal**		
Y1 = Globule size	Minimize		
Y2 = PDI	Minimize		
Y3 = % Transmittance	Maximize		

Table 2: Composition of Liquid SNEDDS of CZ using Box-Behnken Design

Batch	Amount of Capryol 90 (%)	Amount of Tween 80 (%)	Amount of Transcutol P (%)
L-SNEDDS CZ 1	10	22.5	8.75
L-SNEDDS CZ 2	20	22.5	8.75
L-SNEDDS CZ 3	10	30	8.75
L-SNEDDS CZ 4	20	30	8.75
L-SNEDDS CZ 5	10	26.25	7.5
L-SNEDDS CZ 6	20	26.25	7.5
L-SNEDDS CZ 7	10	26.25	10
L-SNEDDS CZ 8	20	26.25	10
L-SNEDDS CZ 9	15	22.5	7.5
L-SNEDDS CZ 10	15	30	7.5
L-SNEDDS CZ 11	15	22.5	10
L-SNEDDS CZ 12	15	30	10
L-SNEDDS CZ 13	15	26.25	8.75

Evaluation of Liquid SNEDDS of CZ

Thermodynamic stability studies

In order to check physical robustness across a range of environmental circumstances, the thermodynamic stability of the prepared CZ-loaded SNEDDS formulations was methodically evaluated using different stress tests, such as centrifugation, heating–cooling cycles, and freeze–thaw cycles [17, 18].

Robustness to dilution

To evaluate the dilution stability of SNEDDS, the formulations were diluted with distilled water at ratios of 1:50, 1:100, and 1:1000. The diluted samples were kept at room temperature for 12 hours and then visually inspected for any signs of precipitation or phase separation, indicating physical instability [19].

Evaluation of Self-Emulsification Behavior

The ability of the SNEDDS to self-emulsify was tested using a USP dissolution apparatus Type II (Veego VDA-8DR). 1 mL of the formulation was introduced dropwise into 200 mL of 0.1 N HCl, maintained at 37 °C, while stirring at 60 rpm using a stainless-steel paddle. The emulsification process was visually monitored, focusing on the rate and clarity of the resulting emulsion. Evaluation was performed using a qualitative grading system as described by Khoo Shui-Mei et.al. (1998) [20].

% Transmittance

The clarity of the emulsified SNEDDS was evaluated by diluting 1 mL of the formulation with 100 mL of distilled water. The resulting dispersion was analyzed using a UV–Visible spectrophotometer (Shimadzu UV-1800, Japan) at 650 nm, with distilled water as the blank. Higher transmittance values indicated greater transparency and the formation of finer emulsions [21].

Dye solubilization test and Cloud point measurement

The type of emulsion was confirmed by using dye solubilization test. Rapid incorporation of the water-soluble dye (eosin) into the system was observed which indicate that the continuous phase was water, which signified the formation of o/w micro emulsion. Cloud point of all liquid SNEDDS was found to be higher than 85°C, which indicate that micro emulsion will be stable at physiological temperature without risk of phase separation [22].

Drug Entrapment Efficacy

The drug content of CZ in the SNEDDS was determined using a methanolic extraction method. One part of the formulation was mixed with nine parts of methanol (v/v) and centrifuged at 10,000 rpm for 30 minutes. The clear supernatant obtained was further diluted 2.5-fold with methanol, and the CZ content was quantified using a UV–Visible spectrophotometer under previously established analytical conditions [23].

Formulation of CZ loaded S-SNEDDS:

S-SNEDDS of CZ was prepared by the adsorption technique using Neusilin® US2 as the solid carrier. The optimized liquid SNEDDS batch (L-SNEDDS CZ 12) was gradually incorporated into Neusilin® US2 in weight ratios of 1:1, 1:1.25, and 1:1.5 (w/w), with continuous mixing in a mortar and pestle to ensure uniform adsorption. The resulting mixture was blended thoroughly to obtain a free-flowing dry powder, which was then dried in a hot air oven at 50°C to remove residual moisture. The dried powder

was sieved through a 60–80 mesh to achieve uniform particle size and stored in an airtight container for further characterization. This method effectively converted the liquid SNEDDS into a solid form with improved flowability, suitable for formulation into oral solid dosage forms [24].

Evaluation of CZ loaded S-SNEDDS:

Micromeritic properties of S-SNEDDS

The flow and packing characteristics of CZ-loaded Solid-SNEDDS (S-SNEDDS) were assessed through measurements of angle of repose, bulk density, compressibility index, and Hausner ratio. The angle of repose was determined using the fixed funnel method to evaluate flow behavior. Bulk density studies involved measuring both loose and tapped densities to understand packing efficiency. The compressibility index and Hausner ratio were then calculated to assess powder flowability and cohesiveness. These evaluations together provided an overall indication of the solid SNEDDS powder's suitability for further processing into solid oral dosage forms [25].

Drug content

To estimate the drug content in the S-SNEDDS formulation, a 100 mg sample was accurately weighed and dispersed in methanol. The mixture was vortexed for 15 minutes to ensure uniform dispersion, followed by sonication for 20 minutes to achieve complete extraction of the drug. The suspension was then centrifuged for 10 minutes to separate any undissolved material, and the clear supernatant was collected, appropriately diluted, and analyzed using a UV–Visible spectrophotometer at 244 nm to determine the CZ content [26].

Reconstitution properties of S-SNEDDS

Dilution study by visual observation

To simulate gastrointestinal conditions after oral administration, the dilution behavior of the S-SNEDDS was examined. A 100 mg sample of the formulation was dispersed in 100 mL of double-distilled water maintained at 37 °C and gently stirred with a magnetic stirrer to promote emulsification. The process of spontaneous emulsification and droplet formation was visually observed. A clear or transparent microemulsion indicated efficient self-emulsification, whereas a turbid or milky appearance suggested poor emulsification performance [27].

% Transmittance, Globule size, PDI and Zeta potential

The reconstituted S-SNEDDS formulations containing CZ was evaluated for percent transmittance, globule size, polydispersity index (PDI), and zeta potential, following the same characterization protocols applied to the liquid SNEDDS.

Aqueous solubility study of CZ and CZ loaded S-SNEDDS formulation

The solubility of pure CZ and the CZ-loaded S-SNEDDS was evaluated using the shake flask method. An excess of pure drug and an equivalent amount of S-SNEDDS (based on drug content) were added separately to 5 mL of distilled water in sealed glass vials. The vials were kept in an orbital shaker at 37 ± 0.5 °C and 100 rpm for 24 hours to attain equilibrium. After incubation, the samples were centrifuged at 10,000 rpm for 10 minutes to separate any undissolved residue, and the clear supernatants were filtered through 0.45 µm membrane filters. The CZ concentration in the filtrate was determined spectrophotometrically at 244 nm. Solubility was expressed in mg/mL, and all experiments were performed in triplicate for accuracy [28].

In-vitro drug release studies

The in-vitro drug release study of S-SNEDDS of CZ and plain CZ were carried out using USP- type-II dissolution test apparatus. Hard gelatin capsule of size '4' was filled with S-SNEDDS of NE (equivalent to 40 mg of CZ) and plain CZ and put into each of 900 mL of 0.01 N HCl with 0.5% Triton X-100 (degassed) at 37±0.5^{0}C with 75 rpm rotating speed (USFDA method). Samples of 5 mL were withdrawn at regular time interval of 5, 10, 15, 20, 30, 45 and 60 min and filtered using 0.45 µm filter. An equal volume of respective dissolution medium was added to maintain the volume constant. Drug content from sample was analyzed using UV-spectrophotometer at wavelength of 244 nm. All measurements were done in triplicate from three independent samples [29].

RESULT AND DISCUSSION:

Solubility studies:

The solubility of CZ in various excipients was assessed using UV spectrophotometry at room temperature, and the findings are presented in Figures 1. The solubility study of CZ in various excipients revealed that

among the oils tested, Capryol 90 showed the highest solubility (19.28 mg/mL), making it the most suitable oil phase for SNEDDS formulation. Among the surfactants, Tween 80 exhibited the greatest solubilization capacity (22.48 mg/mL) due to its high HLB value and excellent emulsification properties. Similarly, Transcutol P demonstrated the highest solubility (16.27 mg/mL) among the co-surfactants, attributed to its amphiphilic nature that enhances drug partitioning. Hence, Capryol 90, Tween 80, and Transcutol P were selected as the optimal oil, surfactant, and co-surfactant, respectively, for the development of CZ-loaded SNEDDS.

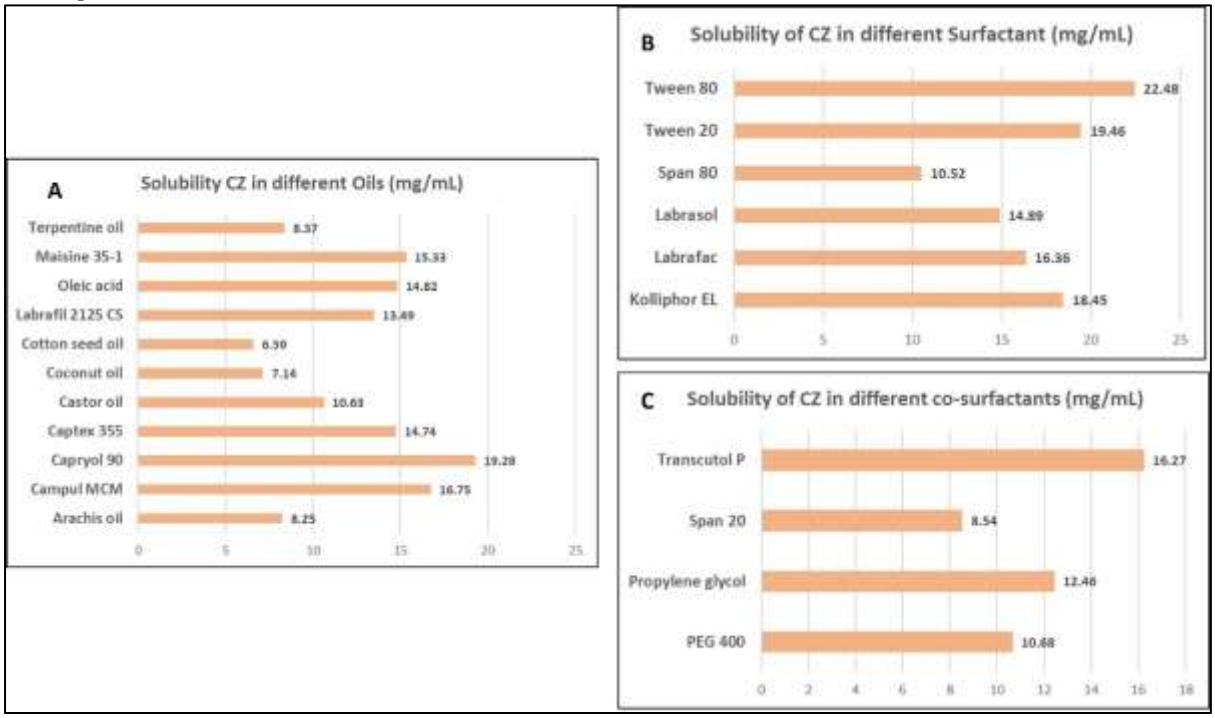

Figure 1: Solubility of CZ in different A. Oils, B. Surfactant and C. Co-surfactant

Construction of pseudo-ternary phase diagram:

The ratio of surfactant to co-surfactant plays a crucial role in achieving a stable and efficient SNEDDS formulation. Pseudo-ternary phase diagrams were constructed using surfactant/co-surfactant ratios (Km values) of 1:1, 2:1, and 3:1 (w/w), as shown in Figure 2. It was observed that increasing the surfactant concentration enlarged the gel-like region, while a higher proportion of co-surfactant expanded the nanoemulsion region, facilitating efficient emulsification. However, an excessive amount of co-surfactant led to decreased system stability and larger droplet size due to the weakening of the interfacial film. Therefore, based on the balance between emulsification efficiency and stability, a surfactant-to-co-surfactant ratio of 3:1 was selected as optimal for SNEDDS formulation.

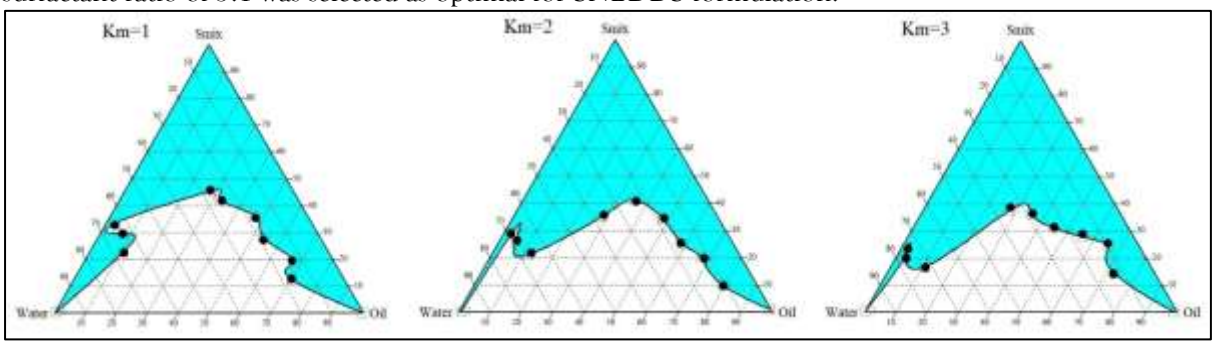

Figure 2: Pseudo ternary phase diagram of Capryol 90, Tween 80, Transcutol P and water at Km=1, 2 and 3

Evaluation of Liquid SNEDDS of CZ using Box-Behnken Design

To evaluate the effect of formulation variables such as the concentrations of Capryol 90, Tween 80, and Transcutol P on globule size, zeta potential, and entrapment efficiency, a Box-Behnken Design (BBD) was employed. Based on this design, thirteen batches of CZ-loaded liquid SNEDDS (L-SNEDDS CZ 1 to L-SNEDDS CZ 13) were successfully prepared and further subjected to various evaluation studies.

Thermodynamic Stability, Dilution Robustness, and Self-Emulsification Efficiency Evaluation

A summary of the outcomes of thermodynamic stability testing, dilution tolerance, and self-emulsification efficiency is presented in Table 3. The thermodynamic stability, dilution robustness, and self-emulsification efficiency studies of CZ-loaded liquid SNEDDS (Table 3) confirmed the stability and suitability of all prepared formulations. All batches successfully passed the heating–cooling, centrifugation, and freeze–thaw tests, indicating good thermodynamic stability without signs of phase separation, precipitation, or drug crystallization. The formulations also demonstrated excellent robustness upon dilution, showing no phase instability or turbidity at various dilution levels. In the dispersibility test, most batches exhibited Grade A emulsification behavior, forming clear or slightly bluish nanoemulsions within one minute, while a few showed Grade B results, indicating slightly less transparency but still acceptable emulsification efficiency. Overall, all CZ-loaded liquid SNEDDS formulations were found to be stable, robust, and efficient in self-emulsification, confirming their suitability for further optimization and solidification.

Table 3: Thermodynamic Stability, Dilution Robustness, and Self-Emulsification Efficiency Evaluation of CZ loaded Liquid SNEDDS

Formulation	Observations based on the thermodynamic stability studies, robust to dilution and dispersibility tests					Inference
	H/C	Cent.	Friz. Thaw	Robust	Disperse.	
L-SNEDDS CZ 1	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 2	✓	✓	✓	✓	Grade B	Passes
L-SNEDDS CZ 3	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 4	✓	✓	✓	✓	Grade B	Passes
L-SNEDDS CZ 5	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 6	✓	✓	✓	✓	Grade B	Passes
L-SNEDDS CZ 7	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 8	✓	✓	✓	✓	Grade B	Passes
L-SNEDDS CZ 9	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 10	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 11	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 12	✓	✓	✓	✓	Grade A	Passes
L-SNEDDS CZ 13	✓	✓	✓	✓	Grade A	Passes

H/C: Heating cooling cycle, Cent.: Centrifugation, Friz. Thaw: Freeze thaw cycle, Robust.: Robustness to dilution Disperse.: Dispersibility test

Dye Solubilization and Cloud Point Evaluation

The type of emulsion formed was confirmed using the dye solubilization method. Rapid absorption of the water-soluble dye eosin into the formulation indicated that water acted as the continuous phase, confirming the formation of an oil-in-water (o/w) microemulsion. Additionally, all liquid SNEDDS formulations exhibited cloud points above 80°C, demonstrating their thermal stability and ensuring that no phase separation would occur under physiological conditions.

Globule size, Zeta Potential and Entrapment Efficacy:

Globule size, zeta potential and entrapment efficacy were taken as dependant factor while applying BBD. Results of all these parameters for all 13 batches of liquid SNEDDS are shown in Table 4.

Table 5: Globule size, Zeta Potential , Entrapment Efficacy and % Transmittance of liquid SNEDDS of CZ

Formulation	Globule size (nm)	Zeta Potential (mV)	Entrapment Efficacy (%)	% Transmittance
L-SNEDDS CZ 1	112.4	-16.5	77.42	77.42
L-SNEDDS CZ 2	132.8	-14.7	75.25	75.25
L-SNEDDS CZ 3	82.4	-28.6	98.23	98.23
L-SNEDDS CZ 4	90.3	-26.6	94.62	94.62

L-SNEDDS CZ 5	98.2	-21.4	89.36	89.36
L-SNEDDS CZ 6	101.2	-20.7	86.02	86.02
L-SNEDDS CZ 7	96.8	-25.8	92.22	92.22
L-SNEDDS CZ 8	97.6	-23.5	91.46	91.46
L-SNEDDS CZ 9	166.7	-14.3	74.67	74.67
L-SNEDDS CZ 10	84.6	-27.5	96.85	96.85
L-SNEDDS CZ 11	110.6	-17.6	81.34	81.34
L-SNEDDS CZ 12	**80.5**	**-29.8**	**98.72**	**98.57**
L-SNEDDS CZ 13	108.3	-18.9	84.15	84.15

Counter and response surface plot showing effect of different variables (A: Amount of Capryol 90, B: Amount of Tween 80 and C: Amount of Tanscutol P) on globule size, zeta potential and entrapment efficacy are shown in Figure 3.

Effect on Globule Size

The response surface plot and regression model equation:

Globule size = +104.80 + 4.01A – 23.09B – 8.15C

indicate that Tween 80 and Transcutol P significantly reduce globule size, while Capryol 90 tends to increase it. A higher concentration of Tween 80 markedly decreased the droplet size due to its strong surface-active properties, leading to efficient interfacial tension reduction and formation of finer emulsions. In contrast, increasing oil content (Capryol 90) caused larger globule formation due to reduced emulsification efficiency. Thus, an optimal balance between oil and surfactant concentrations is essential for achieving small, stable globules that enhance solubility and bioavailability.

Effect on Zeta Potential

The zeta potential followed the regression equation:

Zeta Potential = –22.76 + 2.10A – 6.18B – 0.35C.

Among the variables, Tween 80 had the most significant effect, producing more negative zeta potential values, which correspond to better colloidal stability and reduced droplet aggregation. Capryol 90 slightly increased the zeta potential (less negative), potentially reducing stability at higher levels, while Transcutol P showed a negligible effect. The enhanced negative charge with increasing Tween 80 concentration reflects improved surface charge distribution, indicating superior physical stability of the SNEDDS formulations.

Effect on % Transmittance

The quadratic model equation for % transmittance was:

% Transmittance = +84.15 – 1.24A + 9.95B + 2.09C + 0.36AB + 0.65AC – 1.24BC + 2.07A^2 + 0.16B^2 + 3.55C^2.

Results showed that Tween 80 had the strongest positive influence on transmittance, enhancing emulsion clarity through effective emulsification and droplet size reduction. Transcutol P also improved clarity moderately, while higher levels of Capryol 90 slightly decreased it due to larger droplet formation. The interaction effects revealed synergism between Capryol 90 with both Tween 80 and Transcutol P, improving optical clarity at optimal concentrations. Overall, L-SNEDDS CZ 12 was identified as the optimized formulation with the smallest globule size (80.5 nm), high zeta potential (–29.8 mV), and excellent % transmittance (98.57%), confirming its superior self-emulsification efficiency and stability.

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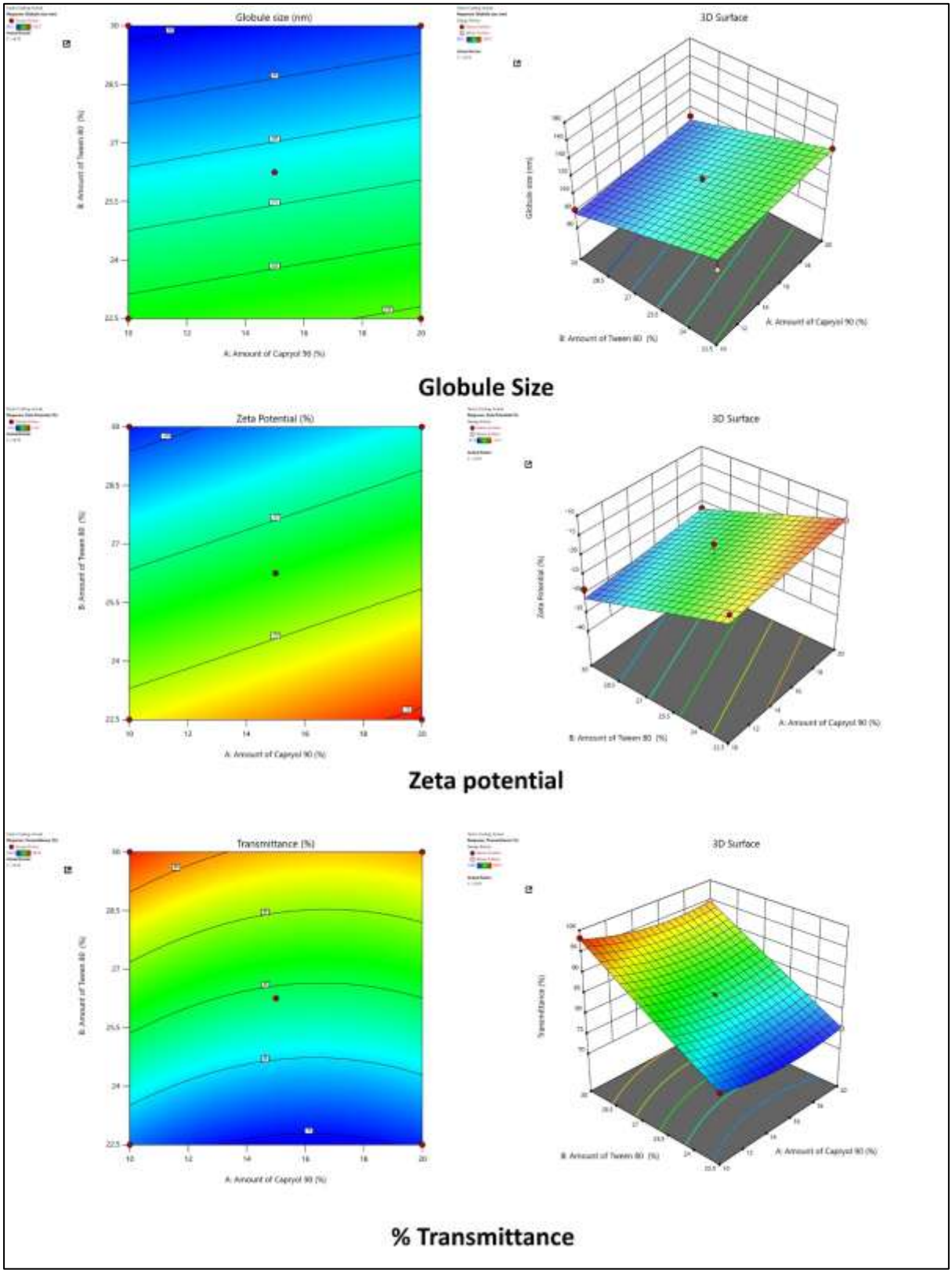

Figure 3: Counter and Response surface plot showing effect of variables Globule size, zeta potential and % Transmittance

Formulation of S-SNEDDS of CZ

Three batches of S-SNEDDS of CZ were successfully formulated by taking optimized formulation of liquid SNEDDS (L-SNEDDS CZ 12) and Neusilin US2 in different proportion of 1:1, 1.25 and 1.5 w/w by absorption technique and used further for evaluation.

Evaluation of S-SNEDDS of CZ

Micromeritic properties of S-SMEDDS and drug content

The flow properties, compressibility, and drug content of three NE-loaded solid self-nanoemulsifying drug delivery system (S-SNEDDS) formulations S-SNEDDS NE 1, S-SNEDDS NE 2 and S-SNEDDS NE 3 were systematically evaluated to determine their suitability for development into solid oral dosage forms. Results are shown in Table 6.

Table 6: Micromeritic properties and drug content of S-SNEDDS formulations of CZ

Formulation	Angle of repose	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner's ratio	Drug content (%)
S-SNEDDS CZ 1	14.63±0.20	0.686±0.03	0.781±0.03	12.16±0.42	1.139±0.03	99.26±1.35
S-SNEDDS CZ 2	13.86±0.36	0.632±0.04	0.743±0.04	14.94±0.26	1.176±0.03	97.63±1.27
S-SNEDDS CZ 3	13.29±0.14	0.589±0.03	0.725±0.03	18.76±0.58	1.231±0.04	96.37±1.45

The micromeritic and drug content evaluation of CZ-loaded S-SNEDDS formulations (CZ 1, CZ 2, and CZ 3) confirmed their suitability for solid oral dosage form development. All formulations exhibited excellent flow properties with angles of repose below 25°, indicating good powder flow, with S-SNEDDS CZ 3 showing the lowest value (13.29°). Bulk and tapped density studies revealed that CZ 1 had the highest densities, suggesting better packing, while CZ 3 showed lower values, indicating higher porosity. Carr's Index and Hausner's Ratio values were within acceptable USP limits, confirming good flowability, with CZ 1 showing the best results (CI: 12.16%, HR: 1.139). Drug content analysis showed high loading efficiency across all batches (>95%), with CZ 1 having the highest (99.26%). Overall, S-SNEDDS CZ 1 exhibited the most favorable characteristics in terms of flowability, compressibility, and drug content, making it the most suitable for further development, while CZ 3 may require optimization to enhance uniformity and compressibility.

Reconstitution properties of S-SNEDDS

Dilution study by visual observation

The emulsification ability of all S-SNEDDS formulations, as presented in Table 7, demonstrated excellent performance. Upon dilution with water, each formulation exhibited rapid and spontaneous nanoemulsion formation without any signs of phase separation or inversion even after 2 hours of storage. This confirmed their strong self-emulsifying efficiency and stability, indicating that all three formulations possess the desired capability to form fine nanoemulsions upon aqueous dilution—an essential attribute for enhancing the oral bioavailability of CZ.

Table 7: Emulsification ability, % Transmittance, Globule size and Zeta potential of S-SNEDDS of CZ

Formulation	Emulsification ability	% Transmittance	Globule size (nm)	PDI	Zeta potential (mV)
S-SNEDDS CZ 1	Good	98.20±1.68	54.2	0.645	-32.6
S-SNEDDS CZ 2	Good	95.43±1.76	58.6	0.482	-30.2
S-SNEDDS CZ 3	Good	90.32±1.59	62.3	0.347	-27.4

% Transmittance, Globule size, PDI and Zeta potential

The evaluation of emulsification characteristics revealed that S-SNEDDS CZ 1 exhibited the highest percentage transmittance (98.20 ± 1.68%), followed by CZ 2 (95.43 ± 1.76%) and CZ 3 (90.32 ± 1.59%), indicating that CZ 1 produced the clearest and most uniform emulsion. Globule size analysis showed CZ 1 had the smallest droplets (54.2 nm), favorable for enhanced solubilization and absorption, while CZ 2 and CZ 3 had slightly larger sizes of 58.6 nm and 62.3 nm, respectively—all within the desired nanometric range. The PDI values ranged from 0.645 (CZ 1) to 0.347 (CZ 3), suggesting uniform droplet distribution across formulations. All batches exhibited negative zeta potentials, contributing to good stability, with CZ

1 showing the highest negative value (-32.6 mV), followed by CZ 2 (-30.2 mV) and CZ 3 (-27.4 mV). Overall, S-SNEDDS CZ 1 demonstrated superior clarity, smaller globule size, and higher surface charge, making it the most stable and promising formulation among the three.

Aqueous solubility study of CZ and CZ loaded S-SNEDDS formulation:

A remarkable enhancement in solubility was observed for Cabozantinib, whose intrinsic solubility of 0.002 mg/mL increased to 0.021 mg/mL in the S-SNEDDS formulation (CZ 1), reflecting a 10.5-fold improvement. The improved solubilization can be attributed to efficient encapsulation and uniform dispersion within the nanoemulsified system, which maintains a supersaturated state and minimizes drug precipitation. These findings demonstrate the potential of S-SNEDDS to significantly enhance the solubility, dissolution, and consequently the oral bioavailability of poorly water-soluble drugs, with the greatest benefit observed in drugs possessing inherently low solubility such as CZ.

In-vitro drug release studies

The dissolution study showed a marked improvement in CZ release from all S-SNEDDS formulations compared to the plain drug. While plain CZ exhibited minimal release (≈2.8% at 10 min), S-SNEDDS formulations achieved rapid and extensive drug release, exceeding 79% within 30 minutes and over 85% within 60 minutes. Among them, S-SNEDDS CZ1 showed the highest release (92.57% at 60 min), indicating superior self-emulsification and solubilization efficiency. This enhanced dissolution is attributed to the nano-sized droplets and optimized surfactant–co-surfactant ratio, confirming the potential of S-SNEDDS—especially CZ1—to significantly improve the solubility and bioavailability of CZ.

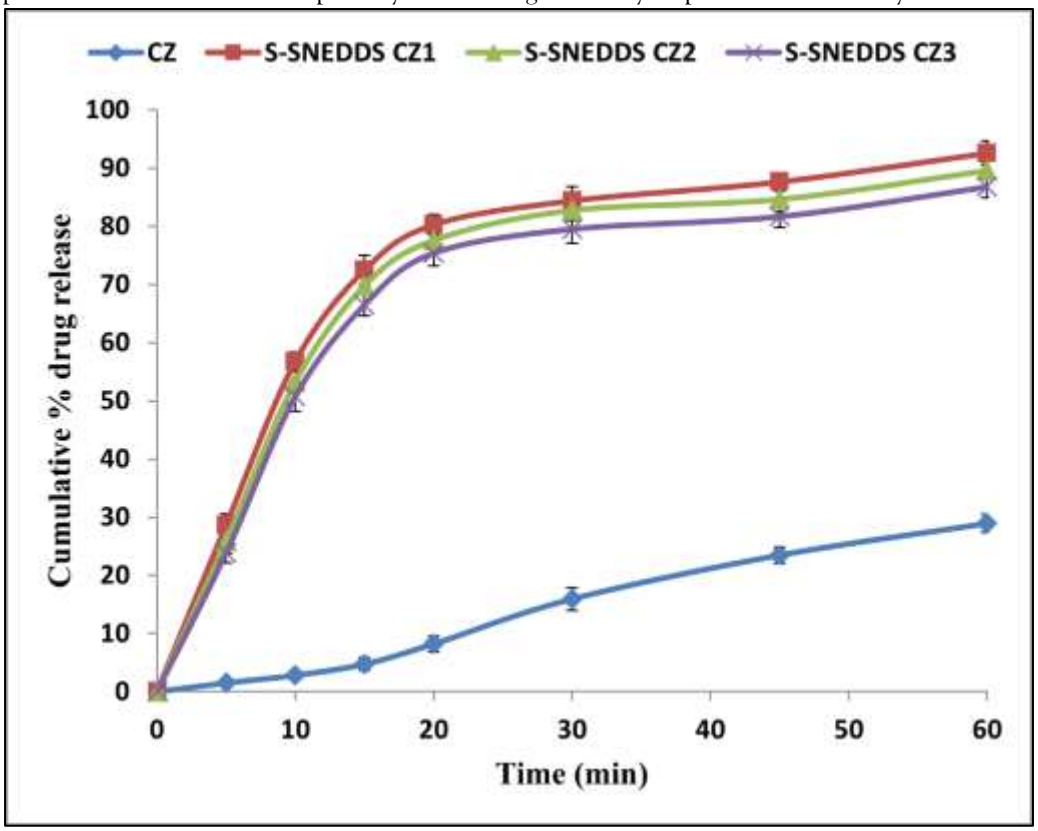

Figure 4: Cumulative % drug release of S-SNEDDS of CZ and plain CZ

CONCLUSION:

The study successfully developed and optimized Cabozantinib-loaded S-SNEDDS using a Box–Behnken Design to enhance solubility and dissolution. Capryol 90, Tween 80, and Transcutol P were identified as the most suitable excipients based on solubility and emulsification efficiency. The optimized liquid formulation (L-SNEDDS CZ 12) exhibited small droplet size, high transmittance, and good stability, confirming effective self-emulsification. Conversion of liquid SNEDDS into solid form using Neusilin US2 produced free-flowing S-SNEDDS with excellent micromeritic and reconstitution properties. Among all, S-SNEDDS CZ 1 demonstrated the best performance, showing the highest drug content, smallest droplet size, and highest clarity. The formulation significantly improved CZ solubility (10.5-fold increase) and dissolution rate (> 92% drug release within 60 minutes), compared to the plain drug (≈ 29%). This enhancement can be attributed to the nano-sized droplets and efficient surfactant–co-surfactant system

facilitating rapid dispersion and sustained solubilization. Overall, the developed S-SNEDDS proved to be a stable and efficient drug delivery system capable of overcoming solubility and bioavailability challenges associated with CZ, suggesting its potential applicability for other poorly water-soluble therapeutic agents.

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