

Formulation and Optimization of Self Emulsifying Drug Delivery System for Enhanced Solubility and Oral Bioavailability of Amisulpride Using Design of Expert Approach

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ABSTRACT

Background: Amisulpride, a Biopharmaceutics Classification System (BCS) Class II antipsychotic drug, exhibits limited aqueous solubility, resulting in poor dissolution and suboptimal oral bioavailability. Self-Emulsifying Drug Delivery Systems (SEDDS) represent an effective lipid-based strategy for improving the solubilization and gastrointestinal absorption of poorly water-soluble drugs. This study aimed to formulate and optimize an Amisulpride-loaded SEDDS using a Quality by Design approach based on Box-Behnken Design (BBD). **Materials and Methods:** Solubility screening was performed to identify suitable formulation components, leading to the selection of oleic acid as the oil, Tween 80 as the surfactant, and PEG 400 as the co-surfactant. A three-factor, three-level Box-Behnken experimental design comprising 15 formulations was employed to optimize the formulation. The prepared SEDDS were characterized for globule size, polydispersity index, zeta potential, percentage transmittance, self-emulsification time, and *in vitro* drug release. The optimized formulation was further evaluated for robustness to dilution, cloud point, thermodynamic stability, transmission electron microscopy, and drug release kinetics. **Results:** The optimized formulation demonstrated a mean globule size of 157.1 ± 0.32 nm, a polydispersity index of 0.272 ± 0.012 , and a zeta potential of -42.11 ± 5.64 mV, indicating the formation of a stable nanoemulsion. The formulation exhibited excellent clarity with approximately 100% transmittance, rapid self-emulsification within 36 ± 1 s, and a cumulative drug release of $98.18 \pm 2.06\%$ after 55 min. Numerical optimization yielded an overall desirability value of 0.953, confirming the suitability of the optimized composition. Stability studies, dilution robustness, and cloud point evaluation demonstrated that the optimized SEDDS remained physically stable without precipitation or phase separation. Drug release data were best described by the first-order kinetic model. **Conclusion:** The Box-Behnken Design successfully optimized an Amisulpride-loaded SEDDS with desirable physicochemical properties, rapid emulsification, excellent dissolution behavior, and good thermodynamic stability. The developed formulation has considerable potential to improve the oral performance of Amisulpride and illustrates the usefulness of Design of Experiments for the systematic development of lipid-based drug delivery systems.

Keywords: Amisulpride, Box-Behnken Design, Design of Experiments, Lipid-based drug delivery, Oral bioavailability, Self-emulsifying drug delivery system, Solubility enhancement.

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INTRODUCTION

Self-Emulsifying Drug Delivery Systems (SEDDS) is a combination of drug, oil, surfactant, and cosurfactant which forms oil-in-water emulsion. SEDDS is said to help enhance

bioavailability of BCS class II drugs (Ke *et al.*, 2016). SEDDS are defined as an isotropic mixture of water-soluble solvents or cosurfactants, solid or liquid surfactants, and natural or synthetic oils (Govindan *et al.*, 2025). According to the globule size SEDDS are classified into Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) and Self-Microemulsifying Drug Delivery Systems (SMEDDS), While SEDDS may have larger globule size than SMEDDS and SNEDDS. By promoting micellization in the gut, the smaller globule size may improve oral absorption (Wasan *et al.*, 2022). The tiny globules created during the self-emulsification process facilitate absorption and transportation via many routes, most ideally the lymphatic system (Pehlivanov, 2020). The efficacy



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of a dosage form may always be impacted by the many classes of formulation excipients found in SEDDS. In order to optimise drug delivery systems and produce stable formulations, experimental design methodologies like factorial design, Box-Behnken Design (BBD), central-composite design, D-optimal design, and mixture design are applied. The most popular method for methodically optimising SEDDS to produce reliable formulations is BBD. Because it is easier to execute and interpret the design, it is the most straightforward and economical method. Its simpler structure, the need for fewer experimental runs, and time economy are further benefits. Many researchers, including Rajput *et al.* (2011) for the formulation of isradipine SEDDS, Shaji and Lodha (2008) for the optimisation of celecoxib SMEDDS, and Nazzal and Khan (2002) for the optimisation of ubiquinone SEDDS, have applied BBD in the systematic optimisation of SEDDS formulations, according to the literature (Beg *et al.*, 2012). By rejecting hepatic first-pass consequences, preventing drug breakdown in the stomach's acidic environment, promoting drug absorption through lymphatic channels, SEDDS have been shown to be a very capable method to boost the oral bioavailability of weakly hydrophilic drugs (Beg *et al.*, 2012). One of the most popular method to improve the stability of APIs taken orally is the use of lipophilic drug delivery vehicles. The literature indicates that there is much disagreement on the nomenclature used for lipid-based methods. Micro and nano emulsions (SMEDDS and SNEDDS) are not primarily determined by the initial globule size. The SNEDDS word should be used if the emulsion's globule size is within the nanoscale range (Salawi, 2022). Additionally, surfactants use extracellular membrane signaling to suppress CYP3A4 biotransformation activities (Uttreja *et al.*, 2025). Amisulpride is used to treat schizophrenia. AMS has a low oral bioavailability of 48% because it is nearly insoluble in water, with a solubility of 0.8 mg/mL (Dubey *et al.*, 2019). Amisulpride is atypical antipsychotic medication that blocks dopamine (D2 and D3) receptors. Because of its less water solubility and first pass metabolism, amisulpride's oral bioavailability was less than 48%. (Ganta *et al.*, 2020). The primary factor influencing a drug's oral bioavailability is its solubility behaviour. Because of the uneven or insufficient absorption of the medication from gastrointestinal tract, bioavailability problems are common. Consequently, one of the most important problems in contemporary pharmaceuticals is accelerating the rate at which poorly soluble medications dissolve following oral intake (Dubey *et al.*, 2019). Particular consideration must be given to active pharmacological compounds with low water solubility when finding the best formulations to improve oral bioavailability. These techniques involve the application of SEDDS, as well as surfactants and cosurfactants (Mujtaba *et al.*, 2024). Due to its ease of preparation and activities that improve intestinal absorption, SEDDS have recently attracted a lot of interest as means of increasing the oral bioavailability of weakly water-soluble medicines (Ke *et al.*, 2016). Some Marketed

formulations of sedds are as ERIPRIDE-50, SULPITAC 400, Reride 300 etc.

SEDDS are relatively new lipid-based technical advancements with great potential to enhance pace and extent of absorption of weakly water-soluble medications. SEDDS are homogenous, anhydrous liquid mixtures made of lipids, surfactants, drugs, and/or cosurfactants that, when diluted in water and stirred, spontaneously create a transparent, stable emulsion. The drug is advantageously presented in a dissolved form by spontaneous production of emulsion, and the resulting tiny globule size offers a wide interfacial surface area for drug release (Agrawal *et al.*, 2015). Aim of research is to prepare and optimize SEDDS to improve oral bioavailability of BCS Class II drug and the objective is to select suitable drug and excipients of natural and synthetic origin for the development of formulation. Then performing pre-formulation studies of drug, excipients and formulation, optimization and characterizing developed formulation then performing *in vitro* studies.

MATERIALS AND METHODS

Materials

Amisulpride was procured from Dhamtec Pharma and Consultants. Tween 80, Polyethylene Glycol 400, Oleic acid, were procured from CDH Laboratories New Delhi, India. The remaining compounds utilized in investigation were belong to analytical rating.

Methods

Screening of excipients

Screening of excipients belong to their capability to dissolve a maximum quantity of drug. Various oils (Labrafac PG, Labrafac lipophilic WL 1349, Oleic acid, Coconut oil), surfactants (Labrasol ALF, Capryol PGMC, Tween 80, Tween 20) and co-surfactants (PEG 400, Span 20, Ethanol, Propylene glycol) were selected according to solubility. Excess of Amisulpride was added to 2 mL of each above mention excipients. The excipients were mixed with a vortex shaker and maintained at 37°C. High-speed centrifuge was then used to centrifuge each system for 10 min at 10,000 rpm. Each system's supernatant fraction was separated and diluted with methanol then at 279 nm the drug's concentration was measured by a UV-visible spectrophotometer (UV-1800, Shimadzu Corporation, Tokyo, Japan) against the blank (Methanol). Three repetitions of examination were performed, then the average results were noted (Yadav *et al.*, 2020).

Ethics statement

No human participants or animals were directly involved in this study.

Fourier Transform Infrared Spectroscopy

Using Perkin-Elmer Paragon 1000 spectrometer, FT-IR spectra of Amisulpride and excipients were acquired. Amisulpride and excipients were mixed with dry Potassium bromide in a ratio of 1:100 (sample: KBr). Then the blend was flattened into a thin and transparent pellet by applying hydraulic press under vacuum (at around 10 tons pressure for 2-3 min). and frequencies ranging from 4000 to 400 cm^{-1} were measured (Negi and Singh, 2013).

Differential Scanning Calorimetry

EXSTARTG/DTA6300 was used to perform DSC. 10 mg of amisulpride were precisely weighed, enclosed in aluminum pan with a nitrogen atmosphere (200 mL per minute), and equilibrated at 25°C before being heated from 25 to 350°C (Negi and Singh, 2013).

X-ray Diffraction

Using X-ray diffractometer (X'Powder PANalytical system, Netherlands) with Cu K radiation produced at 40 mA and 35 kV was used for XRD investigations. Amisulpride was scanned between 5° (2 θ) to 50° (2 θ) (Negi and Singh, 2013).

Construction of Pseudoternary phase diagram

CHEMIX School (Version12.5) was used to prepare Pseudoternary phase diagram for mixes without the addition of drug in order to find out the ideal concentration of lipid phase, surfactant, and co-surfactant for producing SEDDS as well as presence of a maximal self-emulsifying area. The process was described by Olariu *et al.* (2021). The PEG 400 was utilised as co-surfactant, oleic acid as oil and Tween 80 as surfactant. S_{mix} was made by blending Surfactant with co-surfactant in different ratios (1:1, 1:2, 2:1, and 3:2). Oil and precise concentration of S_{mix} was combined in 9 ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1; %w/w) to construct each phase diagram. In a glass beaker set at 37°C, 300 mL of distilled water and 0.3 mL of ternary mixture were slowly mixed using a mechanical stirrer.

The spread of emulsion globules and the tendency of the system to spontaneously emulsify were investigated. After the emulsions kept a side for 2 hr with water serving like blank, transmittance on 638.2 nm was assessed using double beam UV-vis spectrophotometer (UV-1800, Shimadzu Corporation, Tokyo, Japan) (Yadav *et al.*, 2020).

Box-Behnken design (BBD)

Three-factor, three-level BBD was prepared using experimental design software Design of Expert (version 13). One of the various response surface methodology approaches BBD is useful tool to Figure out how formulation variables and ingredients (independent factors) impact the response variables (dependent factors). Our study used statistical screening approach, to evaluate the direct and indirect impact of concentration of formulation

variables on measured responses of formulated SEDDS, the suitability of the desirability function to optimise the formulation. With three centre points, BBD requires 15 experimental runs to measure experimental error along with design precision. The equation provided by BBD is give below.

$$Y = \alpha + \alpha_1 A + \alpha_2 B + \alpha_3 C + \alpha_4 AB + \alpha_5 BC + \alpha_6 AC + \alpha_7 A^2 + \alpha_8 B^2 + \alpha_9 C^2 + \dots \dots \dots \text{(Eq. 1)}$$

Where A, B, and C are independent variables, used in the research and were listed in Table 2. Response of the dependent variables is represented by Y, the intercept is represented by α_0 , and the regression coefficients are represented by α_1 - α_9 for each factor-level combination.

The amount of oil, surfactant, and co-surfactant in every formulation were stated in Table 1.

Preparation of Amisulpride-loaded SEDDS

To prepare the drug-loaded formulations, the concentrations of oil (10-40%), co-surfactant (20-30%), and surfactant (40-60%) were selected after studying pseudoternary phase diagram. Fifteen formulations were formulated using Amisulpride with the amount of 100 mg/g and capsule size 0 was selected for incorporation of preconcentrate. After dissolving the drug in co-surfactant, the desired concentration of surfactant was added. Oil was mixed with homogenised mixture after all the ingredients had been properly mixed with a vortex mixer at 40°C until the clear preconcentrate was achieved and stored for future research (Yadav *et al.*, 2020). Preparation of SEDDS is as per Table 1.

Evaluation of Prepared Formulation

Globule size and zeta potential

Globule size, zeta potential and Polydispersity Index (PDI) of formulations as mentioned in Table 3. (F1-F15) were measured using Malvern Panalytical-MAL1278078 (Software Version: 3.3.1.5). Before the test, to guarantee that the formulation was properly dispersed in aqueous media, a sample by every preparation was diluted with water in a 1:100 ratio, then shaken. For every measurement, three measurements were made (Shah *et al.*, 2013).

Percentage transmittance (% T)

Double beam UV-vis spectrophotometer was applied to evaluate transmittance of the Amisulpride-loaded SEDDS at 638.2 nm after 0.1 mL of formulation was taken and diluted upto 100 mL by using water and continuously stirred. Three replicates of the study were carried out (Yadav *et al.*, 2020).

Self emulsification time

Self-emulsification time of each formulation is time needed for the SEDDS to create uniform dispersion following addition of aqueous phase was measured visually. In summary, 1 mL of every

formulation applied drop by drop to a conventional USP type II dissolution apparatus that included phosphate buffer (250 mL, pH 6.8). To produce mild agitation, paddle speed maintained at 50 rpm and temperature maintained at $37 \pm 0.5^\circ\text{C}$. Developed emulsion of resultant system was clearly visible (Yadav *et al.*, 2020).

Dissolution study

Using the ELECTROLAB DISSOLUTION TESTER (USP) TDT-06L and phosphate buffer (pH 6.8, 900 mL), the dissolution investigation of SEDDS (15 formulations) was conducted at $37 \pm 0.5^\circ\text{C}$. 50 rpm was set for the basket. Hard gelatin capsules of size "0" was taken and 100mg of Amisulpride loaded SEDDS was added. Double beam UV-vis spectrophotometer was used to quantify sample's amisulpride level at 279 nm after an aliquot (3 mL) was obtained at predetermined intervals, filtered, and analyzed. To maintain the sink condition, equivalent amount (3 mL) of dissolution medium was then provided right away. Drug release profile of Amisulpride SEDDS was performed. The dissolution investigations were done three times (Yadav *et al.*, 2020).

Optimization using desirability function

All four responses (Globule size, Percentage transmittance, Self emulsification time, Percentage drug release) were simultaneously optimised in the study using the numerical optimisation technique known as desirability function developed by Derringer and Suich. With this technique, every response had a definite goal (Table 2). Response has a value in the range of 0 and 1, while an undesirable or unsatisfactory response has a value of 0. Each individual response is related with a partial desirability function. The value between 0 and 1 indicates how close the reaction is to its intended value, or the range from the least to the most desirable. The desirability function is used to identify the best and most suitable point in design space, which meets predefined goals for dependent variables (Derringer and Suich, 1980).

After giving the respondents desired goals, we used Design Expert 13 to get the highest desirability value in our study.

Evaluation of optimized formulation

Impact of optimized formulation composition on response variables

Optimised formulation (F1) was chosen and formed based on the desire function. Following the aforementioned process, the created optimised formulation assessed for response variables.

Table 1: Box-Behnken design batch arrangement for prepared SEDDS.

Experimental run	Coded factor level		
	A	B	C
F1	-1	0	1
F2	-1	-1	0
F3	1	0	-1
F4	0	-1	1
F5	1	1	0
F6	0	1	-1
F7	1	-1	0
F8	0	0	0
F9	-1	1	0
F10	1	0	1
F11	-1	0	-1
F12	0	-1	-1
F13	0	1	1
F14	0	0	0
F15	0	0	0
Translation of coded levels in actual units			
Coded levels	Low (-1)	Middle (0)	High (1)
Factor (A) Amount of Oil (%W/W)	10	25	40
Factor (B) Amount of Surfactant (%W/W)	40	50	60
Factor (C) Amount of Cosurfactant (%W/W)	20	25	30

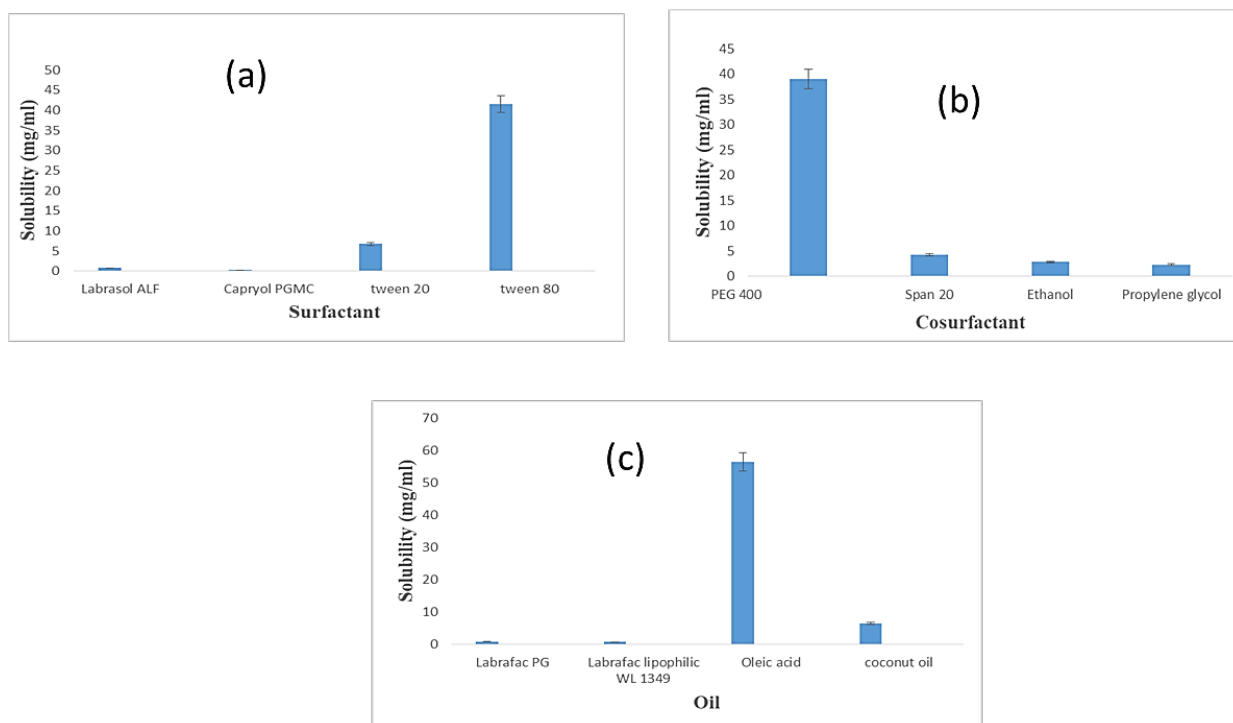


Figure 1: Solubility study of Amisulpride in (a) Various surfactants: Labrasol ALF, Capryol PGMC, Tween 20, Tween 80. (b) Various cosurfactants: PEG 400, Span 20, Ethanol, Propylene glycol. (c) Various oils: Labrafac PG, Labrafac lipophilic WL 1349, Oleic acid, Coconut oil.

For F1, research was carried out on factors such as stability, cloud point measurement, and resilience to dilution.

Robustness to dilution

By diluting SEDDS 50, 100, and 1000 times by using different dissolution medium, such as water, buffer pH 1.2, buffer pH 3.0, and buffer pH 6.8, robustness of SEDDS on dilution was investigated. After 12 hr of storage, samples were examined to check the indications of precipitation. or phase separation (Balakumar, Raghavan, *et al.*, 2013).

Cloud point measurement

It is the key feature of SEDDS made of non-ionic surfactants, cloud point is what allows a stable microemulsion to form successfully. Cloud point value was used to compare the SEDDS. Each formulation was put in water bath with steady temperature growth after being diluted using water at a ratio of 1:250. Cloud point refers to the location where cloudiness occurs (Vilas *et al.*, 2014).

Stability study of optimized SNEDDS

Thermodynamic reliability and the phase integrity of preparation were evaluated under different temperature and centrifugal force conditions. Following test was conducted on optimized formulation to investigate effects of centrifugal force and temperature (Yadav *et al.*, 2020).

Centrifugal test

After dilution of sample 100 times by water and centrifuging for 30 min at rpm of 4000 by using Remi centrifuge (Remi Equipments, Mumbai, India), phase separation was inspected visually (Patel *et al.*, 2016).

Heating-cooling cycles

There are six cycles of chilling and warming between lower temperatures (4°C) and higher temperatures (45°C), with introduction at every temperature for a minimum of 48 hr were conveyed (Tanuj and Nikunj, 2020).

Freeze-thaw cycle

At each of the three freeze thaw cycles, which varied from -20°C to +25°C, the formulation was maintained for at least 48 hr. The formulation was examined to check phase separation and precipitation after 5 min of centrifugation at 3000 rpm. As previously stated, the formulation was diluted by using water and inspected to check instability (Yadav *et al.*, 2020).

Transmission Electron Microscopy (TEM)

Using TEM (Hitachi H-7500), morphological properties of optimized Formulation (F1) of amisulpride were assessed. To ensure adequate dispersion of formulation, finalized formulation sample was then diluted by water (1:100) and then shaken before the measurement. After the formulation was reconstituted, a phosphotungstic acid solution was applied for negative staining (Yadav *et al.*, 2020).

RESULTS

Screening of excipients

Excipients used to formulate SEDDS should have a greater self-emulsification zone presented by pseudoternary phase diagram and should solubilise maximum amount of medicine. Excipients were selected according to their safety, compatibility with the integrated medication, and solubilising potential. Figure 1 shows the equilibrium solubility of Amisulpride in various excipients. Oils were examined in the study to check potential usage as lipid phase in SEDDS manufacturing process. Study clearly demonstrated that Amisulpride was most soluble in oleic acid (56.53 ± 1.56 mg/mL), the surfactant (Tween 80) (41.489 ± 2.51 mg/mL), and the cosurfactant (PEG 400) (39.054 ± 1.57 mg/mL). As a result, every element was chosen to define a stable nanoemulsion area. Solubility results obtained are shown in Figure 1.

FTIR Spectroscopy

FTIR spectra of pure drug and excipients and their physical mixture/formulation were noticed in range of $4000-400$ cm^{-1} to evaluate possible interactions and assure compatibility. FTIR spectrum is shown in Figure 2.

The spectrum of Amisulpride showed characteristic peaks around $3400-3300$ cm^{-1} corresponding to N-H stretching, 1648.43 cm^{-1} due to amide C=O stretching, and 2797.57 cm^{-1} due to C-H group, 1125.39 cm^{-1} due to S=O stretching (Negi and Singh, 2013).

Tween 80 exhibited O-H stretching at 3454 cm^{-1} . and C-H Stretching was observed at 2921.29 and 2857.01 a carbonyl group (C=O) was noticed at 1734.87 cm^{-1} . Methylene group (C-H) was observed at 1456.68 . and C-O-C stretching was observed at 1095.98 cm^{-1} (Andrew *et al.*, 2024; Kura *et al.*, 2014).

PEG 400 showed O-H stretching band at 3450.29 cm^{-1} and C-H bending was present at 1349.06 and 1454.63 cm^{-1} and C-O stretching peak is present at 1095 (Rozenberg *et al.*, 1998).

Oleic acid showed a C-H stretching at 2853.28 and 2922.27 cm^{-1} , a strong C=O stretching peak at around 1708.18 cm^{-1} and a C-O stretching was observed at 1283.7 cm^{-1} (Niu *et al.*, 2017; Rozenberg *et al.*, 1998). In the FTIR spectrum of formulation, all characteristic peaks of drug and excipients were retained with no significant shift. These results indicate the absence of any significant chemical interaction between drug and excipients, confirming the compatibility of Amisulpride with Tween 80, PEG 400, and oleic acid in the formulation.

X-ray Diffraction (XRD)

XRD analysis of Amisulpride was carried out to check whether drug is crystalline in nature or not and purity of drug. In Figure 3 diffractions patterns of AMI were characterized by sharp peaks at 12.13 , 15.85 , 17.61 , 18.77 , 20.27 , 26.07 , 26.83 and 28.97 2θ . This pattern indicates that Amisulpride is crystalline in nature (Negi and Singh, 2013).

Differential Scanning Calorimetry (DSC)

In Figure 4 the characteristic melting point of Amisulpride presented sharp endothermic peak at 129.115°C . It shows that drug is present in pure form as mentioned in given reference (Negi and Singh, 2013).

Pseudoternary phase diagram

Based on preliminary tests on the drug's solubility in various vehicles, oleic acid, Tween 80, and PEG 400 were finalized to create pseudoternary phase diagrams of all systems (having varied ratios of surfactant and cosurfactant). The relation between the components' concentration with phase behaviour during emulsion formation is depicted in the phase diagram. Figure 5 displayed the pseudoternary phase diagrams with oleic acid, Tween 80, and PEG 400. Four systems (A, B, C, D) with various S_{mix} ratios are depicted in Figure 5.

The emulsifying zones are shown in Figure 5 as the darkened area. From the Figure 5 it was observed that in comparison to other systems, Figure 5C showing a large emulsification zone

Table 2: Role of variables in Box-Behnken design.

Sl. No.	Independent variables	Units	Goal for Independent variables
1.	Amount of oil added (A)	mg	Minimize
2.	Amount of surfactant added (B)	Mg	Maximize
3.	Amount of co-surfactant added (C)	Mg	Minimize
Sl. No.	Dependent variables		Goal for dependent variables
1.	Globule size (Y1)	nm	20-200 (nm) (Balakumar, Vijaya Raghavan, <i>et al.</i> , 2013; Beg <i>et al.</i> , 2012)
2.	Percentage transmittance (Y2)	%	80.4-102.8 (%) (Yadav <i>et al.</i> , 2020)
3.	Self-emulsification time (Y3)	Seconds	< 60 (sec) (Balakumar, Vijaya Raghavan, <i>et al.</i> , 2013)
4.	Percentage drug release (Y4)	%	58.21-95.27 (%) (Yadav <i>et al.</i> , 2020)

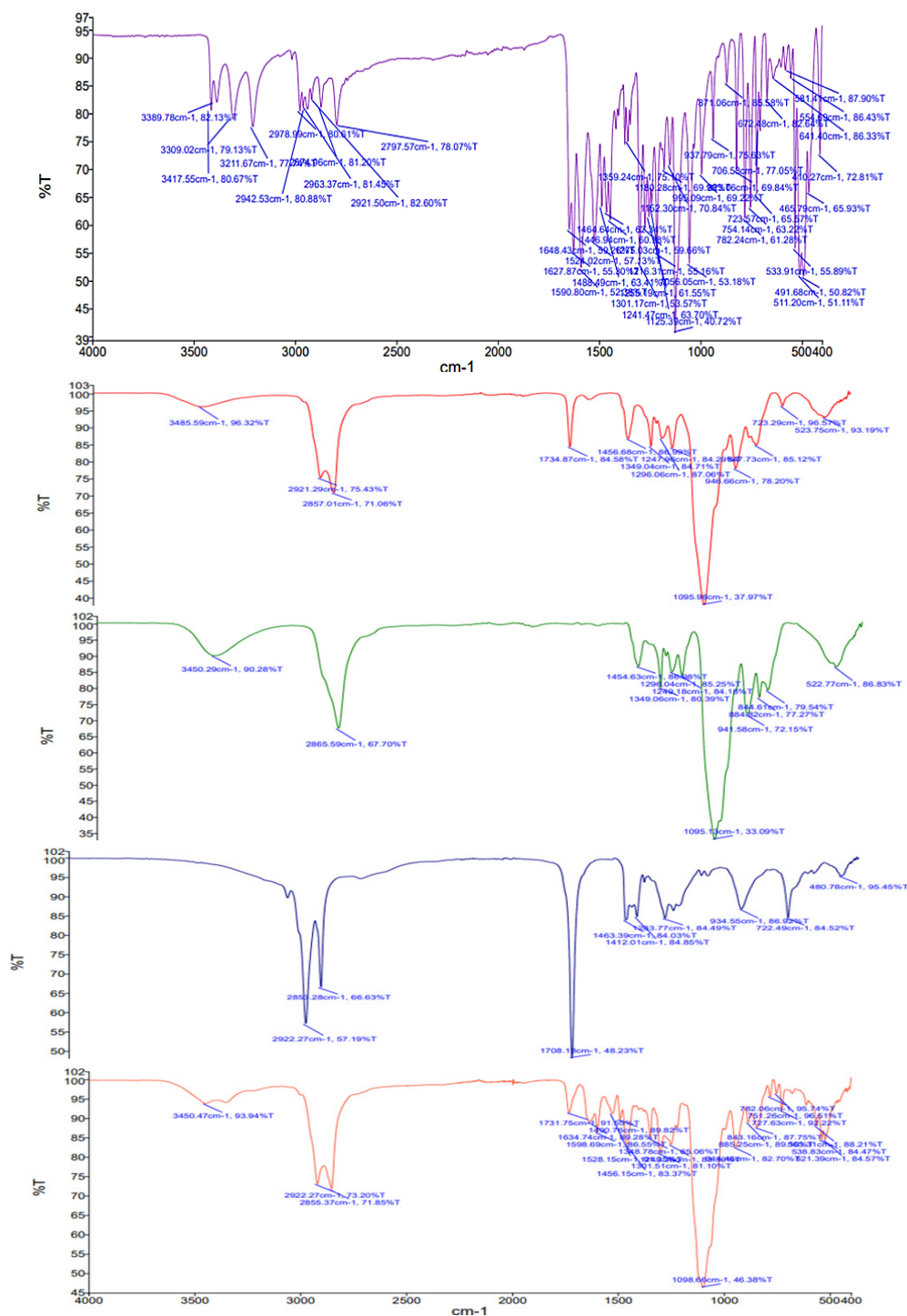


Figure 2: FTIR Spectra (a)-Amisulpride, (b)-Tween 80, (c)-PEG 400, (d)-Oleic acid, (e)-Prepared formulation.

and 2:1 w/w S_{mix} concentration resulted in a emulsion that could emulsify up to 40% w/w of oil phase. Only 30% of the oily phase was emulsified by systems A, B, and D. It was noticed that turbid emulsion for systems A, B, and D was produced by surfactant concentrations below 35%, 23%, and 42% w/w and concentration of the co surfactants below 35%, 46% and 28% respectively. For Figure 5C the constraints of independent variables ($10\% \leq \text{Oil} \leq$

40%, $40\% \leq \text{Surfactant} \leq 60\%$, and $20\% \leq \text{Co-surfactant} \leq 30\%$) were finalised for optimization (Cho *et al.*, 2013).

Experimental design

To find out the influence of independent factors (SEDDS components) on dependent factors, Box Behnken Design selected. Constrictions of independent along with dependent

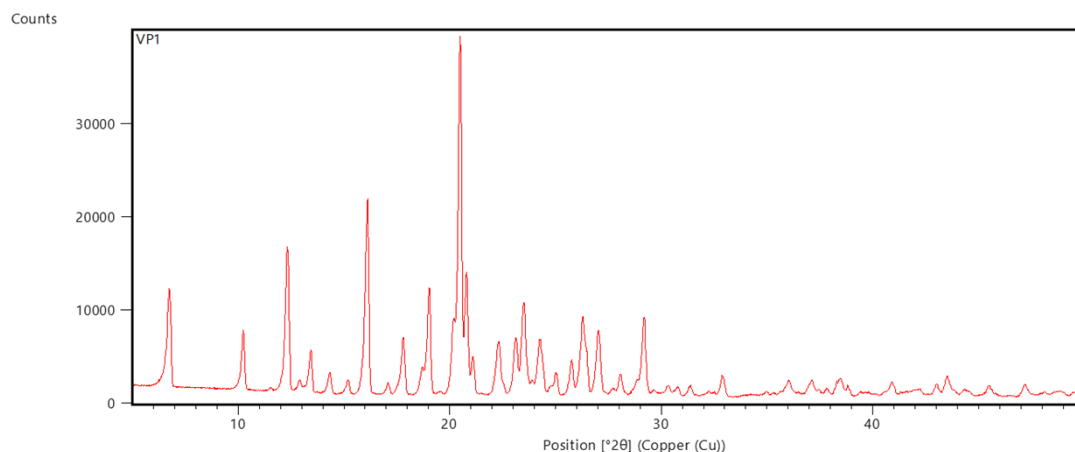


Figure 3: XRD Pattern of Amisulpride.

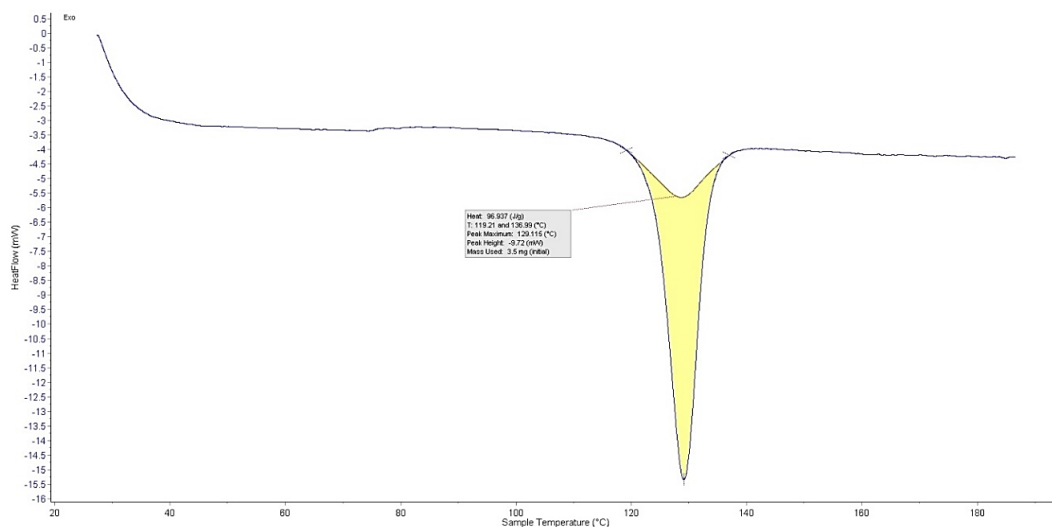


Figure 4: DSC Pattern of Amisulpride.

components are displayed in Table 2. BBD used to develop fifteen preparations, and the response variables were assessed. All of the data was gathered by applying Design Expert 13. Every response fitted separately to quadratic equation, and model's significance evaluated by applying multiple correlation coefficient (R^2) test. To correctly fit quadratic equation, model's p value needs to be fewer in comparison to 0.05 (significant). Data fluctuation near to fitted value is evaluated using lack of fit test, which must be nonsignificant (p value > 0.05) when compared to pure error. Total variance surrounding the mean indicated via R^2 (multiple correlation coefficient test). R^2 range must be nearly 1.

Evaluation of SEDDS

Globule size, zeta potential and the impact of formulation composition on globule size

Emulsion globule size is thought to be a major reason since it regulates rate and degree of release of drug as well as absorption.

Globule size, PDI, and zeta potential of preparations evaluated by Malvern Zeta sizer. Outcomes are mentioned in Table 3.

Globule size of AMS-SEDDS was in range from 157.1 and 1568 nm as provided in Table 3. Quadratic polynomial equation belonging to measured response Y1, is given below (Eq. 2):

Y1 (Globule size)

$$Y1 = 178.13 - 439.55A + 78.82B - 13.27C - 221.58AB + 19.77BC - 5.38AC + 509.05A^2 + 36.20B^2 - 29.80C^2 \dots \text{eq.2}$$

The aforementioned equation demonstrates that the globule size greatly reduces as the quantity of A decreases, reduces as the amount of B increases, and marginally increases as the amount of C decreases. Globule size decreases when A and B decrease together, globule size marginally decreases when B and C increase together, and globule size decreases when A and C decrease together.

The quantitative impact of independent variables (A-C) and their combined effect on response Y1 is represented in the equation above. When the coefficient is positive, it indicates a collaborative effect; when it is negative, it indicates an opposite result of independent factors on response. It was observed that R^2 found to be 0.9792, p value was fewer than 0.05. Independent variables had an important impact on predicting response (Y1), as indicated by result of p value (<0.05), R^2 value (around 1). The globule size is shown in Figure 6 (Yadav *et al.*, 2020).

The contour plots represent the impact of formulation ingredients Oleic Acid, Tween 80 and PEG 400 on globule size within SEDDS. Globule size is a critical parameter for determining the bioavailability, stability, and absorption efficiency of formulation. Smaller globule sizes enable faster emulsification, larger surface area for absorption, and improved lymphatic uptake, these are vital for enhancing oral delivery of weakly soluble drugs (Figures 7a-7c).

In the first plot (oil vs. surfactant), increasing the concentration of Oleic Acid results in a notable increase in globule size, whereas Tween 80 helps to reduce it. This is explained by the amphiphilic nature of Tween 80, which stabilizes oil water interface by forming a surfactant film that decreases interfacial tension and start the breakup of oil into finer droplets. Oleic Acid, being a long-chain fatty acid, contributes to droplet coalescence and increased viscosity if used in excess, leading to larger globules.

In the second plot (surfactant vs. cosurfactant) both surfactant and co-surfactant have a synergistic effect in maintaining a smaller

globule size. PEG 400, hydrophilic co-surfactant, integrates into surfactant film and increases its flexibility and fluidity, which helps in the formation of stable nanosized droplets. PEG 400 disrupts tight packing of surfactant molecules, preventing rigid structures and allowing spontaneous emulsification into smaller globules.

In the third plot (oil vs. cosurfactant) it reveals that an increase in Oleic Acid alone tends to increase globule size, but higher PEG 400 concentrations can counterbalance this effect. PEG 400 assists in decreasing the viscosity of the oil phase and promotes rapid dispersion by enhancing interfacial curvature. This leads to the formation of smaller, more uniform droplets, which are essential for consistent drug release and absorption.

These contour plots emphasize that minimizing globule size in SEDDS is achieved by optimizing the Tween 80 and PEG 400 levels while carefully regulating the oil phase (Oleic Acid). Smaller globules form when interfacial tension is low, surfactant/co-surfactant layers are flexible, and the system favors spontaneous dispersion, leading to enhanced solubilization and bioavailability of lipophilic drugs.

Percentage transmittance and the impact of formulation composition on % transmittance

The % transmittance measured for the confirmation of final emulsion was clear and transparent. The turbid solutions and dispersions provide poorer transmittance as they scatter more radiation, whereas clear solutions and dispersions produce better

Table 3: Observed responses from randomized runs in the Box-Behnken design.

Formulation code	A:Oleic Acid	B:Tween 80	C:PEG 400	Globule size	Zeta potential	Polydispersity index	Percentage transmittance	Self-emulsification time	Percentage drug release after 5 min	Percentage drug release after 55 min
	mg	mg	mg	nm	(mV)		%	Seconds	%	%
F1	111.11	555.55	333.33	157.1±0.32	-42.11± 5.64	0.2724±0.0122	100.1±57.25	36±1.06	13.33±2.01	98.18±2.06
F2	133.33	533.33	333.33	186.1±0.24	-52.66± 2.34	0.288±0.0341	99.3±0.153	45±2.56	15.91±4.87	97.7±3.08
F3	363.63	454.54	181.81	1041.0±0.51	-34.82± 4.12	0.3305±0.0453	97.03±0.77	90±2.57	17.58±4.56	97.25±3.04
F4	263.15	421.05	315.78	1568.0±0.57	-39.04± 3.42	1.0±0.0354	97.5±0.65	98±3.27	17.97±2.06	97.25±4.56
F5	320	480	200	162.9±0.33	-41.26± 5.32	0.2716±0.0453	98.2±1.11	39±3.12	13.46±3.12	97.25±3.57
F6	238.09	571.42	190.47	180.5±0.32	-42.81± 6.12	0.2739±0.0716	95.2±0.71	43±1.56	13.33±3.68	97.25±2.48
F7	380.95	380.95	238.09	321.9±0.34	-46.16± 4.34	0.463±0.04935	97.7±1.32	75±2.51	13.33±2.65	96.79±2.67
F8	250	500	250	200.9±0.32	-43.99± 5.78	0.4062±0.0124	94.3±2.88	59±1.04	13.46±4.01	95.87±2.38
F9	105.26	631.57	263.15	802.7±0.37	-34.97± 4.67	0.6749±0.0365	93.8±2.60	83±3.17	17.97±4.71	96.79±3.78
F10	333.33	416.66	250	191.2±0.16	-42.25± 4.58	0.302±0.0245	95.2±2.56	54±3.07	17.97±2.78	96.33±3.06
F11	125	625	250	1108±2.00	-37.99± 2.47	0.9631±0.0356	93.4±2.15	94±3.18	12.04±4.86	96.79±4.03
F12	294.11	470.58	235.29	246.3±0.10	-45.19± 3.89	0.514±0.0147	94.6±3.02	70±2.87	13.33±3.67	96.33±2.05
F13	217.39	521.73	260.86	234.2±0.50	-42.84± 4.12	0.46±0.0189	92.5±4.06	67±2.05	5.59±2.05	96.79±2.45
F14	250	500	250	199.3±0.20	-42.13±3.56	0.4099±0.0712	91.7±5.12	58±2.06	12.94±3.67	96.37±3.66
F15	250	500	250	195.4±0.10	-43.34± 5.24	0.2987±0.0582	97.4±3.26	59±1.98	13.33±4.23	98.33±4.78

Note: Mean±SD, $n=3$.

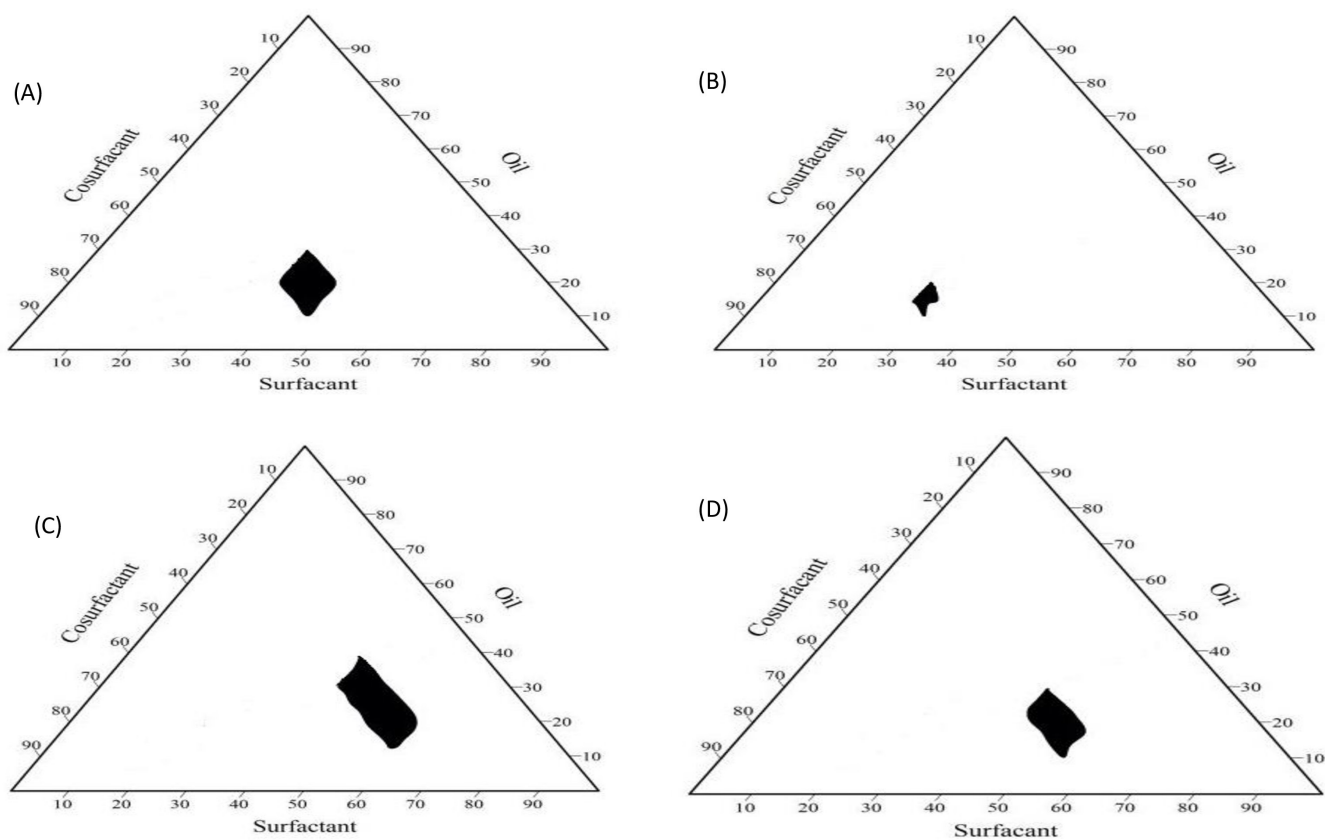


Figure 5: The self-emulsion region is indicated by the darkened area. (a) (1:1) S_{mix} in System A. (b) (1:2) S_{mix} in System B. (c) (2:1) S_{mix} in System C. (d) (3:2) S_{mix} in System D.

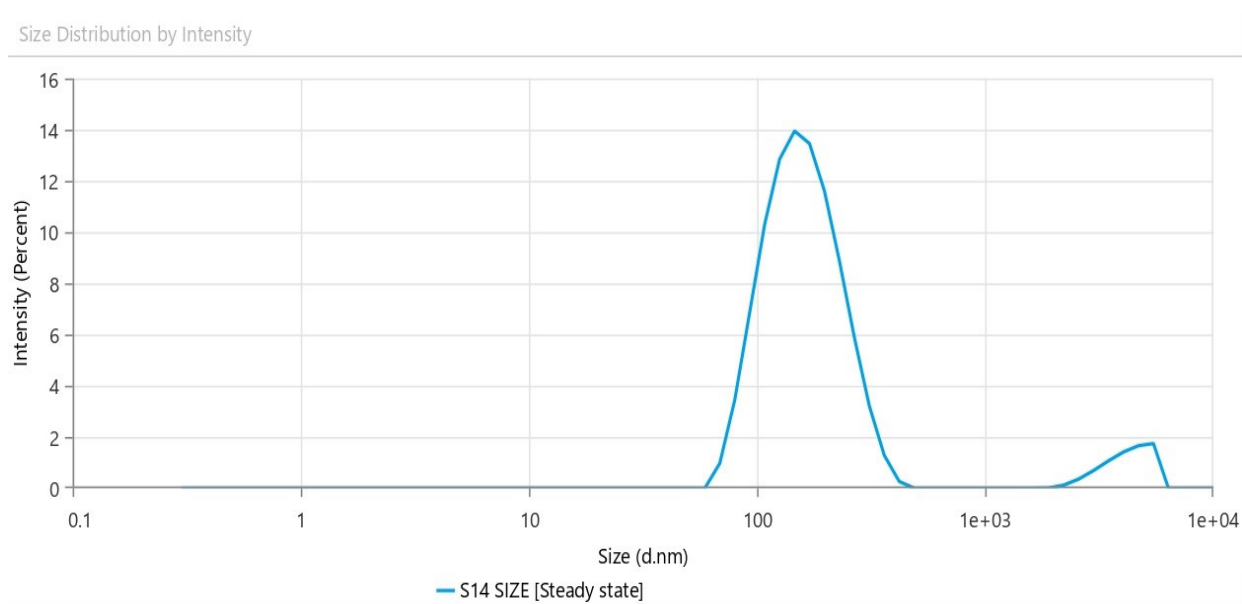


Figure 6: Globule size F1 formulation.

Table 4: Drug release Kinetics.

Formulation code	Zero-order model (R ²)	First-order model (R ²)	Higuchi model (R ²)	Korsmeyer-Peppas model (n)
F1	0.8605	0.9813	0.9432	0.6608
F2	0.8351	0.9626	0.9536	0.65
F3	0.9687	0.9873	0.944	0.6377
F4	0.8336	0.9698	0.9423	0.6443
F5	0.8504	0.9639	0.9435	0.6561
F6	0.8825	0.9623	0.9556	0.6407
F7	0.8723	0.9741	0.9541	0.6405
F8	0.8672	0.9651	0.9553	0.6311
F9	0.8324	0.9785	0.7956	0.6397
F10	0.8335	0.9773	0.9427	0.6361
F11	0.8181	0.9558	0.912	0.6639
F12	0.8419	0.9785	0.9408	0.6449
F13	0.9544	0.9287	0.928	0.6471
F14	0.8725	0.9826	0.9522	0.6432
F15	0.8695	0.9783	0.9358	0.6567

Footnote: Data represent the coefficient of determination (R²) obtained from linear regression analysis of the respective drug release kinetic models.

transmittance. The range of the transmittance percentage is 91.7 to 100.1% in Table 3. It was observed that the % transmittance increased as the quantity of oil in the combination reduced and the quantity of Surfactant or cosurfactant increased. Quadratic polynomial equation for the measured response Y2(% transmittance), is shown below (Eq. 3):

$$Y2=98.93-0.3288A-0.0250B+1.53C-1.77AB-0.3825BC+1.63AC-1.90A^2-1.21B^2-2.65C^2\ldots \text{eq.3}$$

The above equation shows that as the amount of A decreases the Percentage transmittance increases and as the concentration of B decreases a very slight decrease is observed, as concentration of C increases the Percentage transmittance also increases and combined decrease in AB shows slight increase the percentage transmittance, combined decreases in BC decreases the percentage transmittance and combined increase in AC increases the Percentage transmittance.

Regression study of Y2 presented a positive sign for C (cosurfactant) and showed negative indication for A (oil). This implied that percentage transmittance rises as the amount of co-surfactant increases while the amount of oil decreases (Yadav *et al.*, 2020).

The 3D surface plots depict the influence of formulation components (A), (B), and (C), on percentage transmittance of SEDDS, which serves as a surrogate measure of emulsion clarity and stability. High transmittance values, observed in the orange-red regions, indicate the formation of transparent nanoemulsions with smaller globule sizes, crucial for enhancing drug solubilization and absorption (Figures 8a-8c).

In the first plot (oil vs. surfactant), transmittance increases with increasing Tween 80 and decreasing Oleic Acid, suggesting improved emulsification because to the surfactant's efficacy to minimize interfacial tension and stabilize the globules. Tween 80, a non-ionic surfactant, embeds its hydrophobic tail into the oil phase while its hydrophilic head aligns with the aqueous phase, forming a stable interfacial film. Conversely, higher Oleic Acid concentrations may lead to phase separation or larger droplet formation due to its lipophilic character and viscosity.

In the second plot (surfactant vs. cosurfactant) it demonstrates a synergistic enhancement in transmittance as both components increase. PEG 400, a hydrophilic co-surfactant, disrupts interfacial rigidity, allowing Tween 80 molecules to pack more efficiently at the oil-water interface, thus facilitating spontaneous nanoemulsion formation.

In the third plot (oil vs. cosurfactant) it also reveals increased transmittance with rising PEG 400 levels and decreasing Oleic Acid, highlighting the co-surfactant's role in promoting water uptake and minimizing droplet coalescence.

These interactions reflect the molecular orchestration required for forming optically clear and thermodynamically stable SEDDS. By optimizing surfactant-to-oil ratio and leveraging synergistic behavior of PEG 400 and Tween 80, formulators can achieve superior emulsification performance, crucial to enhance the oral bioavailability of oil soluble drugs.

Self-emulsification duration and the impact of formulation composition on this duration (Y3) Table 3 displays the findings of the self-emulsification investigation. Emulsification time was

found to range between 36 to 98 sec. The quadratic equation of measured response Y3(self-emulsification) is provided beneath in (Eq. 4):

$$Y_3 = 43.33 - 11.12A + 0.5000B - 3.88C - 6.50AB + 1.75BC - 2.00AC + 34.21A^2 + 2.46B^2 + 2.71C^2 \dots \text{eq.4}$$

The aforementioned equation demonstrates that self-emulsification time decreases with decreasing concentration of A, decreases with increasing B concentration, decreases with decreasing concentration of C, decreases with combined decrease in AB, decreases with combined increases in BC, and decreases with combined decrease in AC.

Quantitative impact of independent variables on measured result (Y3) is represented by polynomial equation above. The aforementioned equation presented a strong fit for response variable (Y3) because R^2 value of 0.9659 is near to the corrected R^2 of 0.9045 (Yadav *et al.*, 2020).

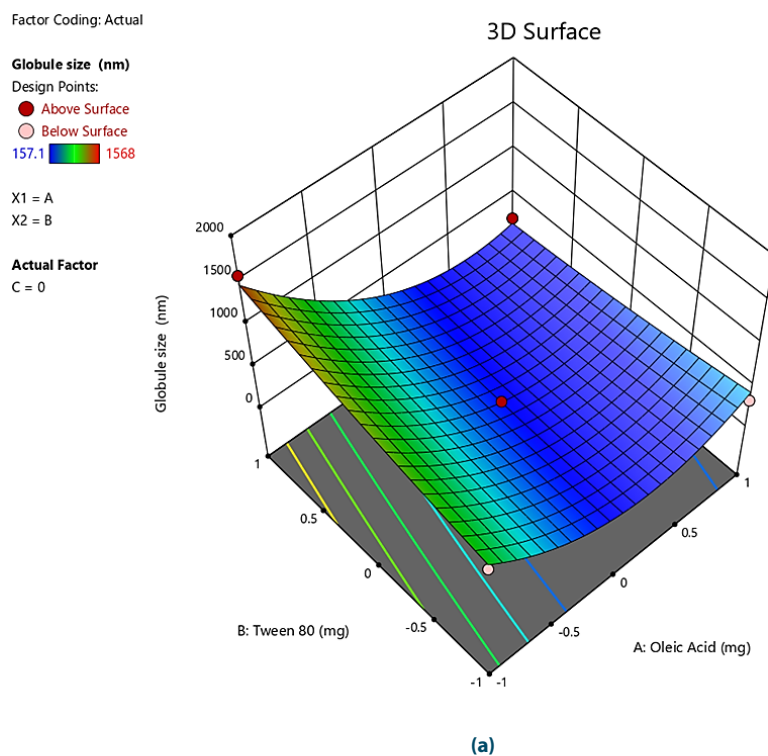
The contour plots illustrate the impact of formulation components-Oleic Acid (A), Tween 80 (B), and PEG 400 (C)-on self-emulsification time of SEDDS, which is a critical performance metric reflecting the spontaneity and efficiency of emulsion preparation upon dilution. The goal in SEDDS is to minimize self-emulsification time, enabling rapid dispersion and formation of fine droplets in gastrointestinal tract, thereby enhancing drug solubilization and absorption (Figures 9a-9c).

In the first plot (oil vs. surfactant), the shortest emulsification times are observed with decreased levels of Oleic Acid and higher levels of Tween 80. This trend suggests that an increased

concentration of Tween 80, a non-ionic surfactant, enhances the emulsification efficiency by effectively reducing the interfacial tension and facilitating the immediate formation of nano-sized globules. Tween 80 stabilizes the oil droplets by orienting its hydrophilic polyoxyethylene groups toward the hydrophilic phase and its lipophilic tail within the lipid phase, reducing the energy barrier for emulsification.

In the second plot (surfactant vs co-surfactant) it shows that increasing both Tween 80 and PEG 400 concentrations reduces emulsification time. PEG 400 acts as a co-surfactant that disrupts interfacial rigidity, increases the fluidity of the interfacial film, and synergistically interacts with Tween 80 molecules. To enhance the mobility of surfactants at the interface, promoting faster and more efficient droplet formation.

In the third plot (oil vs. co-surfactant) it reveals that higher concentrations of Oleic Acid are associated with longer emulsification times, while increased PEG 400 reduces it. Oleic Acid, being a viscous and hydrophobic oil phase, can hinder spontaneous emulsification if present in excess. Excessive oil content demands greater surfactant coverage to stabilize the interface, slowing the emulsification process. In contrast, PEG 400 helps to increase water affinity and reduce oil viscosity, thereby assisting in faster emulsification. These observations highlight the importance of optimizing surfactant and co-surfactant concentrations while minimizing oil content to ensure rapid, efficient self-emulsification-a hallmark feature of well-designed SEDDS. These molecular-level interactions directly contribute to improved oral bioavailability by promoting swift dispersion and droplet formation in the GI tract.



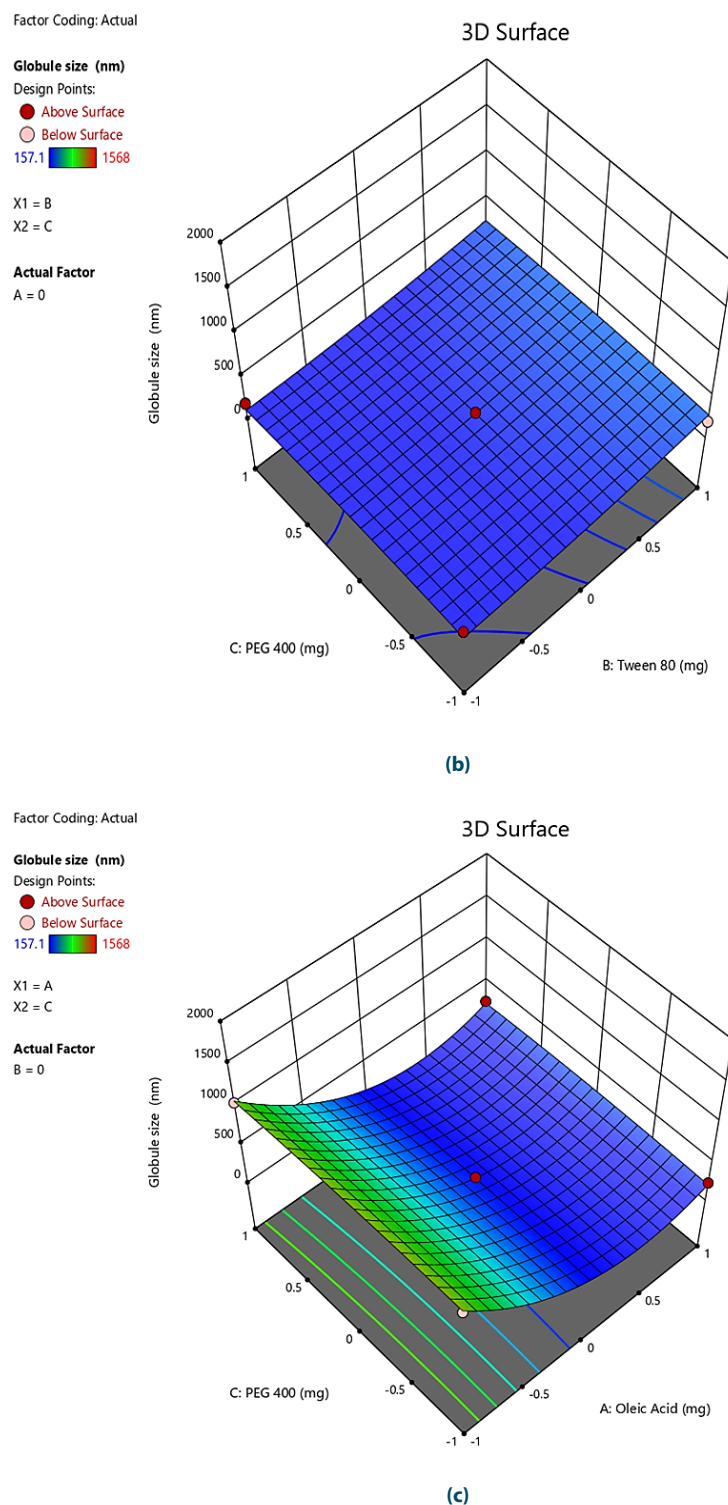


Figure 7: Globule size: (a) effect of oil (oleic acid) and surfactant (tween 80), (b) effect of surfactant (tween 80) and cosurfactant (PEG 400), (c) effect of cosurfactant (PEG 400) and oil (oleic acid).

%Drug release after 55 min

The USP type II dissolution equipment was used in the current study to conduct an *in vitro* drug release evaluation. Hard gelatin capsule was filled with each composition, which contained 100 mg of drug. At various times, % of drug release in phosphate buffer (pH 6.8) was recorded. Figure 10 depicted the study's outcome. In

Table 3, the minimum and maximum drug release is presented as drug release after 5 min and drug release after 55 min.

The quadratic polynomial equation for measured response (% Drug release), Y4, is provided beneath as (Eq. 5):

$$Y4 = 98.07 - 0.2875A - 0.0525B + 0.2250C - 0.3450AB - 0.2300BC - 0.0100AC - 0.7025A^2 - 0.6925B^2 - 0.5775C^2 \dots \text{eq.5}$$

The aforementioned equation demonstrates that percentage of drug release decreases as concentration of A decreases, a very slight decrease is observed as the amount of B decreases, percentage of drug release decreases as concentration of C increases, and the % of drug release decreases when the concentration of AB decreases, the % of drug release drops when the amount of BC decreases, and % of drug release decreases when concentration of AC decreases.

The impact of factors on response Y4 is shown in equation above. R^2 of 0.8978 was in desirable range with the corrected R^2 of 0.7137 (deviation is less than 0.2), indicating goodness of fit to response variable. Model's usefulness in navigating the design space is confirmed by the sufficient precision ratio of 6.9114, which shows an adequate signal. The regression study for Y4 exposed a positive sign for co-surfactant and opposite indication for oil. This indicated that whereas co-surfactant had a synergistic effect on response, oil concentration had an opposite effect (Yadav *et al.*, 2020).

The 3D surface plots in the uploaded image demonstrate the impact of formulation variables Oleic Acid (A), Tween 80 (B), and PEG 400 (C)-on the Percentage drug release from SEDDS, an essential parameter determining the system's efficiency in solubilizing and releasing the drug for absorption. The percentage drug release reflects the combined impact of emulsification behavior, droplet size, and drug solubilization capacity (Figures 11a-11c).

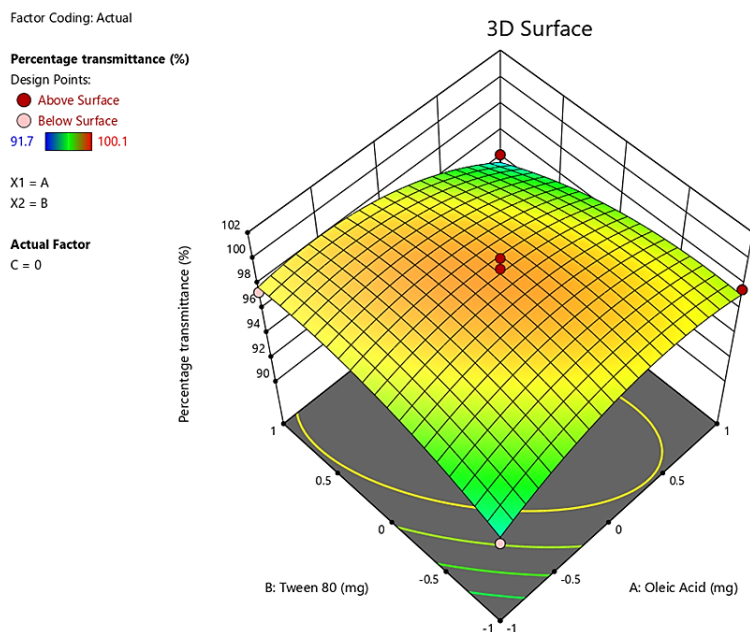
In the first plot (oil vs. surfactant), it is observed that increasing Tween 80 enhances drug release, while high concentrations of Oleic Acid slightly reduce it. Tween 80, a hydrophilic non-ionic surfactant, decreases interfacial tension and increases surface

area present for drug diffusion by initiating the preparation of smaller and more constant droplets. In contrast, Oleic Acid, being lipophilic and viscous, can hinder droplet breakdown and reduce the release rate if not sufficiently counterbalanced by surfactant. Excess oil can also trap the drug within the lipid core, delaying diffusion.

In the second plot (surfactant vs co-surfactant), it shows a synergistic effect, where increasing both components maximizes drug release. PEG 400, acting like co-surfactant, intercalates between Tween 80 molecules at the interface, increasing the fluidity and permeability of the interfacial film. This facilitates faster and more uniform dispersion of oil droplets and enhances the diffusion of drug from the lipid phase into the surrounding hydrophilic environment. Molecularly, the amphiphilic nature of PEG 400 enhances drug partitioning into the micellar or nanoemulsion system, thus increasing release.

In the third plot (oil vs co-surfactant), it again confirms that higher PEG 400 content improves drug release, even when Oleic Acid concentration is moderately high. PEG 400 likely offsets the negative impact of excess Oleic Acid by reducing viscosity and enhancing interfacial dynamics. They involve PEG 400, decreasing the rigidity of the surfactant film, facilitating quicker drug mobility from the lipid matrix to the external medium.

These plots emphasize that optimal drug release from SEDDS is achieved by a careful balance of oil, surfactant, and co-surfactant. Surfactant and co-surfactant together lower energy barrier for emulsification, promote globules disintegration, and increase drug availability in the aqueous phase. The molecular coordination of these excipients ensures maximum drug solubilization and diffusion.



(a)

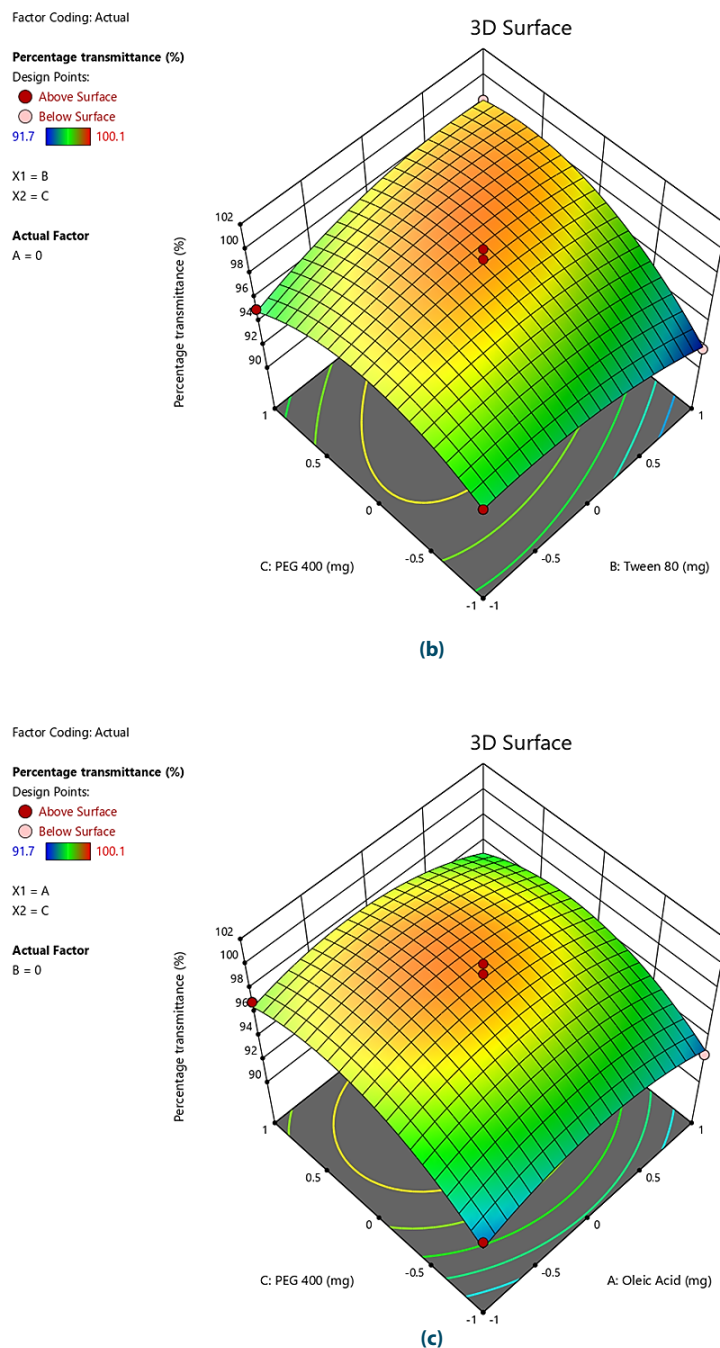


Figure 8: Percentage transmittance: (a) effect of oil (oleic acid) and surfactant (tween 80), (b) effect of surfactant (tween 80) and cosurfactant (PEG 400), (c) effect of cosurfactant (PEG 400) and oil (oleic acid).

Desirability function for identification and evaluation of optimum formulation

The current study used Design of Expert (version 13) to implement the desirability function technique. For every response, the limitations were established. Table 2 gives the range in which independent variables were set. Y1 is intended to be 157.1 ± 0.32 nm, Y2 is intended to be $100.1 \pm 57.25\%$, Y3 is intended to be 36 ± 1.06 sec, and Y4 is intended to be $98.18 \pm 2.06\%$ of the

responses. In order to conclude all replies in a single assessment, the desirability function computes each desirability function. It will aid to predict the independent factors ideal concentration. Optimal formulation (F1) pleased maximum no. of response variable required and best desire function then finalized. A=10% w/w, B=50% w/w, and C=30% w/w make up the chosen optimal formulation, and its overall desirability was determined to be 0.953.

Robustness to dilution

To accurately represent *in vivo* condition and ensure development of a uniform emulsion, optimized formulation (F1) was checked using various dilution folds (10, 100, and 1000 times) in three distinct dilution media such as water, 0.1M HCl buffer (pH 1.2) and phosphate buffer (pH 6.8). Even after 24 hr of the trial, no

drug precipitation was seen due to the progressive rise in dilution and the modification of the dilution media.

Cloud point measurement

The optimized formulation in our investigation showed cloud point at 60.2°C.

Factor Coding: Actual

Self emulsification time (Seconds)

Design Points:

● Above Surface

○ Below Surface

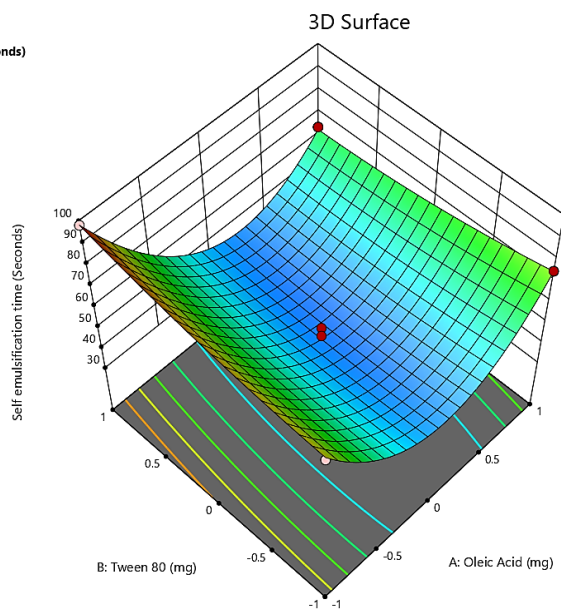
36 98

X1 = A

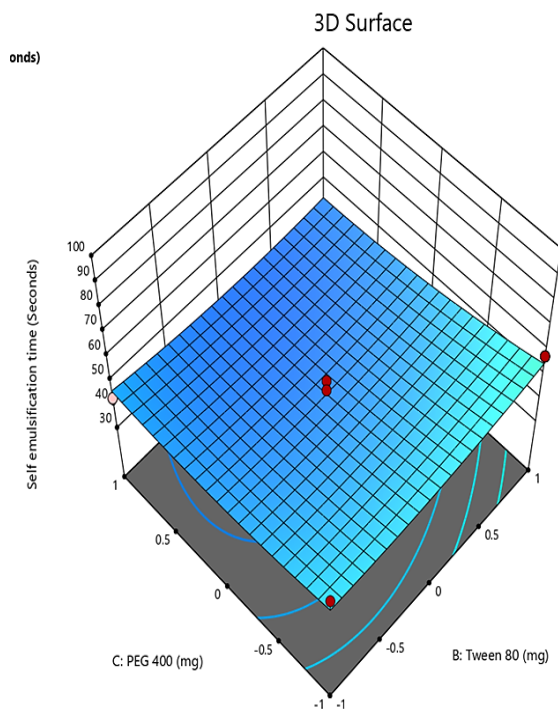
X2 = B

Actual Factor

C = 0



(a)



(b)

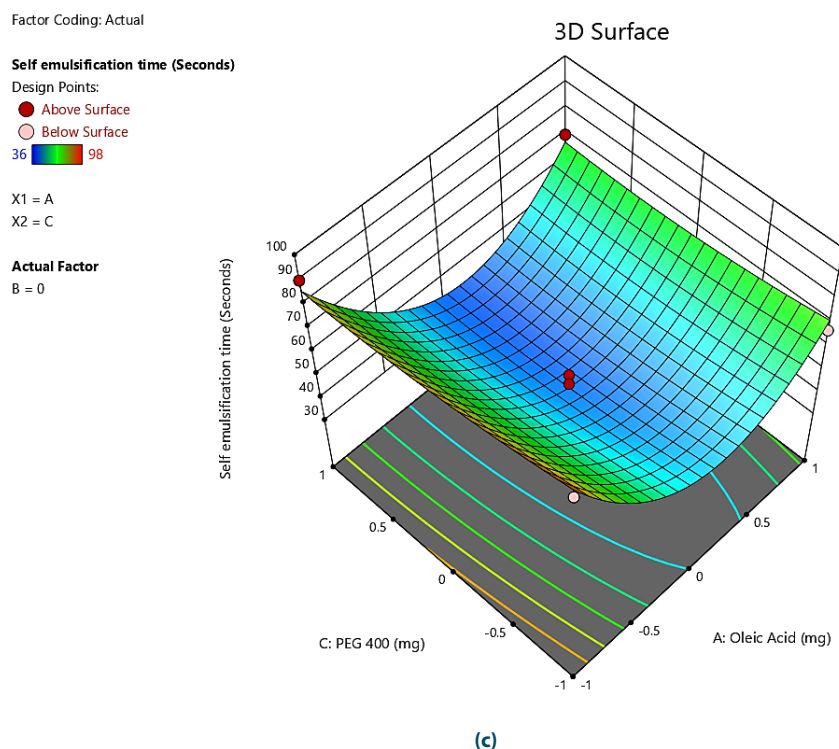


Figure 9: Self emulsification time: (a) effect of oil (oleic acid) and surfactant (tween 80), (b) effect of surfactant (tween 80) and cosurfactant (PEG 400), (c) effect of cosurfactant (PEG 400) and oil (oleic acid).

Stability studies of optimized SEDDS

After aqueous dilution, the thermodynamic stability of the optimized SEDDS preconcentrate and its emulsion was assessed. No signs of uncertainty, including color, odor, creaming, precipitation and phase separation, were found in the study.

Centrifugal test

No phase separation, creaming or precipitation observed after centrifugation.

Heating-cooling cycles

No phase separation, creaming, or change in transparency after cycles.

Freeze-thaw cycle

No phase separation or precipitation after cycle.

Drug release kinetics

Kinetics Studies

Details by *in vitro* study plotted in several kinetic models to investigate the release kinetics (Marasini *et al.*, 2012).

As we can see in Table 4 the correlation coefficient (R^2) result of First order reaction is higher than that of other models, indicating the system follows First order Kinetics Model. First order kinetics model is concentration dependent, meaning it increases proportionally as the concentration of drug in dosage form increase and vice versa (Medarametla *et al.*, 2024). The

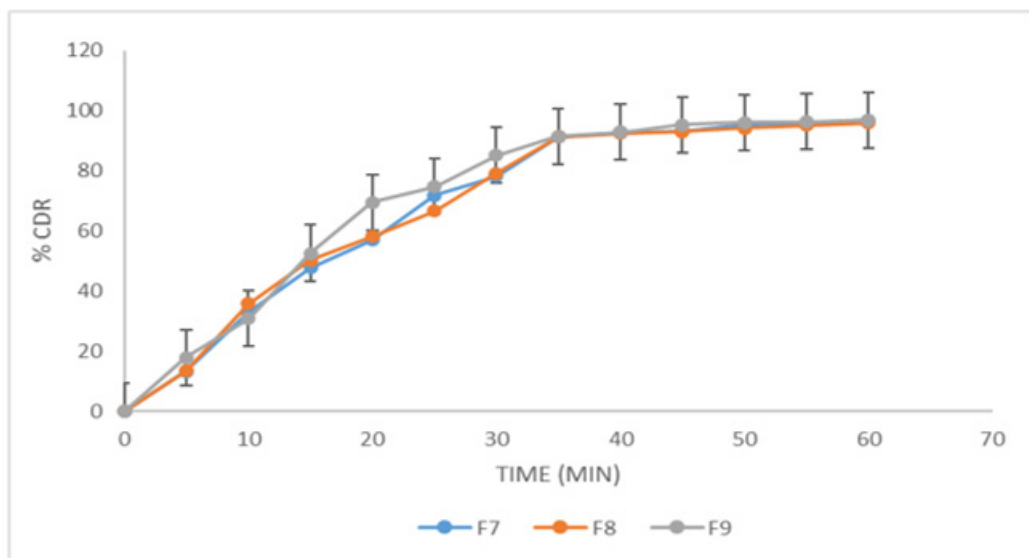
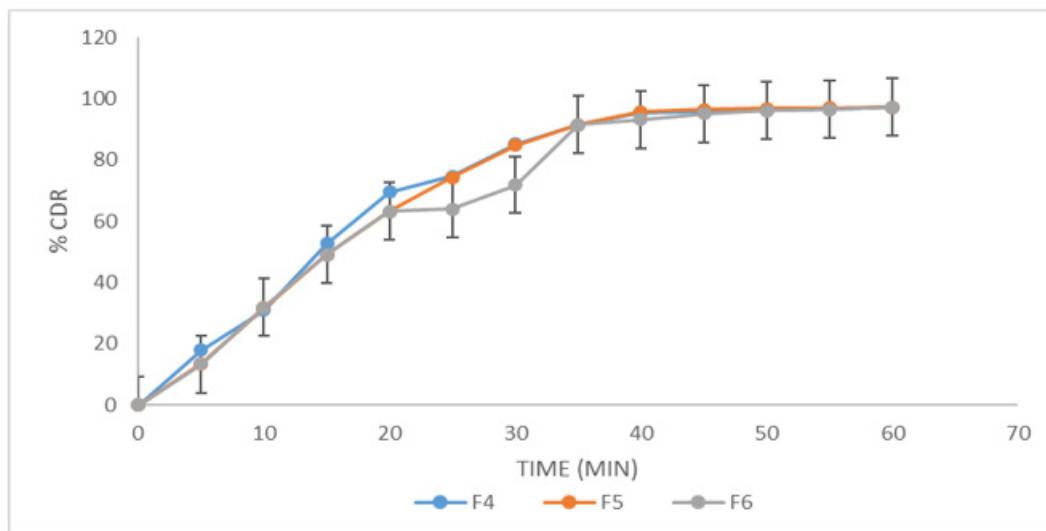
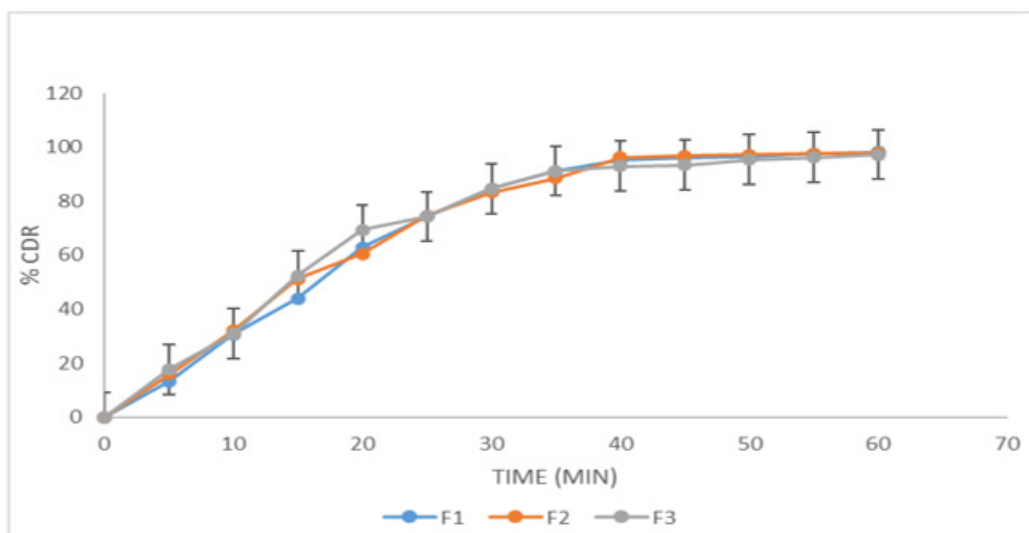
drug's release mechanism is described by the value of n . In this case, n -values more than 0.45 but lesser than 0.89 (i.e., $0.45 < n < 0.89$) indicate anomalous transport (a non-Fickian transport mechanism).

TEM

Figure 16 shows the TEM micrographs of optimized Formulation (F1) showing nanoemulsion globules of finalized formulation were similar, spherical and separate.

DISCUSSION

Oleic acid was shown to have a high solubility of AMS when compared to other oils. Greater solubility of the medication in Oil phase is essential for self-emulsification since drug in SEDDS must be remain in dissolved state and produce large concentration gradient that will act like as driving factor for drug's penetration by the GI tract. Oleic acid was chosen for the lipid phase for upcoming investigation due to its superior ability to solubilize AMS. Because of their high viscosity and gritty nature, other oils were not chosen as lipid phase for formulation preparation. The choice of surfactants is essential in the Oil phase because they are accountable. for emulsion stability. Additionally, they speed up a drug's adsorption by causing reversible change in intestinal mucosa's permeability. Thus, Tween 80 and PEG 400, two non-ionic surfactants, were chosen to prepare SEDDS. Because they aid in the formation and stabilization of micelles with Tween 80 in the hydrophilic phase, cosurfactants are a crucial part of SEDDS. They also enhance the drug's solubility in micelles and



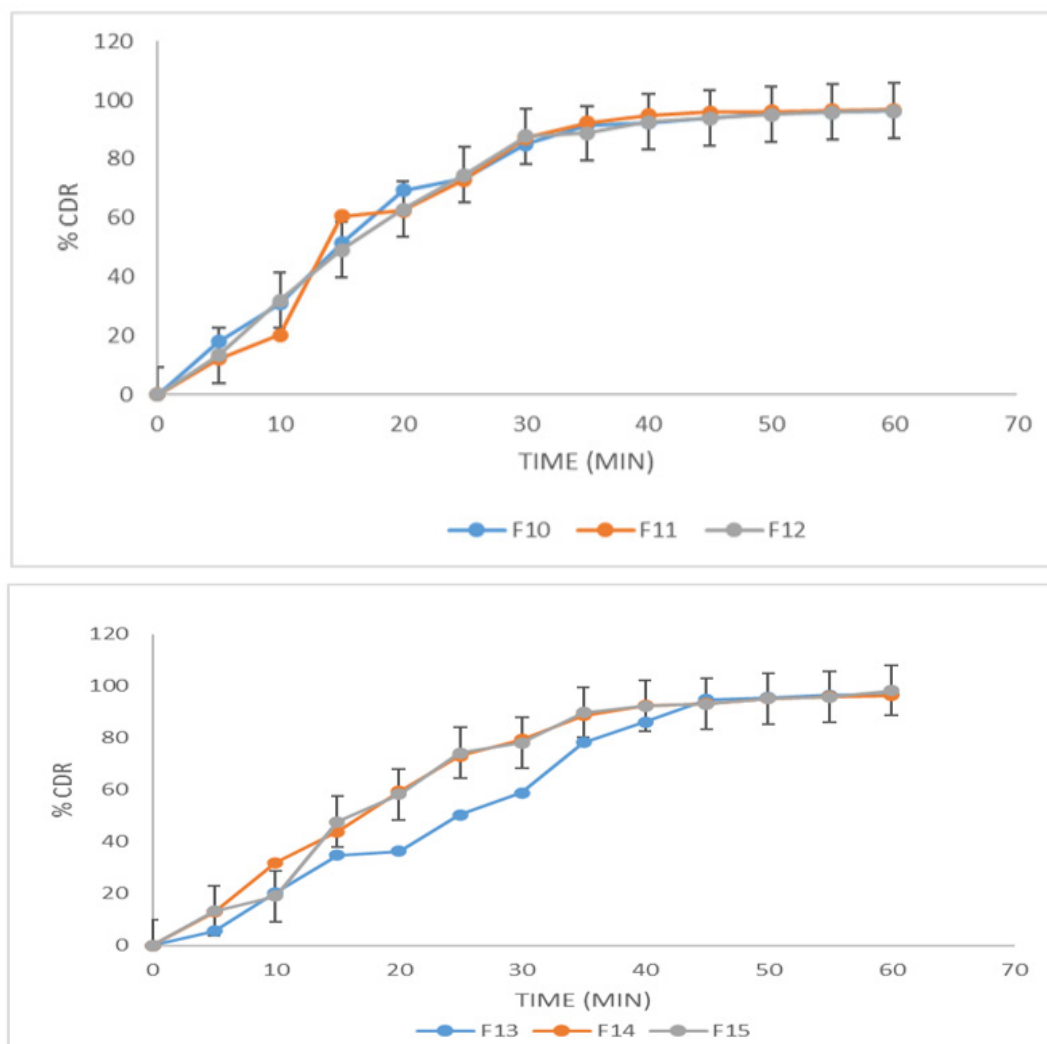


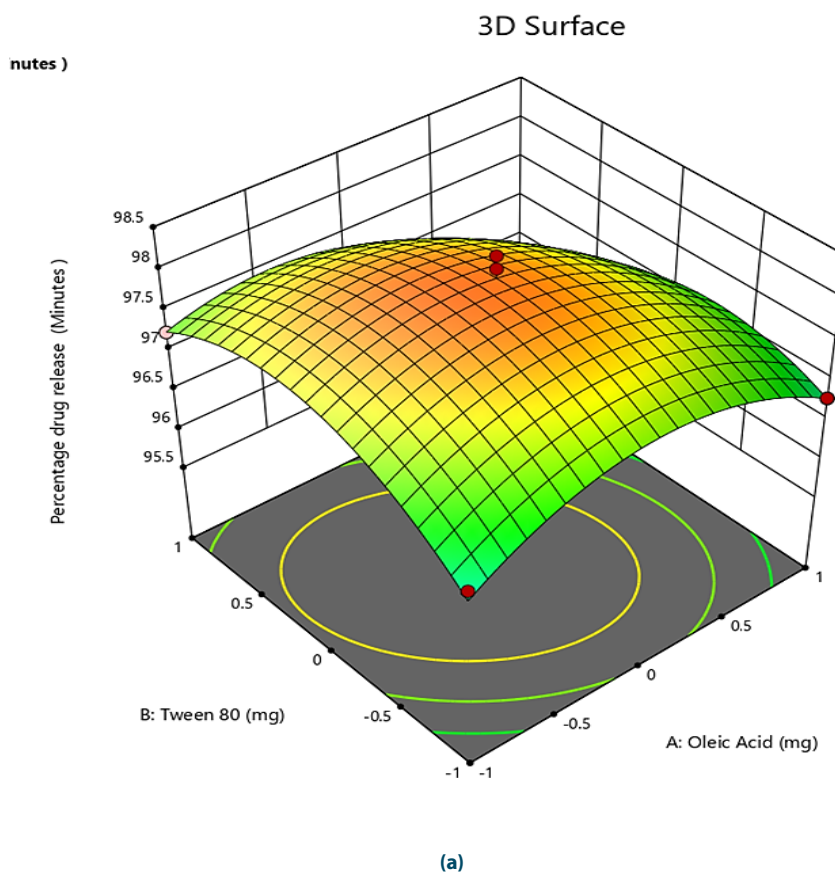
Figure 10: % Drug release from F1 to F15 formulation.

stop the substance from precipitating. PEG 400 was chosen since it solubilizes the most medication (Byeon *et al.*, 2019). Furthermore, Tween 80's low affinity for oil resulted in less surfactant adsorption on the oil globules. The segment surrounding the shaded area on the phase diagram depicts weak emulsification properties, while the shaded area shows the nanoemulsification area that delineates the best chances or likelihood to create nanoemulsion. High oil emulsification is not present in a system with a high surfactant level. Since the cosurfactant amount is insufficient to diminish this region, it is possible that a liquid crystal area will form at greater surfactant concentration. Because system 5-C had a bigger self-nanoemulsification zone, it was chosen to define the nanoemulsion's borders. A suitable concentration of S_{mix} (2:1) may be the cause of system larger nanoemulsion region. Because a perfect S_{mix} may emulsify more oil, the molecular structures of the cosurfactant (PEG 400) and surfactant (Tween 80's linear structure) allow PEG 400 to easily penetrate into surfactant monolayer then establish an appropriate arrangement with Tween 80. As a result, a larger emulsion zone was seen. Conventional experiments are more labor-intensive and material-intensive

for developing and optimizing complicated processes (Yadav *et al.*, 2020). RSM among other experimental designs, will assist in resolving these issues. This methodology offers comprehensive information with the fewest amount of experiments, making it superior to traditional optimization techniques. Response surface designs come in a variety of forms, such as BBD and central composite design. BBD a three factor-three level model, it requires lesser trial runs, is rotatable, and it requires no combination of extreme points of cubic region instantaneously. This lowers the possibility of getting inadequate outcomes. To understand effect of all independent variables on dependent components, BBD was selected and utilized for investigation. Fifteen formulations were prepared with the BBD, and response variables were assessed. The PEG 400 fluidizes hydrocarbon of interfacial layer created by the lipid and surfactant, creating empty space between the surfactant molecules. The emulsion's physical stability is controlled by its zeta potential. The capability of colloid particle used at shear plane under the electric zone is called zeta potential. Results proved that globule size reduced as amount of Tween 80 increased (Figure 13) (Wani and Patil, 2013). This may be explained by localization of

surfactant on interface, which creates compact layer and barrier surrounding the globules, lowering interfacial tension and preventing oil globule coalescence. Presence of many emulsifier for the emulsification may be the cause of more transmittance percentage and decreasing lipid content. It is evaluation of impact of emulsification, or the capacity of SEDDS to disperse appropriately and quickly when diluted with water and gently stirred. This helps ensure that the medicine is disseminated in the dispersed emulsion without additional precipitation and shows how long the emulsification process takes. It was discovered that when the concentration of S_{mix} increased, the emulsification time reduced. It was also evident that the emulsification time increases in proportion to the oil content (Shivaraj *et al.*, 2025). As the oil concentration rises, the emulsification process tends to slow down because the high oil content increases the system's viscosity, which necessitates strong shear forces for dispersion. Additionally, it was shown that the emulsification time decreased linearly with an increase in surfactant content. This might be the result of the interface becoming more stable as the surfactant content rises. Dissolution testing is a crucial tool for forecasting a formulation's or product's consistency and medication release properties. Dissolution testing may occasionally be useful in determining the drug's *in vivo* dissolution profile (dissolution limited systems). The cumulative percent drug release after 5 min decreased linearly with an increase in oil content, according

to the model graphs that displayed the effect of formulation composition on dissolving after 5 min. The globule size and percentage transmittance results were in agreement with this (Figure 14). The larger oil content would cause the system to become more viscous, which can slow the emulsification and postpone medication's release. Self-emulsification time results showed a similar pattern. Furthermore, a modest interfacial layer would be accessible for drug release since, as was mentioned in section above, the globule size of formulations with an increased lipid content was larger than that of the others (Yadav *et al.*, 2020). The foundation of desirability function is the transformation of every reaction into dimension-free value. Desirability function has range from 0 and 1. Score of 1 suggests most suitable answer for components under investigation, while a value of 0 is observed when these elements provide unfavorable outcomes. This method is used to create the necessary resilient formulation that satisfies all replies' maximum requirements while adhering to the specified limitations (Figure 15). Polynomial equation developed and results from independent factors on solutions were investigated, approach was optimized by the desirability approach. The results made evident, that all obtained results were consistent with predicted values, advising that BBD in conjunction with desirability approach is auspicious method for the optimization and evaluation of SEDDS. Drug precipitation is more likely to occur at larger dilutions *in vivo*, which could have a



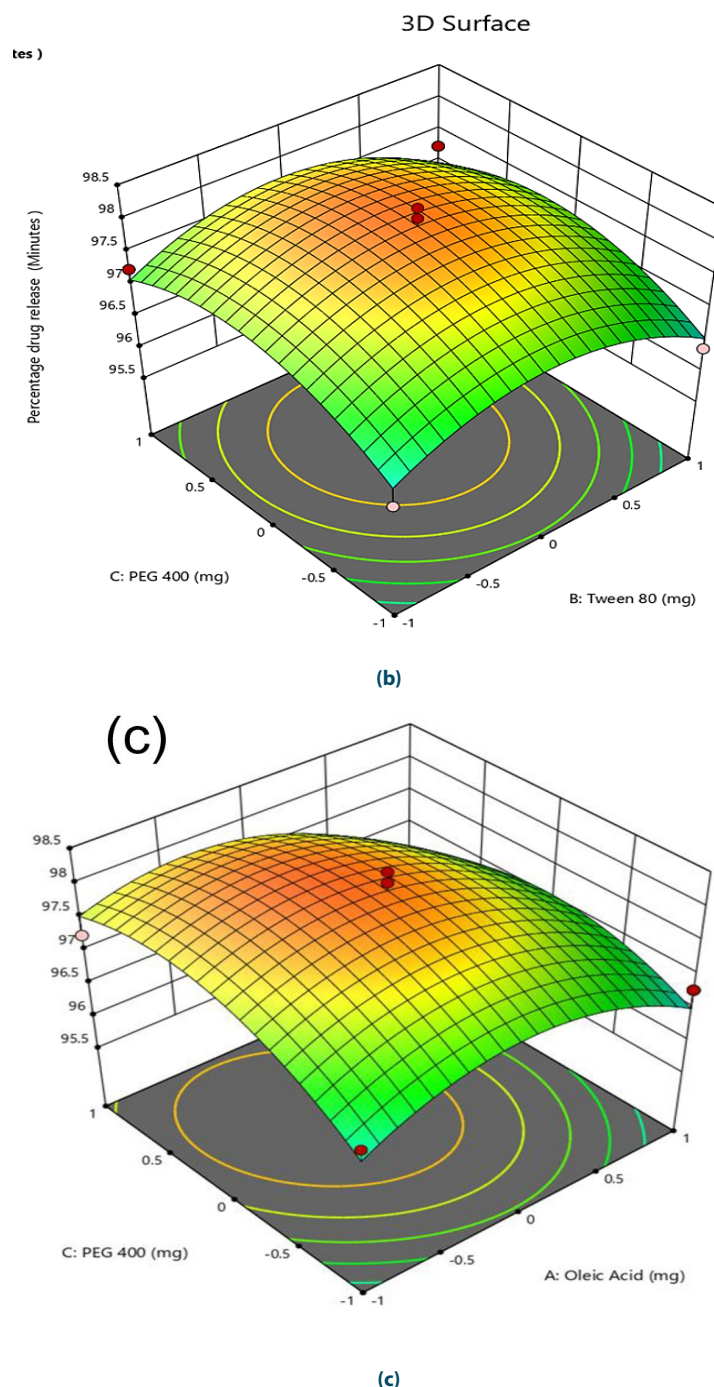


Figure 11: Drug release time: (a) effect of oil (oleic acid) and surfactant (tween 80), (b) effect of surfactant (tween 80) and cosurfactant (PEG 400), (c) effect of cosurfactant (PEG 400) and oil (oleic acid).

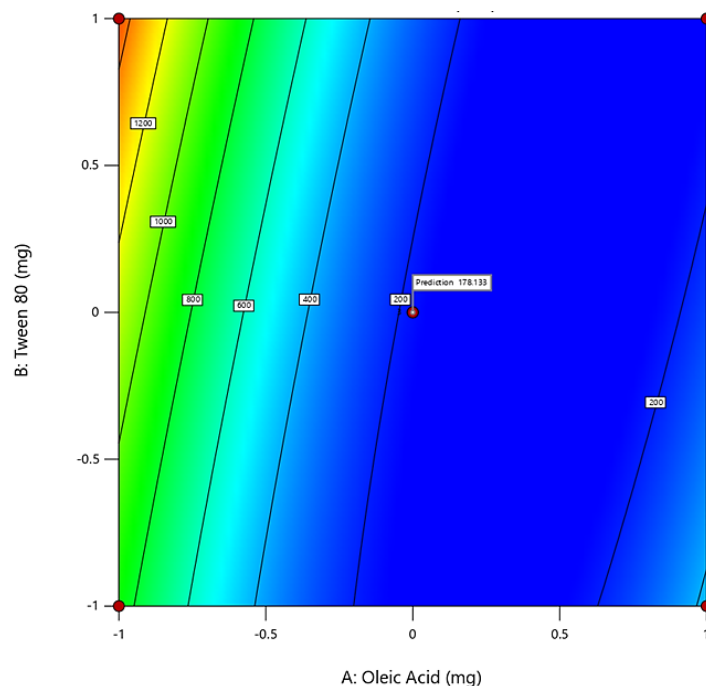
major impact on the drug's performance and absorption (Verma *et al.*, 2021). In order to guarantee that a consistent emulsion is created from SEDDS, robustness to dilution was carried out. The outcomes made it abundantly evident that the improved formulation would continue to function *in vivo* and was resilient to dilution. An emulsion's cloud point is temperature where the medication that has been dissolved stops being in solution and precipitates, making the emulsion hazy. An essential metric for evaluating potential of emulsions having non-ionic surfactants

(Prieto and Calvo, 2013). According to the stability research, preconcentrate should be capable to tolerate temperature changes during storing without experiencing phase separation and drug precipitation. preconcentrate and the emulsion that results after diluting it with water optimized formulation preconcentrate along with its resulting emulsion following dilution with water determined to be stable and to exhibit no signs of instability, according to the stability study's findings.

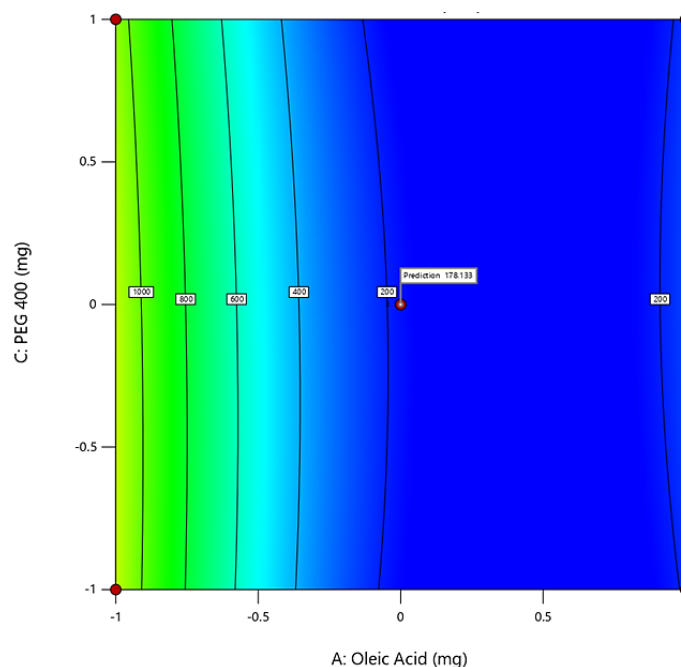
CONCLUSION

In order to improve the poorly soluble drug's dissolving profile, the current study illustrates the BBD approach for designing and improving SEDDS having BCS class II medication (Amisulpride). The impacts of several formulation factors (oil, surfactant, and co-surfactant) on responses were determined using polynomial equations and model graphs. The investigation made it abundantly evident that the measured responses are significantly impacted by formulation variables. Large globules in the emulsion, a lower percentage of transmittance, a longer self-emulsification time,

and a lower drug release (Figure 16) were all consequences of the formulation's high oil content. As the surfactant concentration rose, the opposite result was seen; this could be because of the enhanced stability and decreased interfacial tension at the contact. Drug release study demonstrated an improved dissolving profile of Amisulpride included in SEDDS. Values of formulation excipient and drug for creation of optimum Amisulpride SEDDS can be predicted with the use of the polynomial equation and model graphs. Additionally, there were no indications of instability in the optimized formulation. The study's findings indicated that SEDDS may be able to improve the dissolving



(AB)



(AC)

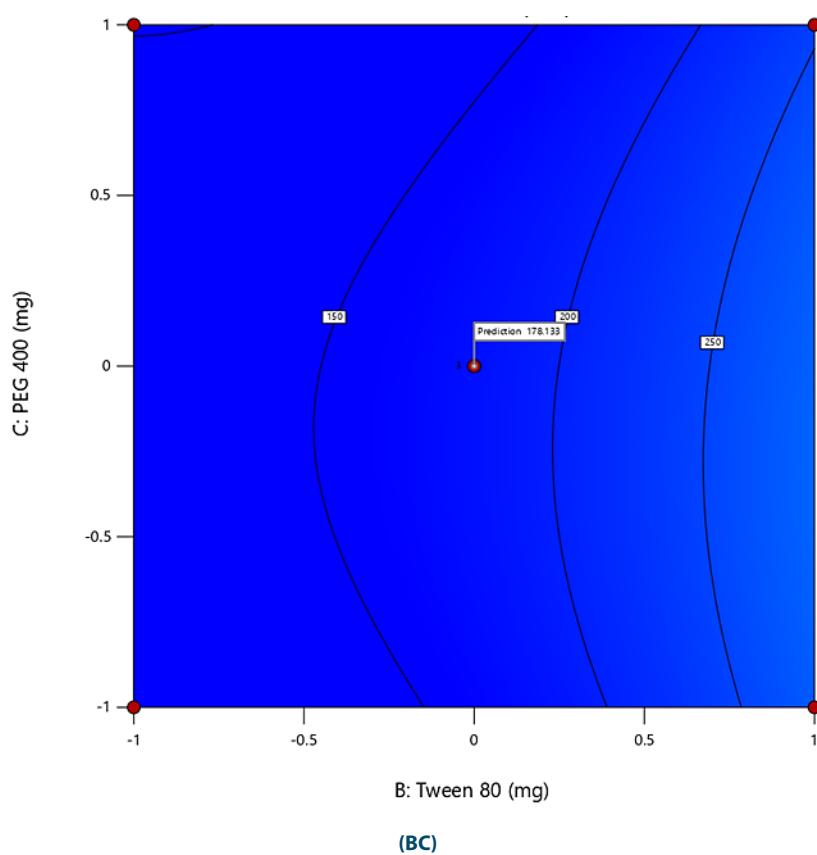
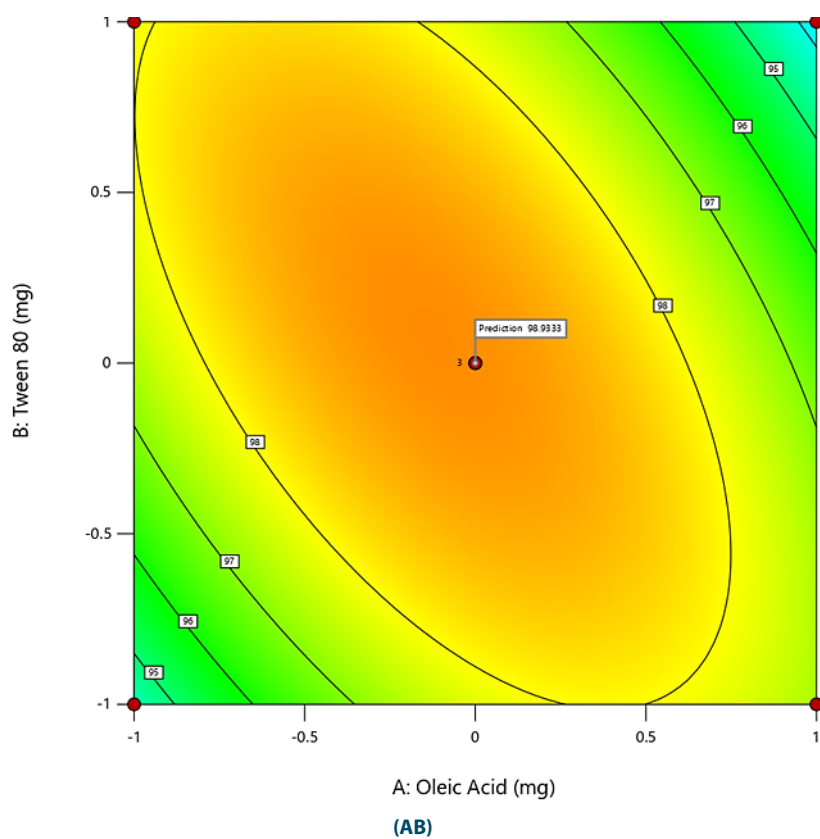


Figure 12: Globule size.



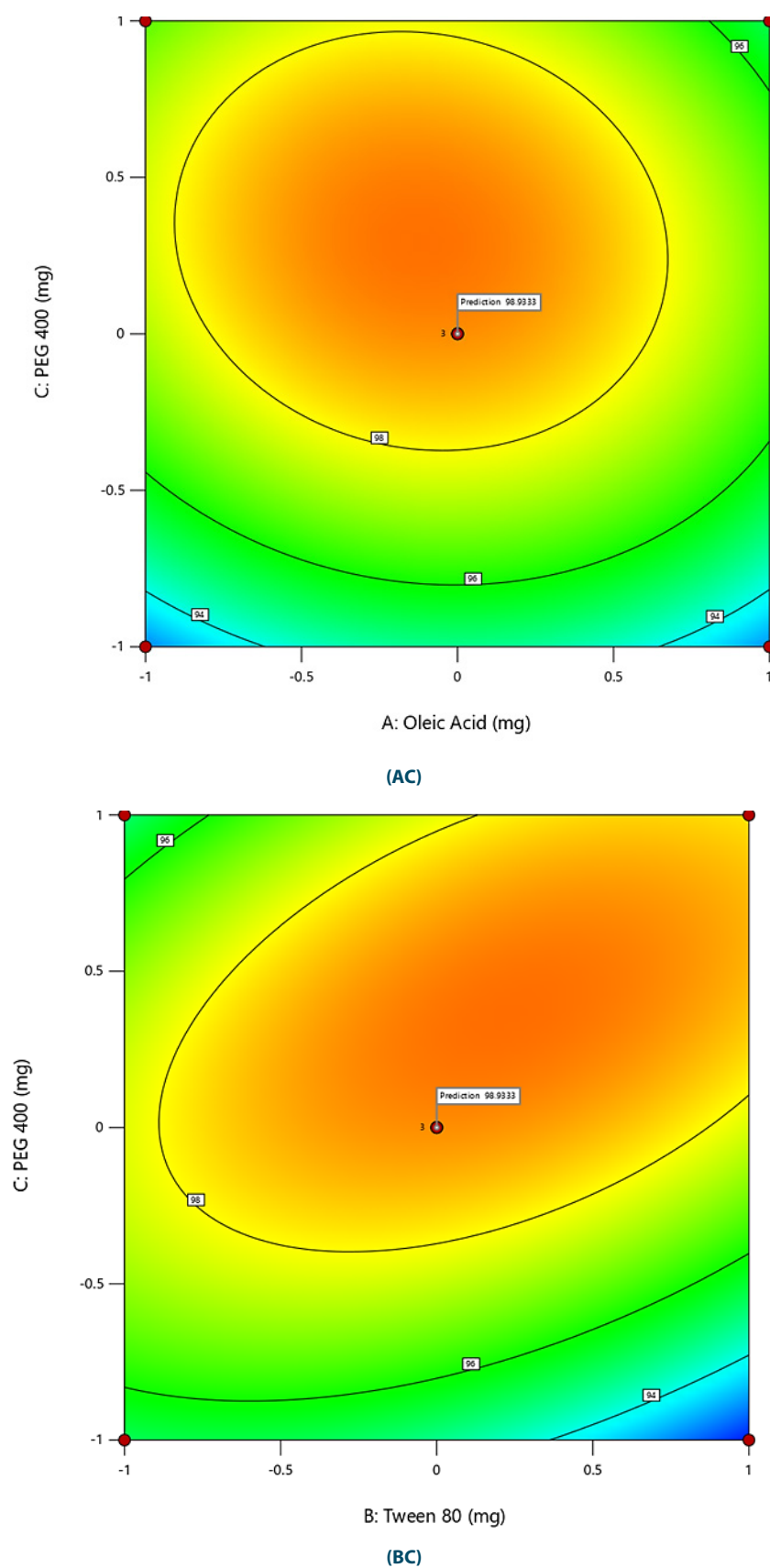
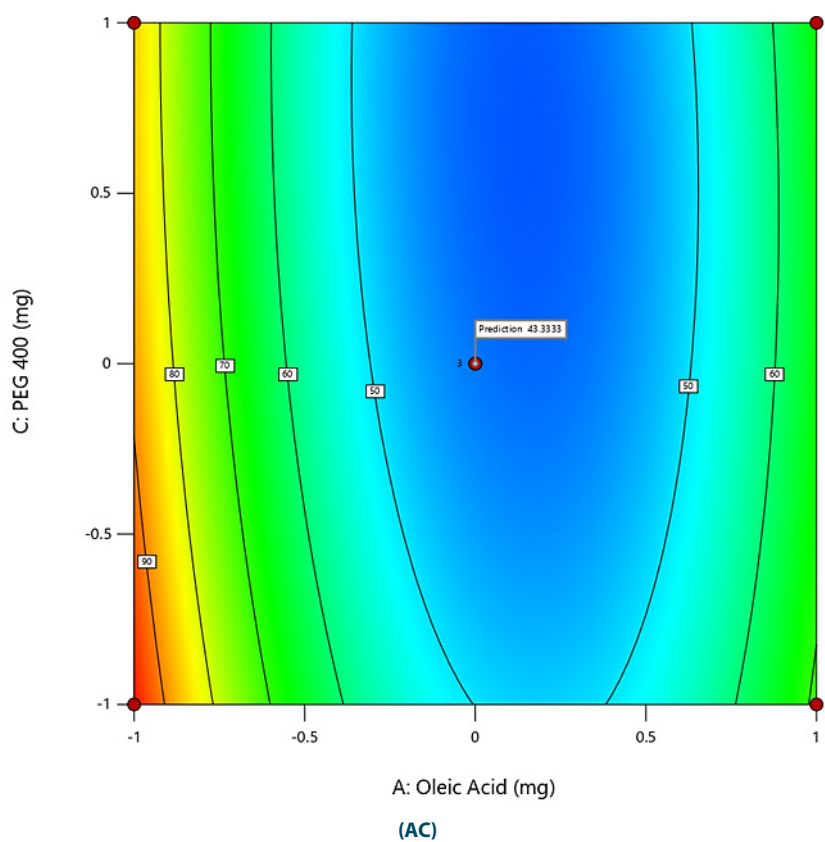
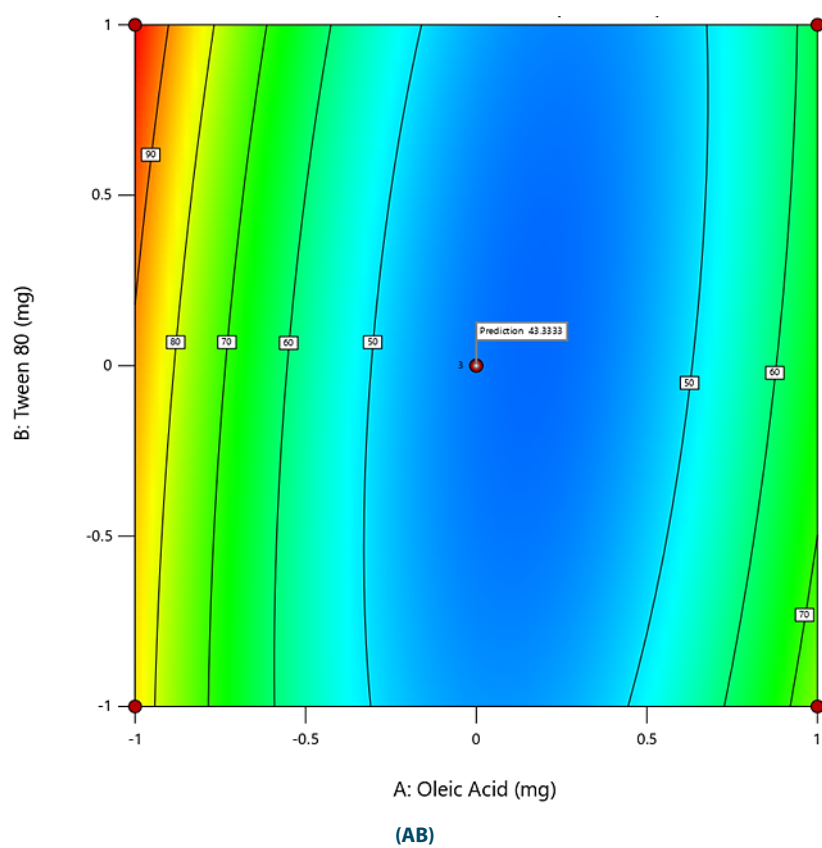


Figure 13: Percentage transmittance.



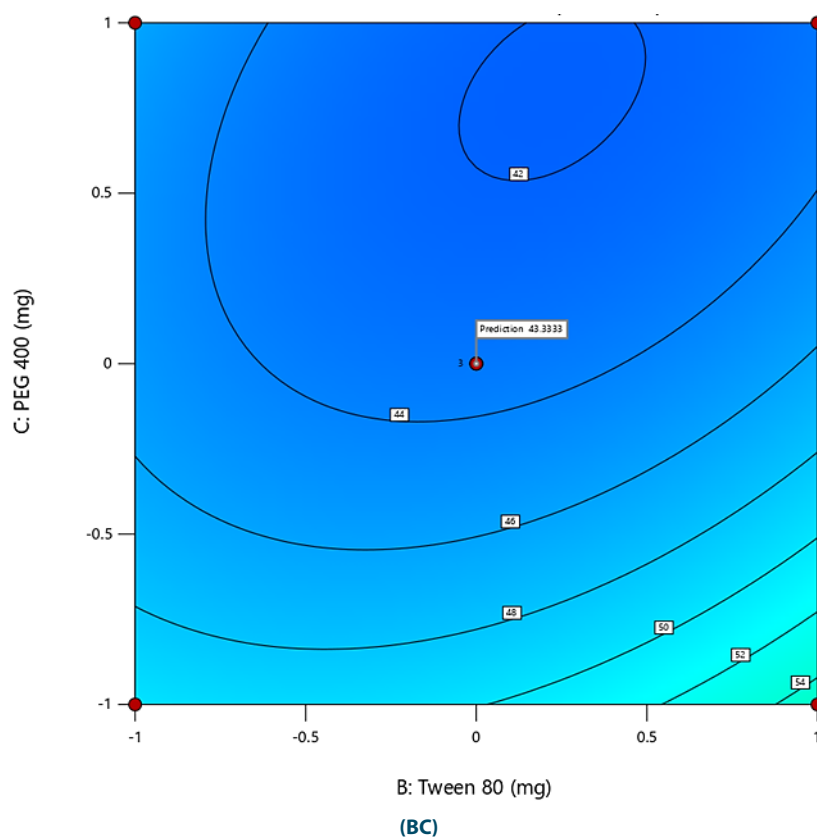
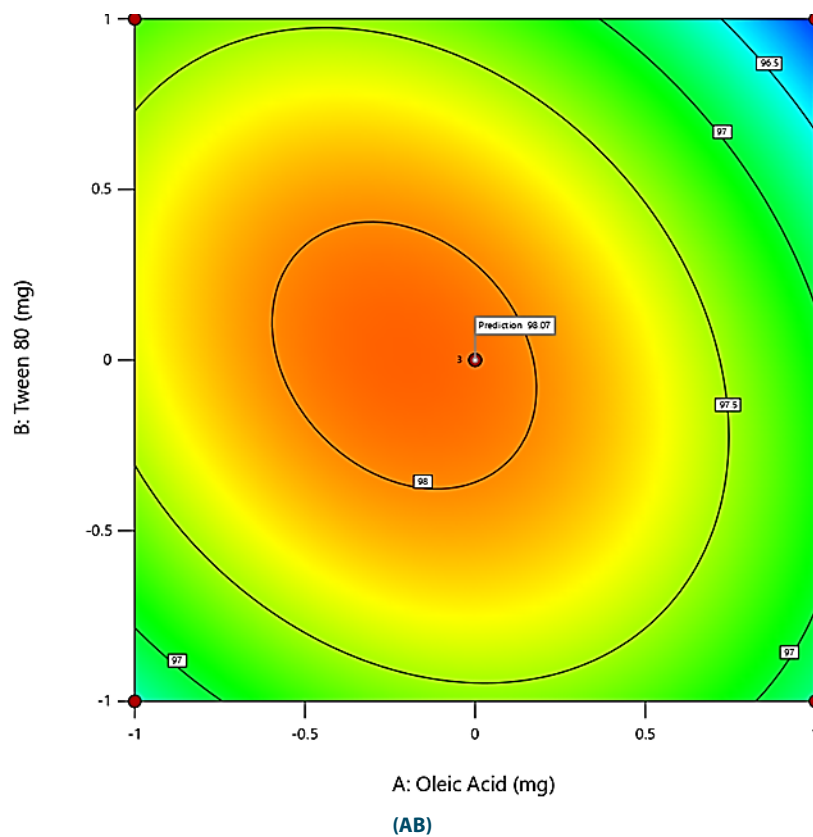


Figure 14: Self emulsification time.



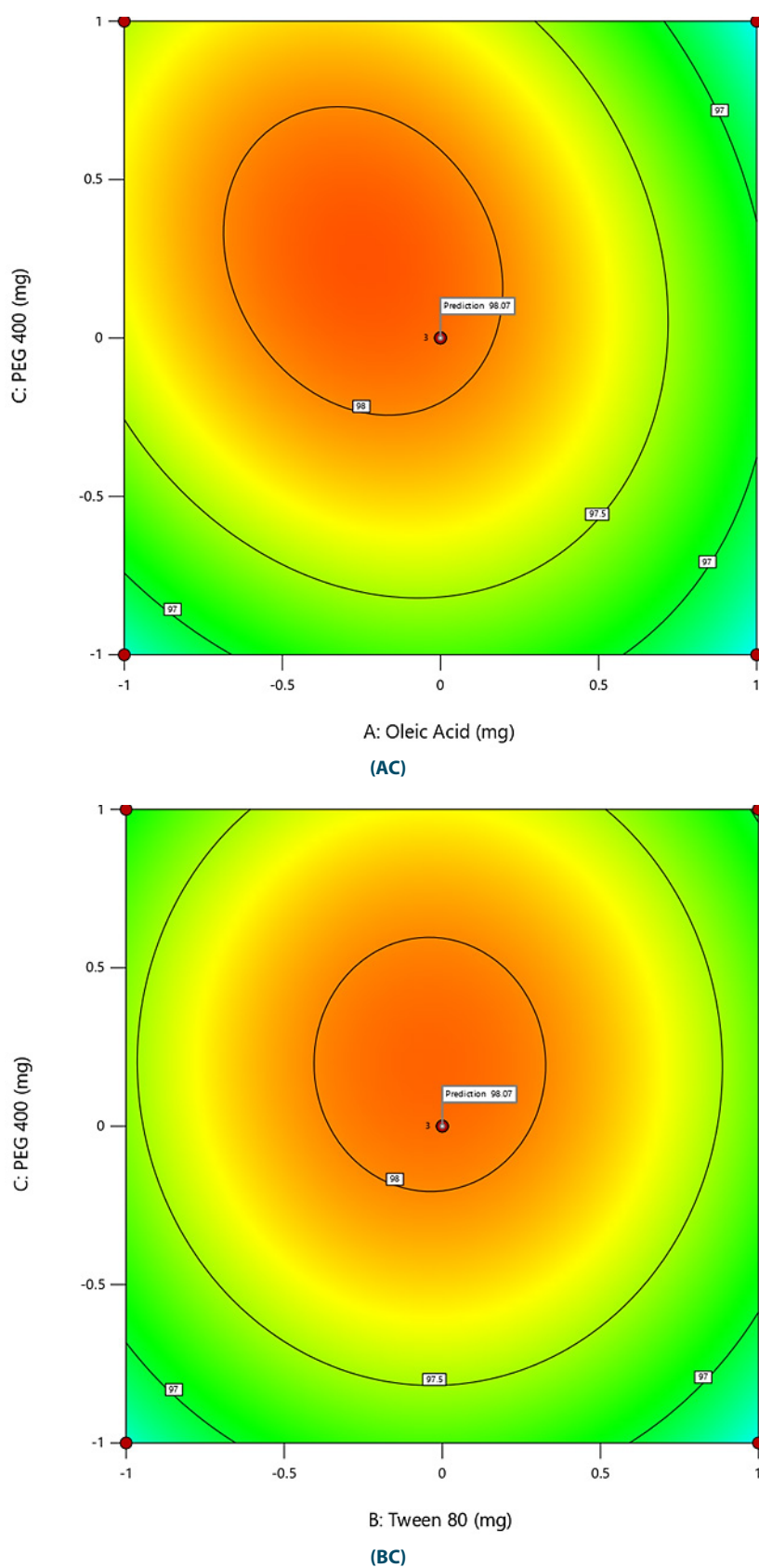


Figure 15: Percentage drug release.

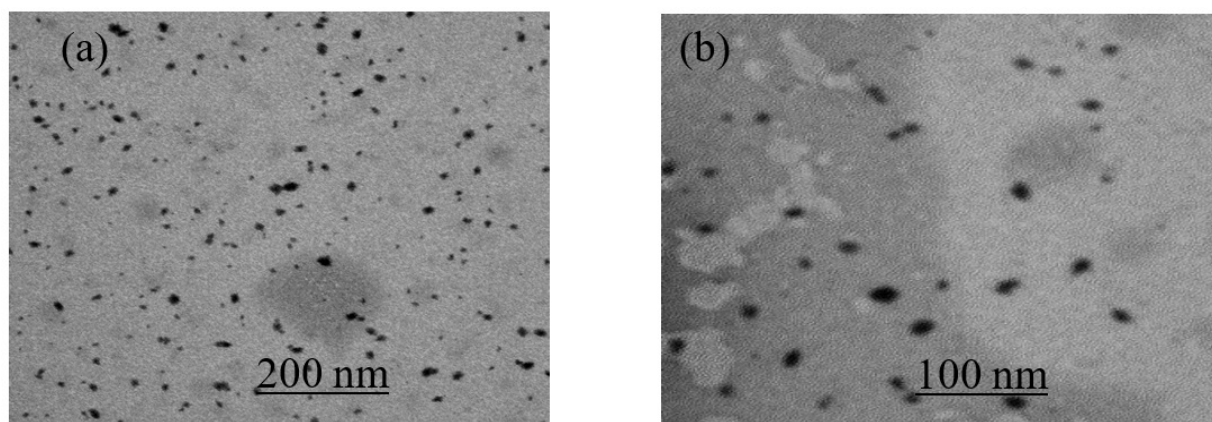


Figure 16: Transmission electron microscopic visual of the optimized formulation of Amisulpride.

profile of medications that are weakly soluble. Additionally, a viable method for analyzing impact of preparation factors and optimizing their results for creation of an effective optimized preparation is BBD with desirability function. Furthermore, the scope of this study is not limited to the factors under investigation.

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ABBREVIATIONS

BCS: Biopharmaceutics Classification System; **SEDDS:** Self-Emulsifying Drug Delivery Systems; **BBD:** Box-Behnken Design; **SMEDDS:** Self-Microemulsifying Drug Delivery Systems; **SNEDDS:** Self-Nanoemulsifying Drug Delivery Systems; **AMS:** Amisulpride, **PDI:** Polydispersity Index; **FTIR:** Fourier Transform Infrared Spectroscopy; **DSC:** Differential Scanning Calorimetry; **XRD:** X-ray Diffraction; **TEM:** Transmission Electron Microscopy; **RSM:** Response Surface Methodology; **GI:** Gastrointestinal; **PDI:** Polydispersity Index; **nm:** Nanometre; **Mv:** Millivolt; **SD:** Standard Deviation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

VK: Writing original draft, Methodology, Validation, Investigation. **VR:** Supervision, Writing-reviewing and editing.

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