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FORMULATION AND OPTIMIZATION OF DOMPERIDONE-LOADED LIQUID SNEDDS: CHARACTERIZATION AND IN-VITRO EVALUATION

Sara Taha Rasool [1,*], and Adnan Burhan Qader [1]

[1] Department of Pharmaceutics, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq.

*Corresponding author email: sara.rasool@pha.hmu.edu.krd

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ABSTRACT:

This research concentrated on developing and optimizing domperidone-loaded Self- nanoemulsifying drug delivery system (SNEDDS) to enhance solubility, stability, and availability. Domperidone (DOM), a lipophilic drug characterized by its limited solubility in water, was integrated into SNEDDS formulations utilizing a range of oils, surfactants, and cosurfactants. Solubility studies indicated that orange oil exhibited the highest solubility for DOM at (47.94 mg/mL ± 0.085) against oils, Cremophor EL among surfactants, and Transcutol HP against cosurfactants. The solubility enhancement can be attributed to the formation of nanoemulsions, which effectively diminish particle size and enhances surface area, leading to improved dissolution and accelerated absorption. The optimization of the formulation was conducted utilizing a pseudo-ternary phase diagram, twelve successful formulations were evaluated and characterized for self-emulsification, stability, and drug release. *In-vitro* characterization demonstrated that F1 formula (Orange oil+ Cremophor EL+ Transcutol HP) using (2:8, oil: S_{mix} ratio) released DOM at rates up to 3.7 times greater than those of commercial products. The rapid emulsification times, ranging from (13.75 ± 0.528 to 32.17 ± 1.193 seconds), consistent droplet sizes, and a low PDI (0.28 ± 0.03 to 0.68 ± 0.2) have significantly improved bioavailability.

KEYWORDS: Availability, Domperidone (DOM), Self-Nanoemulsifying Drug Delivery System, Solubility Study.

1. INTRODUCTION

Oral medication administration is considered more convenient and non-invasive method for delivering therapeutic drugs. It is the preferred route due to its simplicity of use, patient comfort, and the ability to provide consistent, controlled doses over time. Patients generally find oral dosage forms, such as tablets, capsules, and liquids, to be simpler to manage than other forms of drug administration, such as injections or infusions (Bhalani *et al.*, 2022; Qader *et al.*, 2024).

A significant number of unique drug candidates exhibit low solubility in water, hence reduced and variable oral bioavailability. Lipid-formulation systems such as self-nanoemulsifying drug delivery systems (SNEDDS) have proven to be useful solutions to counteract the problem (Buya *et al.*, 2020). SNEDDS consist of isotropic mixtures comprising an oil phase and a surfactant, often supplemented with a co-surfactant or co-solvent. In response to mild agitation in aqueous gastrointestinal fluids, SNEDDS spontaneously form fine oil-in-water nano-emulsions with typically nanometer-sized droplets (usually <200 nm) (Alqahtani *et al.*, 2021 ; Buya *et al.*, 2020).

Apart from increasing solubilization, SNEDDs can confer numerous biopharmaceuticals. Nanoscale droplets offer an extensive interfacial surface area, hence enhancing medication release and absorption rates. Surfactants and lipids in SNEDDS can interact with biological membranes to enhance drug transport; studies indicate that SNEDDS formulations can fluidize enterocyte membranes and block P-glycoprotein efflux pumps, thus enhancing the transcellular permeability of encapsulated pharmaceuticals (Baloch *et al.*, 2019)

Domperidone (DOM) ($C_{22}H_{24}ClN_5O_2$), a dopamine D_2-receptor antagonist and lipophilic agent classified as a Class II BCS (its chemical structure shown in Figure 1), is extensively utilized to treat gastrointestinal conditions such as nausea and vomiting. Notwithstanding its therapeutic advantages, DOM's inadequate water solubility and significant metabolism in the first pass leads to low oral bioavailability (Nagpal *et al.*, 2016). It exhibits partial insolubility in water (0.0925 mg/mL) and has low oral bioavailability (13-17%), and its log P 3.9 (Bhatia *et al.*, 2024)

DOM's lipophilicity and high permeability make it ideal for inclusion into SNEDDS preconcentrates, whereby it can be dissolved in an oil/surfactant mixture and shielded against early precipitation in the stomach environment. Presenting DOM in a solubilized, easily absorbed form should help SNEDDS increase its effective concentration in the intestine. Furthermore, if the SNEDDS facilitates lymphatic absorption of DOM, first-pass hepatic extraction may be significantly reduced, thereby enhancing systemic exposure. Generally, the SNEDDS method fits the necessity of improving the solubility and absorption of DOM without changing its therapeutic aim or mechanism (Alqahtani *et al.*, 2021; Okur *et al.*, 2024).

Liquid SNEDDS (L-SNEDDS) are often prepared as pourable liquids or semi-solids suitable for encapsulation in soft

* Corresponding author

or hard gelatin capsules for delivery. The liquid state of SNEDDS can be converted into a solid intermediate (S-SNEDDS) by adsorption onto solid carriers or spray-drying for enhanced handling; nevertheless, the emphasis in this context is on the liquid preconcentrate. The objective of formulation development is to achieve a DOM-loaded SNEDDS that is optimized for minimal droplet size, low polydispersity, high drug solubilization, and effective self-emulsification upon dilution (Govindan *et al.*, 2024).

This study aims to develop, optimize, and characterize an SNEDDS loaded with DOM to improve stability, solubility, and bioavailability by conducting *in-vitro* drug release and Self-emulsification characterization.

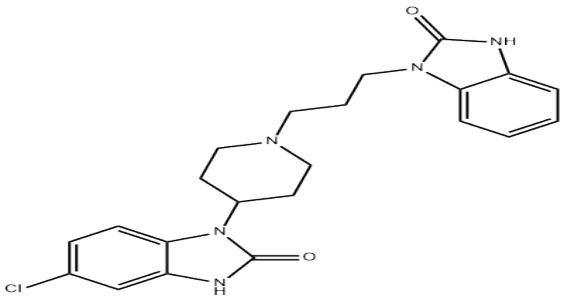


Figure 1: Chemical structure of DOM.

2. MATERIALS AND METHOD

Materials:

Domperidon(DOM) was provided by Pioneer Pharmaceutical Manufacturer, Sulaymaniyah. Iraq. Capryol 90, Labrafac MC60, Labrafil M 1944CS, and Transcutol HP were received from GATTEFOSSE SAS, France. Cremophor EL, Polyethylene glycol (PEG) 200 supplied by Simson PL. India. Labrasole got from AV-Souwv, Biotech. China. Tween 20, PEG 400, PEG 600, and propylene glycol (PG) were received from the Reagent of the Library. India. Tween 60, Tween 80, and HCL, 37% (Scharlau Chemie, Spain), Span 20 (Sino Pharma- China), Cedar oil (BDH- England), and all other oils used in the study supplied by AVONCHEM. U. K. Absolute ethanol (Merc, Germany). Dena Kanii, Erbil supplied deionized water. Iraq.

Methods:

Characterization of Domperidone:

Preparation of Calibration Curve:

To make a 40µg/ml stock solution of DOM, 25 mg of DOM was dissolved in 100 mL of absolute ethanol, with 4 mL transferred to a 25 mL volumetric flask, and absolute ethanol added to form 1000µg/25 ml. Serial dilution was then performed. The absorbance of each solution against the blank was measured at λ max (286 nm) as shown in (Figure 2), by UV spectroscopy (Shimadzu 1900- Japon) absorbances against concentrations were plotted to create a calibration curve (Qasim *et al* ., 2024).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is a commonly used analytical method for characterizing medications and excipients in pharmaceutical sciences. Detecting vibrations in chemical bonds when exposed to infrared (IR) radiation, gives vital information on molecular structures. The resulting FTIR spectrum is a crucial tool for structural identification, purity evaluation, polymorphism analysis, and drug-excipient compatibility investigations since it acts as a distinct fingerprint of a chemical. (JASCO FT/IR- 4600, Japon) used and the spectra was recorded in the wavelength range of 4000 cm^{-1} to 400 cm^{-1} with the KBr pellet technique. The procedure entails distributing the sample in potassium bromide (KBr) and compressing it into a disc by applying a pressure of 50 kg/cm^2 using a hydraulic press (Nagpal *et al.*, 2016)

Differential Scanning Calorimetry (DSC)

Shimadzu DSC-60A plus Series (Japan) was used for DSC thermogram analysis. Software "LabSolution TA, version 1.01 SP1" assessed the figure (peak area and integration). Samples with weights ranging from 3 to 5 mg were positioned in flat-bottomed aluminum pans and subsequently sealed hermetically with aluminum lids utilizing a pan press (Thermal Scientific Inc, Amarillo, TX). The pan was gradually heated from 20 to 300°C at 10°C/min. The reference standard was an empty sealed aluminum crucible.

Solubility Study of DOM in Different Oils, Surfactants, and Co-Surfactants:

The solubility of DOM was systematically analyzed in a range of oils, surfactants, and cosurfactants. A glass tube was filled in each case with 3 mL of each vehicle and subjected to an excess amount of DOM. Glass tubes were then placed in a thermostatically controlled vibrating shaker bath (Stuart Scientific, SBS30, U.K.) at 25 ± 0.5 ◦C for 72 hours for proper mixing after their preparation with vortex mixer (ISOLAB, Germany). The contents of each vial were centrifuged and then filtered by 0.45 µm syringe filter. Absolute ethanol was then added for dilution and subsequent determination of drug content by using UV-spectrophotometry (Shimadzu 1900, Japan) at DOM's maximum wavelength of 286 nm. The experiments were performed thrice (A. Ahmed *et al.*, 2022; Qader *et al.*, 2022).

Construction of Pseudo-Ternary Phase Diagram:

Pseudo-ternary phase diagrams were utilized to optimize the oil ratios in terms of the $S._{mix}$ (surfactant to co-surfactant ratio). The diagram was prepared at room temperature using the aqueous titration process to evaluate the concentration of the components for the present range of SNEDDS. The selection of oil, surfactants, and cosurfactants was done after conducting miscibility studies and then arranged in various combinations for the evaluation of phases. Various combinations of the surfactant/cosurfactant mixtures ($S._{mix}$) in varying proportions of 1:1, 1:2, 2:1, and 3:1 were used for emulsification of the chosen oil. Phase diagrams were established through vortexing of mixed volume ratios of oil and $S._{mix}$ (9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9) in a glass tube to get an emulsion mixture in the clear and homogeneous form in the solution state, then titrated with the aqueous solution. Phase clarity evaluation of the mixture of lipid and $S._{mix}$ was performed through visual observation (Hussein & Qader, 2021; B. Nair *et al.*, 2022). The volume of water required to induce a phase transition from clarity to turbidity was documented, and pseudo-ternary charts were generated utilizing the ProSim drawing tool (Taher *et al.*, 2015). All the ratios in this study are reported as Volume-to-volume ratios (*v/v*%).

Preparation of DOM loaded Liquid- SNEDDS:

After identifying the self-nano emulsifying region, SNEDDS formulations were made with the appropriate component ratios. Several effective SNEDDS formulae were

created, and DOM concentration was maintained at the same level in each mix. Five milligrams of DOM dissolved in 1 ml of each SNEDDS formulation.

In short, a vortex mixer was used to thoroughly mix oil, surfactant, and co-surfactant after they had been accurately weighed and placed in a stoppered glass tube (Nasr *et al.*, 2016; Dalal *et al.*, 2021). The oil and S_{mix} mixture was mixed with a certain amount of DOM until the medicine was fully dissolved *v/v%* (Mittal *et al.*, 2025). Formulas were then prepared and kept at room temperature until used again.

Characterization and Evaluation of DOM-Loaded Liquid SNEDDS:

The subsequent characteristics were employed to assess the formulations.

Thermodynamic Stability Study:

The SNEDDS formulations were centrifuged, heat-cooled, and freeze-thawed. The formulations' physical properties were visually examined after each procedure for six cycles. For the heating-cooling cycle test, the formula was held at 45 ± 1°C and 25 ± 1°C for 24 hours. The formulas that passed heating- cooling test and underwent freeze-thaw and stress testing. Six freeze-thaw cycles were performed between -20 ±2°C and 25 ±1°C with at least 24 hours of storage time at each temperature. After 20 minutes of centrifugation at 4000 rpm, formulas showing no cracking, creaming, and phase separation indicated stability (Hussein & Qader., 2021).

Robustness to Dilution:

Studying how dilution affects emulsion properties allowed for the simulation of in-vivo dilution behaviours. The test involved the combination of 1 mL of formulation with media at dilutions of 10, 100, and 1000 times, employing pure water, 0.1 N HCl, and phosphate buffer at pH 6.8 within a beaker, while employing a magnetic stirrer to maintain continuous stirring at 100 rpm (Qader *et al.*, 2022) At 37 ± 0.5 °C, the media's temperature was maintained and then placed to be kept in volumetric flasks. This test was conducted to confirm that the formulation was homogeneous. After being kept for a full day at room temperature, the visual examination was performed on the systems that were received to look for indications of phase separation, turbidity, or precipitation (Nasr *et al.*, 2016; B. Nair *et al.*, 2022).

Determination of the Efficiency of Self-Emulsification:

A USP dissolving apparatus type II assessed the produced formulation's self-emulsification effectiveness. To conduct the test, 500 mL of distilled water was mixed with 1 mL of the formulation in a beaker. The paddle was rotated at 50 rpm to provide mild agitation. The last view of the nano-emulsion and the rate of emulsification were used to visually evaluate the created formulations (Mohite *et al.*, 2024).

A grading system was utilized to visually assess the formulation's *in-vitro* performance:

Grade A: These systems effectively form a clear and transparent nanoemulsion in one minute.

Grade B: Production of a lower clear nanoemulsion.

Grade C: Development of milky emulsion in 2 minutes.

Grade D: Suboptimal white emulsion formed, with more than 2 minutes of emulsification required.

Grade E: Development of substantial oil globules demonstrating inadequate emulsification

Self-Emulsification Time:

Emulsification time for all SNEDDS recipes (1 mL) was evaluated in 300 mL of water at 37±0.5°C. The components were gently mixed with a magnetic stirrer at a steady speed of 100 rpm. The amount of time needed to emulsify SNEDDS formulations and create nano-emulsion was recorded in seconds (Buya *et al.*, 2020 ; Nasr *et al.*, 2016).

Turbidity Measurement (% of Transmittance)

A UV-visible double-beam spectrophotometer (Shimadzu-1900, Japan) was utilized to measure the transmittance of diluted samples (100-fold with water) at 650 nm in triplicate using spectrophotometry. Distilled water was used as a blank (Nasr *et al.*, 2016).

Surface Morphology:

TEM was utilized to assess the surface morphology of optimized SNEDDS. Samples underwent a one hundredfold dilution with distilled water prior to analysis. A droplet of the resulting nanoemulsion on a Carbon-Cu grid was treated with two percent phosphotungstic acid. At 70-90kV, the (PHILIPS, CM120, The Netherland) was used for the analysis (Ke *et al.*, 2016).

Globule size and Poly Dispersity Indes (PDI)

The size of the globule regulates the degree and speed of drug release and absorption and is hence an essential factor in the self-emulsification efficacy. Each of the SNEDDs was diluted one hundred times using distilled water before it was measured using one- millilitre of the formulation. The PDI value shows the homogeneity of the size of particles in the formulation. Improved stability of the nanoemulsion is ensured by globules of uniform size (Eleftheriadis *et al*., 2019 ; Verma & Kaushik., 2020).A Zeta Sizer (Anton Paar Instrument, Austria) was employed to evaluate the globule size and PDI of SNEDDS.

Zeta potential:

The Zeta potential of SNEDDS was evaluated through the measurement of electrophoretic mobility. using one ml of each SNEDDS diluted hundred time with distil water. Assessments were conducted using an Anton Paar Zeta sizer, through using (Litesizer DLS/ Anton Paar) cuvette (Verma & Kaushik., 2020; Eleftheriadis *et al*., 2019).

Drug Loading Efficacy:

For the estimation of DOM concentration, 1 mL of the SNEDDS solution with 5 mg of DOM was diluted in volumetric flasks using absolute ethanol and well-mixed by inverting and shaking the flasks two to three times (Qader *et al.,* 2022). Three triplicates were prepared and drug concentration was found after appropriate dilution at 286 nm by using the UV-visible spectrophotometric method (Shimadzu 1900- Japan) (Nasr *et al.*, 2016). Drug loading efficiency was calculated using formula (1):

$$\text{Drug loading efficiency (\%)} = \frac{\text{DOM content in 1ml SNEDDS}}{\text{Actual amount of DOM initially added to SNEDDS}} * 100 \quad (1)$$

***In-vitro* DOM- SNEDDS Release Study:**

Utilizing USP type II (Paddle type) dissolution equipment (Pharma Test, PT-DT7, Germany), *in- vitro* drug release study

was conducted. Free gelatine capsules (size "00") containing 10mg of DOM were used to fill SNEDDS, the samples were then placed in 900 mL of 0.1 N HCl dissolution media and set in at 37 ± 0.5 °C. The paddle speed was held at 50 rpm all the time. A 5 ml aliquot was removed at 5, 10, 15, 30, 45, 60, 90, and 120-minute intervals and then filtered through 0.45µm membrane filters. The concentration of DOM was quantified via spectrophotometry (Shimadzu-1900) at a wavelength of 284 nm. The created optimized batch's dissolving profile was contrasted with that of the marketed product and the pure drug (Laddha *et al*, 2014; Nasr *et al.*, 2016). A statistical analysis of the *in- vitro* release data was conducted utilizing the similarity factor (*f*2). The *f*2 test results vary from 0 to 100, Two dissolution profiles were deemed similar when the *f*2 value is equal to or greater than 50. the release patterns of the optimized SNEDDS formulations were compared to a reference (Marketed DOM) (El-Sayyad *et al.*, 2017). The equation of similarity factor proposed by Moore and Flanner is represented in equation (2).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t) \right]^{-0.5} \times 100 \right\} \quad (2)$$

Where n= the number of time intervals at which the % of dissolution was assessed.

Rt = the % dissolved of one formulation at a specific time point

Tt = denotes the % dissolved of the formulation to be compared at the identical time point.

3. RESULTS

Characterization of Domperidone:

Preparation of A Calibration Curve:

Based on λ max at a wavelength of 286 nm (Figure 2), by UV spectroscopy (Shimadzu 1900- Japan). Using absolute ethanol as blank. The calibration curve of DOM in absolute ethanol was constructed (Figure 3). The plots showed good linearity between concentration and absorbance, the correlation coefficient obtained was 0.9987, and the linear regression equation of (y = 0.0293x - 0.0087) (Singh and Rai, 2013).

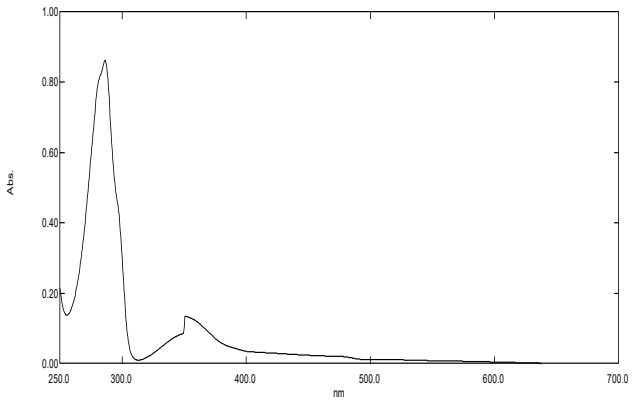


Figure 2: Lambda max of drug in absolute Ethanol

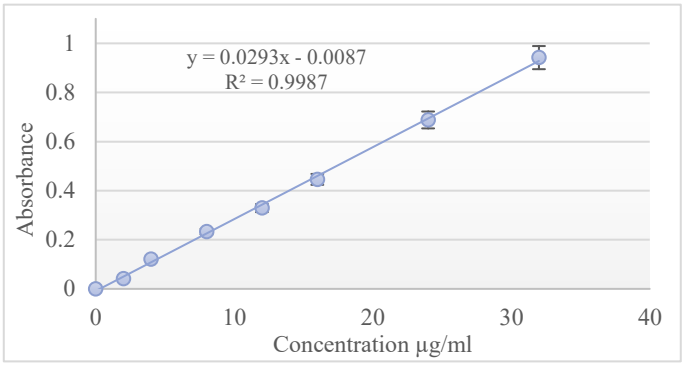


Figure 3: Calibration Curve of a drug in absolute Ethanol.

Fourier Transform Infrared Spectroscopy (FTIR)

The DOM IR Spectrum confirms functional groups with unique peaks. Peaks at 3016.12 cm^{-1}, 2935.13 cm^{-1}, and 2819.42 cm^{-1} indicate aromatic and aliphatic C-H stretching vibrations. The peak at 1685.48 cm^{-1} is due to the amide functional group stretching with (C=O), a crucial part of DOM's structure. C-N stretching causes the 1265.07 cm^{-1} and 1212 cm^{-1} peaks, confirming the presence of the benzimidazole ring. The bands confirm the drug's aromatic character at 833.87 cm^{-1} and 728.84 cm^{-1} of aromatic C-H out-of-plane bending vibrations (Bhatia *et al.*, 2024). FTIR spectra of pure DOM appear in Figure 4.

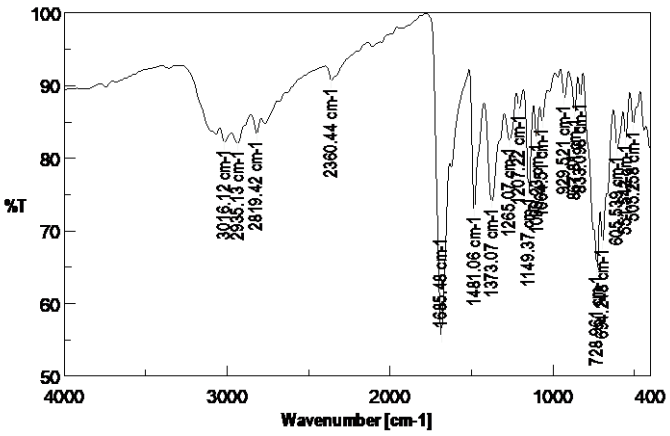


Figure 4: FTIR spectra of pure DOM

Differential Scanning Calorimetry (DSC)

The thermal behaviour of DOM displayed a clear sharp endothermic peak at 248.28 °C, which was corresponding to its melting point, indicated high crystallinity of pure drug (Bhatia *et al.*, 2024) as appear in (Figure 5).

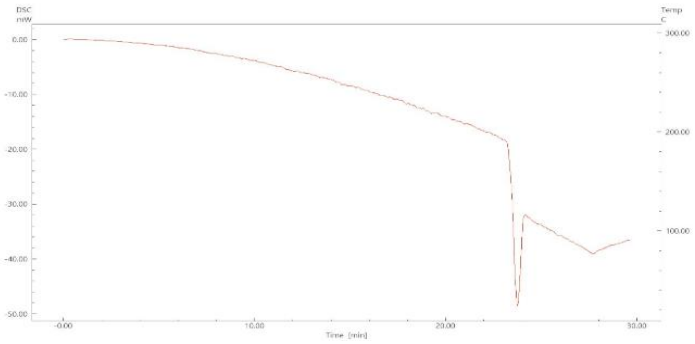
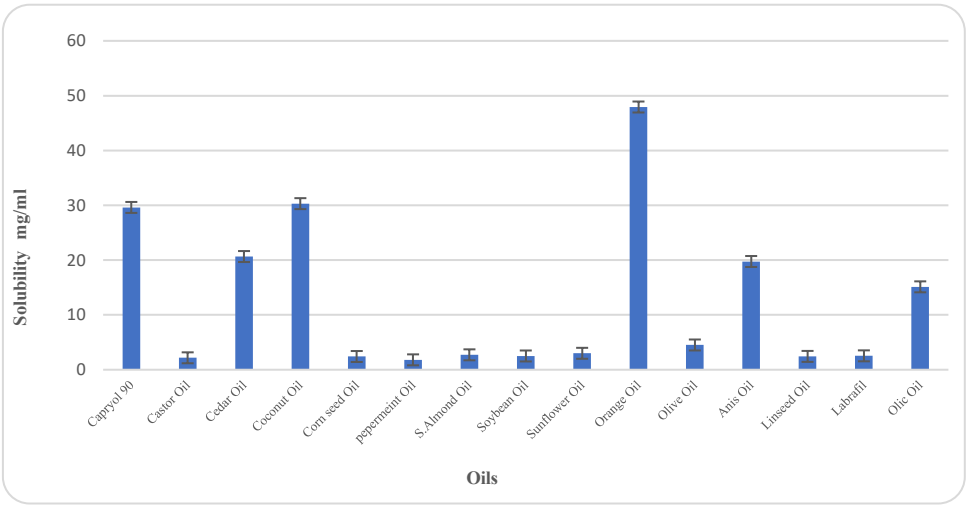


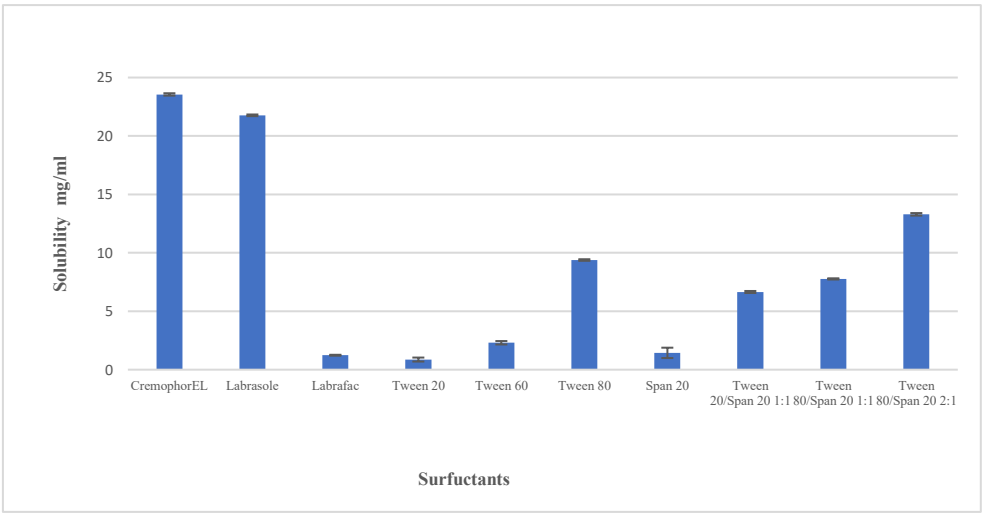
Figure 5: Differential scanning calorimetry of pure DOM

Study of the solubility of DOM in various oils, surfactants, and co-surfactants:

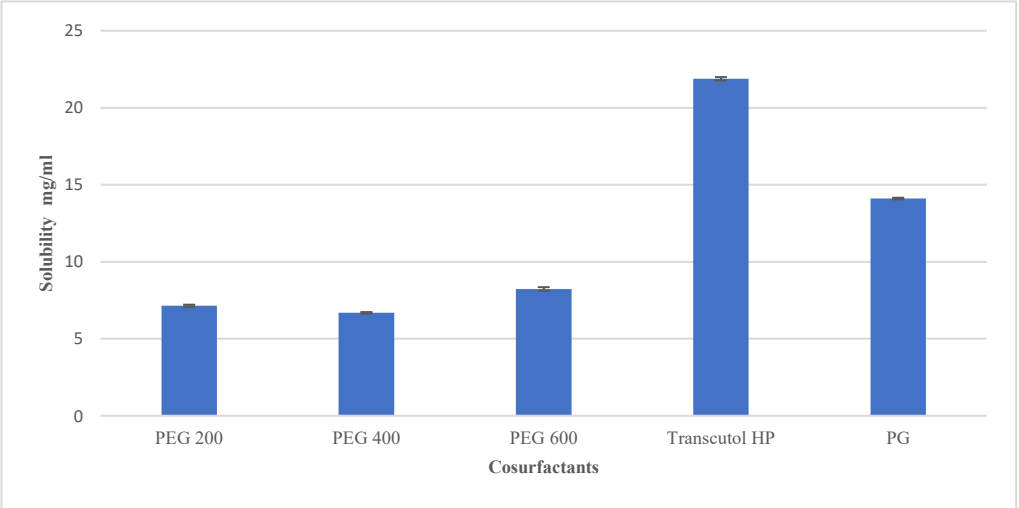
(Figure 6 A, B and C) depicts the solubility of DOM across various oils, surfactants, and co-surfactants.



(A)



(B)



(C)

Figure 6: Solubility of DOM in (**A**) in various oils; (**B**) in various surfactants; (**C**) cosurfactants.

Development of A Pseudo-Ternary Phase Diagram :

Based on the miscibility study, various S.$_{mix}$ ratios (1:1, 1:2, 2:1, 3:1) were used to create phase diagrams, and it was discovered that varied S.$_{mix}$ mapped distinct nanoemulsion regions (isotropic regions). Different phase diagrams were created for different formulation possibilities.The dimensions of the nanoemulsion zone in the diagrams were compared; a larger size correlates with enhanced self-nanoemulsification efficiency (Nasr *et al.*, 2016). Figure 7 shows phase diagrams for successful formulation, prepared latterly, labelled as (F1 to F12).

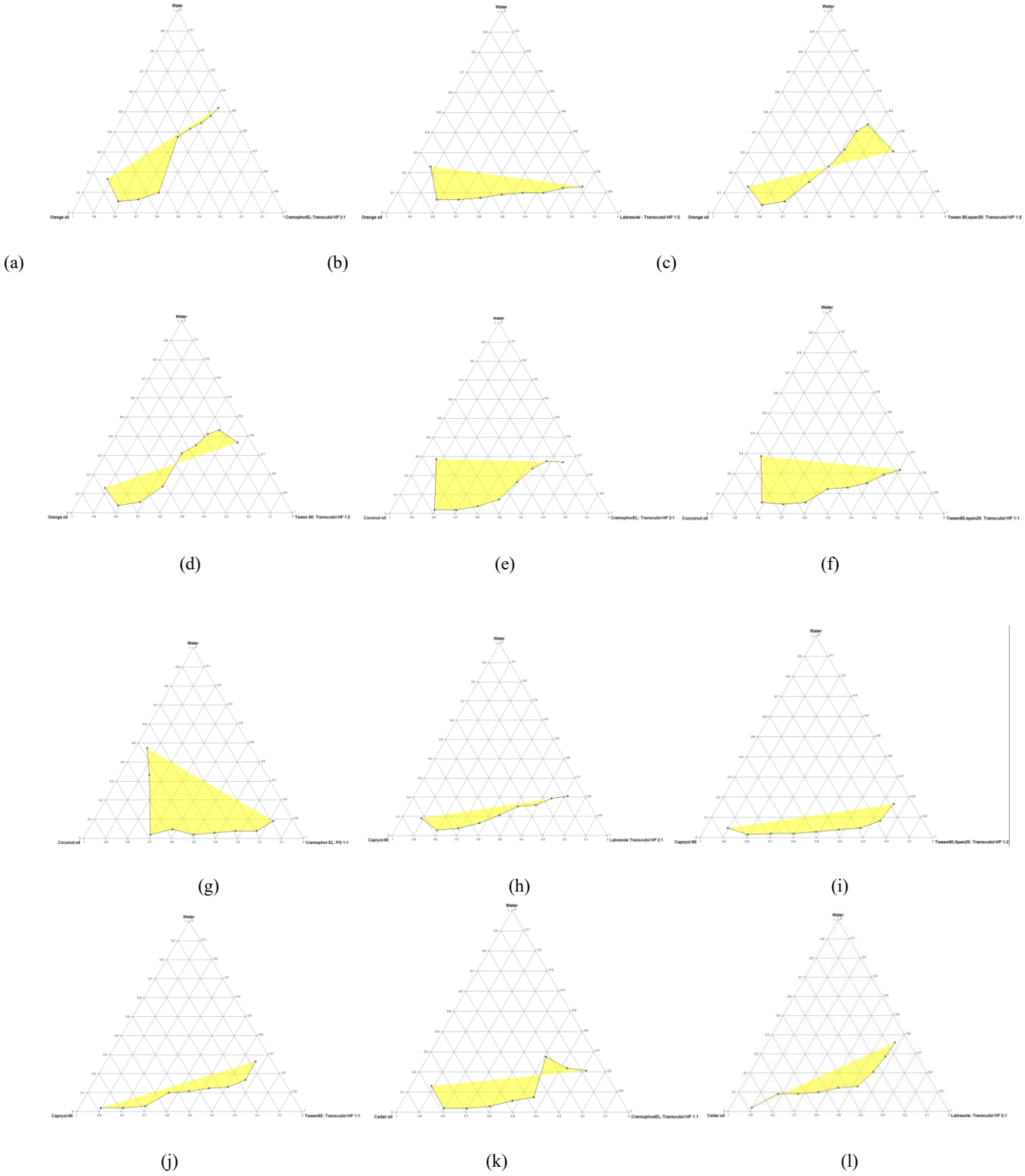


Figure 7: Pseudo-ternary phase diagram for a. F1, b. F2, c.F3, d.F4, e.F5, f. F6, g. F7, h. F8, i. F9, j. F10, k. F11, and l. F12

Preparation of DOM Liquid- SNEDDS:

Twelve formulations were developed through formulation optimization and the pseudo tertiary phase diagram, utilizing 378 formulation possibilities. Figure 8 shows all 12 most successful formula images. The oil, surfactant and cosurfactants were precisely weighed and mixed in a stopper glass tube using a vortex mixer to produce a homogeneous mixture. DOM was mixed with the oil and S.mix using continuous stirring until the drug was fully dissolved; the proportions of the excipients are given in Table 1. Formulations were left at room temperature for storage until required, ensuring that the medication quantity in each formulation remained stable at 5 mg of DOM per ml of SNEDDS (Mittal *et al.*, 2025 ; Nasr *et al.*, 2016).

Table 1: Optimized content of excipients of DOM liquid SNEDDS

Formulas	Oil	Surfactant	Co-surfactant	S.*mix*	Oil: S.*mix* ratio	Oil *(v/v%)*	Surf. *(v/v%)*	Co-surf. *(v/v%)*
F1	Orange	Cremophor EL	Transcutol HP	2:1	2:8	20	53.33	26.67
F2	Orange	Labrasole	Transcutol HP	1:2	2:8	20	26.67	53.33
F3	Orange	Tween80:Span20	Transcutol HP	1:2	2:8	20	26.67	53.33
F4	Orange	Tween 80	Transcutol HP	1:2	2:8	20	26.67	53.33
F5	Coconut	Cremophor EL	Transcutol HP	2:1	2:8	20	53.33	26.67
F6	Coconut	Tween80:Span20	Transcutol HP	1:1	2:8	20	40	40
F7	Coconut	Cremophor EL	(PG)	1:1	2:8	20	40	40
F8	Capryol-90	Labrasole	Transcutol HP	2:1	2:8	20	53.33	26.67
F9	Capryol-90	Tween80:Span20	Transcutol HP	1:2	2:8	20	26.67	53.33
F10	Capryol-90	Tween 80	Transcutol HP	1:1	2:8	20	40	40
F11	Cedar	Cremophor EL	Transcutol HP	1:1	2:8	20	40	40
F12	Cedar	Labrasole	Transcutol HP	2:1	2:8	20	53.33	26.67

Figure 8: DOM loaded liquid -SNEDDS formulas

Description and Assessment of DOM-Loaded Liquid SNEDDS:

Study of Thermodynamic Stability:

Physical stability testing was conducted to assess the resulting compositions' stability at both low and high temperatures and high shear. The result is demonstrated in Table 2.

Robustness to Dilution:

Results of the robustness to dilution test, presented in Table 2, demonstrated that most formulations remained stable when diluted with deionized Water, 0.1 N HCL, and phosphate buffers adjusted to pH 6.8.

Assessment of Self-Emulsification Efficiency:

Table 2 presents the outcomes of a visual assessment of the formulations' *in-vitro* performances, utilizing the grading system previously specified from A to E (Nasr *et al.*, 2016).

Self-Emulsification Time:

The result of self- emulsification time is shown in Table 3, ranging from (13.75 to 32.17 seconds). And visual observations of the formulations show that most formulations rapidly formed clear nanoemulsions within less than one minute.

Turbidity Measurement (% of Transmittance)

A 100-fold dilution with distilled water revealed that the DOM SNEDDS formulations' percentage transmittance ranged from 99.983% ± 0.055 to 24.367 ± 0.208, as indicated in Table 3.

Surface Morphology by Transition Electron Microscopy (TEM)

Figure 9 displays TEM images of Four DOM-loaded successful SNEDDSs (F1, F4, F5, and F7) based on previous characterization studies.

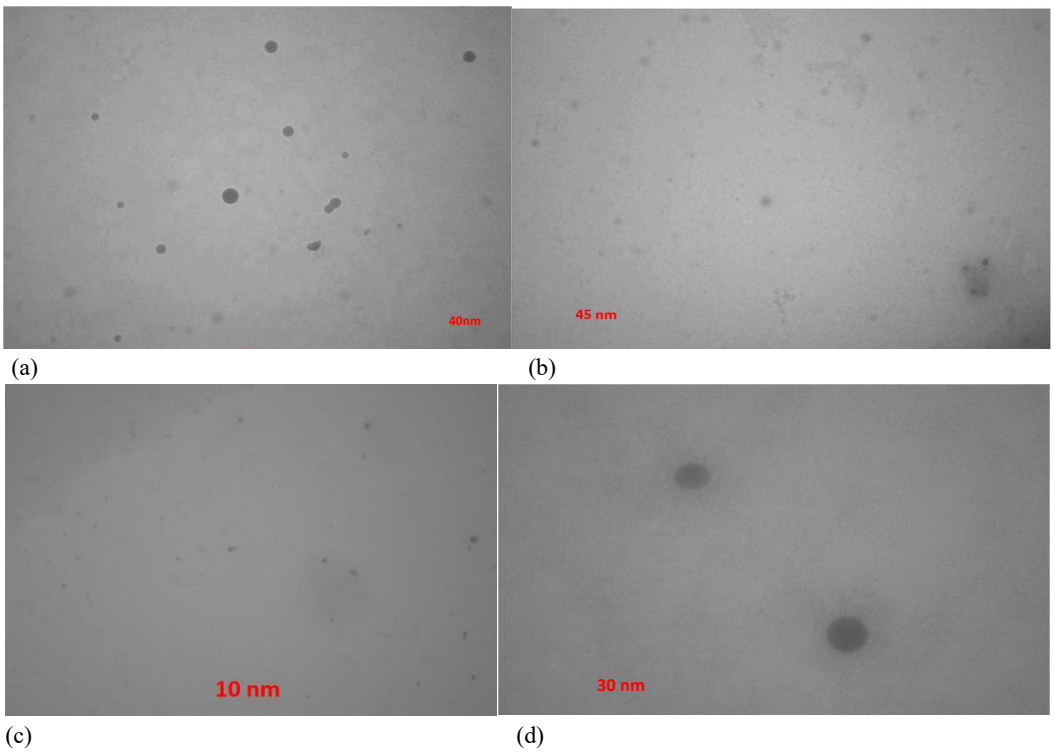


Figure 9: TEM photograph for (a) F1, (b) F4, (c) F5, and (d) F7.

Globule Size and (PDI) Determination:

From 12 formulations, eight formulation sizes at the nanosized region below 200 nm, globule size for all formulations shown in Table 3. The PDI for all formulas between (0.28 ± 0.03 to 0.68 ± 0.2) below one, all within the accepted range. PDI for all formulas detected in Table 3. Four successful formulations (F1, F4, F5, and F7) based on previous characterization studies chosen for *In-vitro* drug release profile, particle diameter (nm) for these Formulas were shown in Figure 10.

Zeta potential:

Table 3 presents the zeta potential values for each formulation, which were observed to fall within the range of (-0.07 ± 0.1 to -12.7 ± 0.078 mV), zeta potential diagram for (F1, F4, F5, and F7), were cleared in Figure 11.

Drug Loading Efficacy:

The efficiency of drug loading varied between 87.94% and 103.32%, indicating their results in Table 3. demonstrating that the formulations effectively incorporated substantial quantities of DOM.

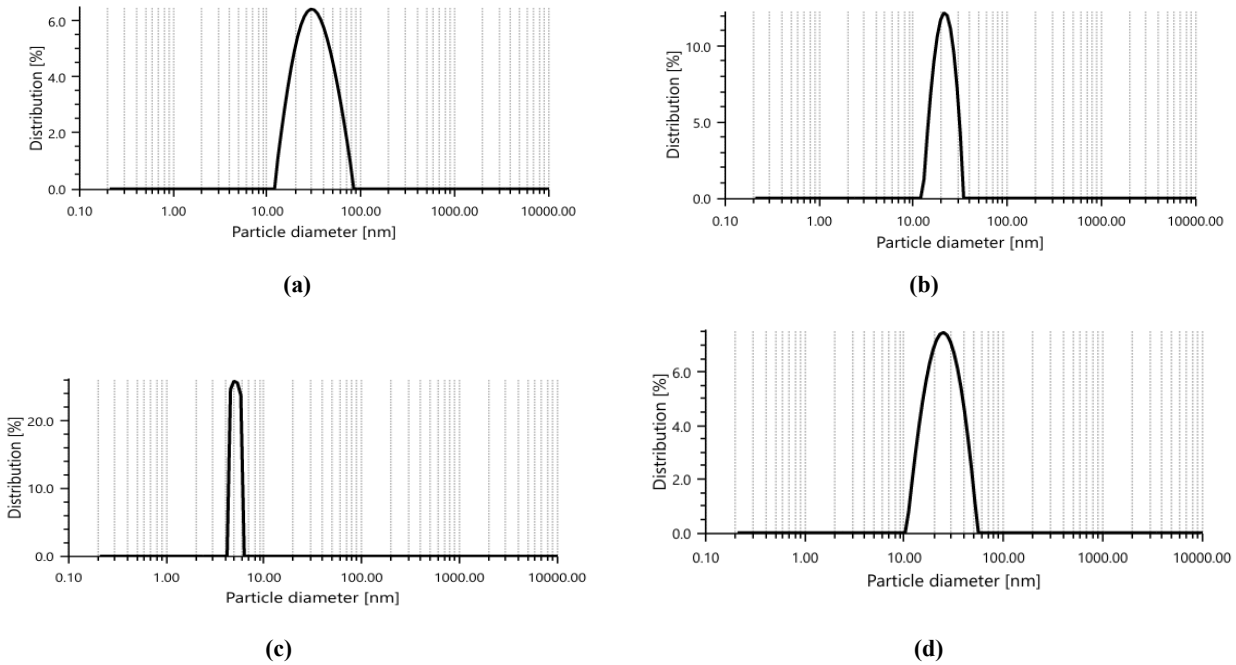


Figure 10: Globule size in nm for (a) F1, (b) F4, (c) F5, and (d) F7

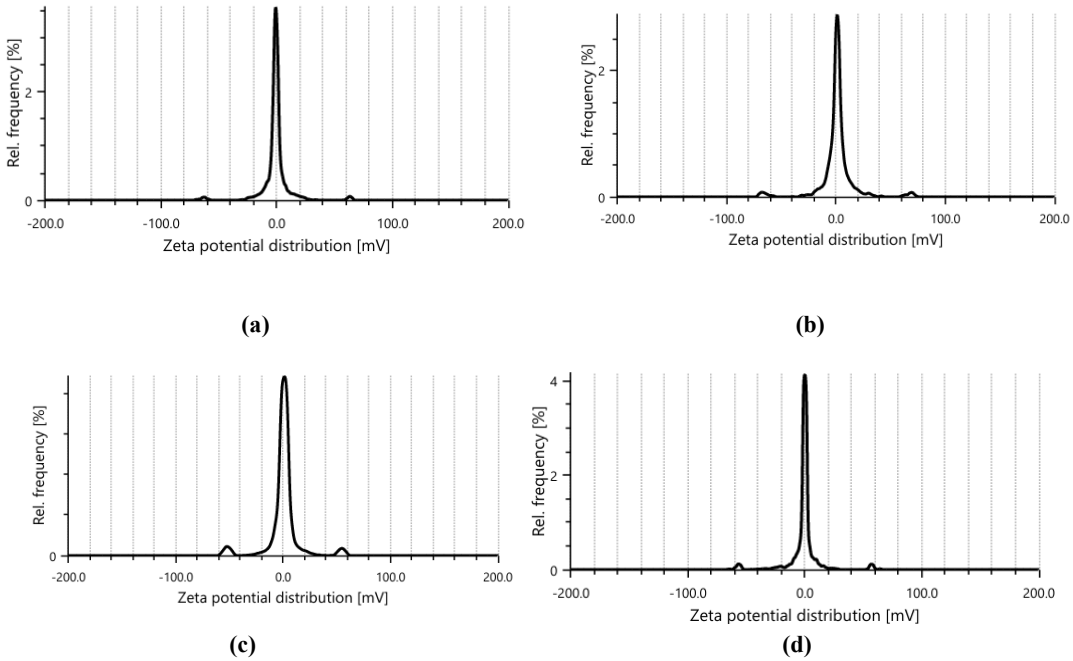


Figure 11: Zeta potential for (a) F1, (b) F4, (c) F5, and (d) F7

Table 2: Thermodynamic studies, the efficiency of self-emulsification, and robustness to dilution of DOM- loaded liquid SNEDDS

Form.	Heat-Cool Cycles	Freeze-Thaw Cycles	Centrifugation Test	Grade	Deionized water			0.1 N HCL			Phosphate buffer pH 6.8		
					10	100	1000	10	100	1000	10	100	1000
F1	√	√	√	**A**	√	√	√	√	√	√	√	√	√
F2	√	√	√	B	χ	χ	χ	χ	χ	χ	χ	χ	χ
F3	√	√	√	A	χ	χ	√	χ	χ	√	χ	χ	√
F4	√	√	√	**A**	√	√	√	√	√	√	√	√	√
F5	√	√	√	**A**	√	√	√	√	√	√	√	√	√
F6	√	√	√	A	√	√	√	√	√	√	√	√	√
F7	√	√	√	**A**	√	√	√	√	√	√	√	√	√
F8	√	√	√	B	χ	χ	√	χ	χ	√	χ	χ	√
F9	√	√	√	B	χ	χ	√	χ	χ	√	χ	χ	√
F10	√	√	√	A	χ	√	√	χ	√	√	χ	√	√
F11	√	√	√	A	χ	√	√	χ	√	√	χ	√	√
F12	√	√	√	B	χ	χ	χ	χ	χ	χ	χ	χ	χ

The (√) indicates that the formulations passed the test, with no precipitation, phase separation cloudiness, or turbidity& and the (χ) mean phase separation or turbid

Table 3: Self-emulsification time, % transmittance, Drug Loading Efficacy of drug-loaded formulas, globule size, PDI, zeta potential for DOM-L-SNEDDS

Formulation	Self- Emulsification time	%Transmittance	Drug Loading Efficacy (%)	Globule size (nm)	PDI	Zeta Potential (mV)
F1	**21.44 ± 0.05**	**97.83 ± 0.31**	**103.32 % ± 0.11**	**37.52 ± 2.26**	**0.28 ± 0.03**	**-0.23 ± 0.23**
F2	39.02 ± 0.71	67.63 ± 0.15	89.53% ± 0.18	240.73 ± 4.1	0.35 ± 0.01	-8.4 ± 0.87
F3	24.13± 0.16	81.17 ± 0.51	88.01% ± 0.19	159.9 ± 3.41	0.29 ± 0.001	-0.37 ± 0.21
F4	**18.71± 0.57**	**99.86 ± 0.05**	**93.71% ± 0.004**	**42.55 ± 3.09**	**0.68 ± 0.2**	**-0.13 ± 0.06**
F5	**23.95± 0.15**	**97.47 ± 0.35**	**97.44% ± 0.28**	**5.45 ± 0.39**	**0.67 ± 0.37**	**-0.03 ± 0.06**
F6	18.17 ± 0.33	96.63 ± 0.15	94.01% ± 0.099	31.59 ± 0.82	0.29 ± 0.013	-0.1 ± 0.1
F7	**32.17± 1.19**	**97.43 ± 0.30**	**100.7% ± 0.102**	**16.68 ± 0.64**	**0.55 ± 0.48**	**-0.07 ± 0.1**
F8	24.28 ± 0.46	54.45± 0.97	87.94% ±0.29	171.5 ± 2.5	0.44 ± 0.14	-10.17 ± 0.65

F9	13.75 ± 0.53	55.28 ± 0.27	88.91% ± 0.003	421.6 ± 3.83	0.31 ± 0.02	-1.9 ± 0.81
F10	15.2 ± 0.52	98.13 ± 0.29	91.57% ± 0.09	139.97 ± 4.43	0.34 ± 0.04	-0.27 ± 0.03
F11	19.07 ± 0.16	95.2 ± 0.89	94.88% ± 0.13	342.2 ± 2.05	0.31 ± 0.03	-12.7 ± 0.078
F12	21.78 ± 0.44	24.37 ± 0.21	95.3% ± 0.043	241.03 ± 1.96	0.33 ± 0.08	-11.1 ± 0.17

- Value expressed as mean ± SD, n=3

***In-vitro* DOM SNEDDS Release Study:**

The *in-vitro* drug release study (Figure 12) demonstrated the release profile of DOM SNEDDS formulations (F1, F4, F5, and F7). Concerning the pure medication and commercially marketed tablet. The SNEDDS formulations demonstrated a markedly superior Comparison of medication release profiles between pure DOM and commercially available tablets, F1, F4, F5, and F7 formulas showed greater than 70% of drug release at first 30 minutes, and with specific formulations like F1 and F4 facilitating up to 95% drug release within a 120-minute timeframe. It was obvious that all of the SNEDDS had *f*2 values (similarity factor) that were lower than 50, which indicates that they were not similar to reference (Sabri & Hussien, 2020)

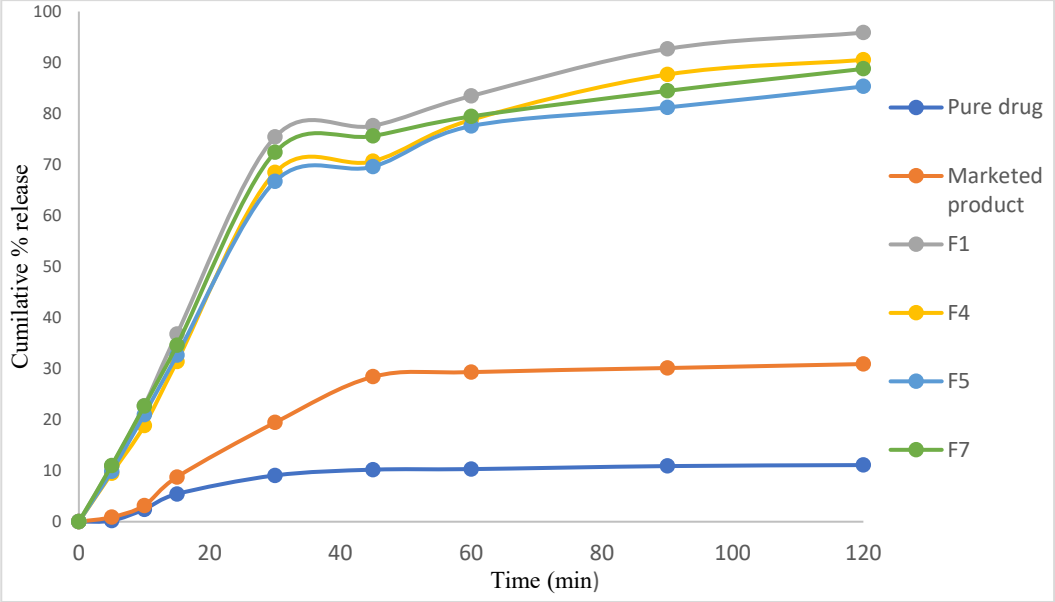


Figure 12: The graphical depiction illustrates the *in- vitro* release profile of DOM SNEDDS in 0.1N HCl is compared to that of the pure drug and the marketed product

4. DISCUSSION

DOM powder purity was measured by recording melting point (242-244 C^0), and DSC thermogram show a distinct endothermic peak at 248.28 °C, corresponding to the melting point, indicates the great crystallinity of the pure substance (Bhatia *et al.*, 2024). Solubility study of drug applied in a wide a range of vehicles to select proper oils, surfactants, and cosurfactants with maximum solubility.

The oil phase is crucial for keeping the medication solubilized in the formulation and preventing its precipitation (Modi *et al.*, 2023). Solubility studies highlighted the superior solubilizing potential for DOM in orange oil; drug solubility was (47.94 ± 0.085 mg/ml). orange oil, exhibits a strong affinity for lipophilic compounds, rendering it an effective solvent for poorly water-soluble drugs, this may be attributed to the medium chain length (ten carbons) (Mayta & Rodríguez, 2018). then, followed by coconut oil at 30.3 ± 0.148mg/ml, capryol-90 29 ± 0.046 mg/ml, and cedar oil 20.65 ± 0.31mg/ml among other various oils tried. Surfactants play an essential role in SNEDDS by reducing interfacial tension, which aids in the dispersion mechanism and creates a flexible film around the globules. Non-ionic hydrophilic surfactants are regarded as more appropriate than ionic surfactants for the formulation of nanoemulsions. Mainly because they exhibit lower toxicity compared to ionic surfactants (Nagi *et al.*, 2017). The study revealed that Cremophor EL exhibits a DOM solubility of (25.55 mg/mL ± 0.102), marking it as the highest among the tested substances (Laddha, *et al*, 2014). Cosurfactants reduce the bending stress present at the oil/water interface (Nasr *et al.*, 2016). Transcutol HP as cosurfactant shows the greatest DOM solubility (Abd-Elhakeem *et al.*, 2019).; followed by Propylene glycol (PG). These vehicles were selected to prepare several effective SNEDDS formulas, at different $S._{mix}$ ratios, based on a miscibility study that was conducted to evaluate the clarity, turbidity, and phase separation of a variety of oils in the presence of a variety of surfactants and co-surfactants at varying ratios.

Pseudo- ternary phase diagrams were developed to delineate self-nanoemulsifying regions and to determine appropriate concentrations of oil, surfactant, and cosurfactant for the formulation of SNEDDS (Nasr *et al.*, 2016; Qader *et al.*, 2022). The nanoemulsion phase was recognized as the area in which clear and transparent formulations were achieved upon dilution, as determined through visual inspection of the samples. Pseudo-ternary phase diagrams indicated that the region designated for nanoemulsion (the yellow area) was most extensive in the formulae have 1:1, and 2:1 ratio rather than 1:2 ratio duo to use high amount of surfactants, Tween 80, and Cremophor EL with

high HLB value, could emulsify oil better in oil- water interphase (Rathore *et al.*, 2022).

Based on formulation optimization and Pseudo- ternary phase diagrams, through utilizing 378 formulation possibilities. Twelve most successful formulas were created and labelled as F1to F12, the medication quantity in each formulation remained stable at 5 mg of DOM per ml of SNEDDS (Table 1) details the content of each formula.

Freeze-thaw cycles, centrifugation, and heat-cool cycles among the thermodynamic stability tests validate that the SNEDDS formulations loaded with DOM are stable under stress and different conditions. Ensuring that the SNEDDS does not phase separate or drug precipitate upon storage and transportation depends on the stability of formulations at various temperatures and mechanical conditions (Nasr *et al.*, 2016)**.** The robustness to dilution indicates the formulations' capacity to maintain stability without precipitating or forming distinct phases separation after dilution, as it is crucial for their performance in the gastrointestinal tract (Buya *et al.*, 2020). Our findings show these formulations contain labrasole, and span 20 as surfactant, formed less clearly nanoemulsion compared to others. The self-emulsification time (ranging from 13.75 to 32.17 seconds) and visual observations of the formulations show that most formulations rapidly formed clear nanoemulsions, indicating the efficient self-emulsifying properties of the SNEDDS. Their result is shown in Table 3. This rapid formation is key to ensuring the drug is quickly available for absorption after oral administration, improving its bioavailability (Abd-Elhakeem *et al.*, 2019). Percentage (%) of transmittance, ranged from 99.983% ± 0.055 to 24.367 ± 0.208, their result matches with robustness to dilution, formulation makes less clear nano emulsion have lower transmittance (Nasr *et al.*, 2016; Qader *et al*., 2022)**.**

TEM photographs show clear particles that there was no globule aggregation and that the globules of all formulae were evenly distributed. TEM investigation demonstrated that all selected successful four formulae produced uniform, spherical droplets <50 nm, meeting the nanometric size range requirements for nanoemulsifying formulae (Nasr *et al.*, 2016). Droplet size is one of the most important SNEDDS performance component since it affects both the absorption drug and the rate and amount of drug release. Also, it has been noted that the interfacial surface area increases with decreasing particle size, potentially improving bioavailability and accelerating absorption. Systems meeting the SNEDDS criterion have a mean droplet size of less than 200 nm (Nasr *et al.*, 2016).From twelve formulations, eight formulation sizes at the SNEDDS region below 200 nm, globule size for all formulations shown in Table 3, and particle size (nm) showed in (Figure 10).

The poly-dispersibility index (PDI), a dimensionless metric that ranges from 0.0 to 1.0 and represents particle homogeneity, is utilized to represent the distribution of droplet sizes. A greater homogeneity of particles results in a PDI score approaching zero. The PDI for all formulas between (0.28 ± 0.03 to 0.68 ± 0.2) below one, all within the accepted range (Taher *et al.*, 2015). PDI for all formulas detected in Table 3. The stability of colloidal dispersions is contingent upon the zeta potential, which underscores its significance. For smaller globules, a high zeta potential will indicate electrical stability, as an increase in surface charge counteracts particle aggregation (Verma & Kaushik., 2020). Zeta potential values were found to be in the range of (-0.03 ± 0.06 to -12.7 ± 0.078 mV), indicating that the formulations exhibit low negative charge, this low negative charge for formulas due to the use of non-ionic surfactants that create a -vely charged interface at neutral pH (Abd-Elhakeem *et al.*, 2019; Verma and Kaushik, 2020). Non-ionic surfactants stabilize the particle by stearic hindrance rather than electrostatic repulsion (Nasr *et al.*, 2016). Drug loading efficiency varied between 87.94% and 103.32%, demonstrating that the formulations effectively incorporated substantial quantities of DOM, essential for optimizing therapeutic efficacy and reducing the necessary formulation volume. High drug loading efficiency indicates the formulation's ability to deliver an adequate dose within a reduced volume, which is crucial for patient compliance and administration convenience (Qader & Hussein, 2021). Based on previous characterization studies four successful formulations (F1, F3, F5, and F7) chosen for *in-vitro* drug release profile.

The *in-vitro* drug release profile (Figure 12) of four effective DOM SNEDDS formulations (F1, F4, F5, and F7) was analysed in comparison to the pure drug and commercial tablets. The SNEDDS formulations demonstrated significantly enhanced drug release relative to pure DOM and marketed tablets, with formulations such as F1 and F4 allowing for up to 95% drug release within 120 minutes. The nanoemulsion's capacity to expand the drug's surface area, facilitating speedier absorption and dissolution, is responsible for this improved release (Mohite *et al.*, 2024; Laddha *et al.*, 2014) The results are consistent with prior research showing the superiority of SNEDDS in improving the bioavailability of poorly soluble medications (Laddha *et al.*, 2014). The similarity factor ($f2$) was computed to see if the dissolution profile of SNEDDS formulations would resemble that of the commercial tablets. The ($f2$) calculation indicated that the releasing profile of L-SNEDDS is dissimilar to that of the commercial tablet ($f2 < 50$) (El-Sayyad *et al.*, 2017; Sabri & Hussien, 2020). The results demonstrate that F1-releasing profile at 30 minutes. 3.9-fold and 8.3-fold increases above the marketed product and pure DOM.

CONCLUSION

This study effectively created formulations of liquid SNEDDS aimed improving the availability and solubility of DOM, a medication that has limited oral absorption and poor water solubility. Among various oils and surfactants tested, orange oil and Cremophor EL displayed the greatest solubility for DOM. F1 and F4 were the most notable of the 12 evaluated formulations due to their quick emulsification times, small droplet sizes (less than 50 nm), and significant drug loading (up to 103%). Over 95% of the DOM was released in 120 minutes by these formulations, which is up to 3.1 times more effective than commercial tablets. The increased surface area of nano-sized droplets enhances release and absorption efficiency. This concept highlights SNEDDS as an effective solution for oral formulations and holds tremendous promise for enhancing the administration of additional poorly soluble medicines.

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Ethical Statement:

The Ethical Committee of Hawler Medical University-College of pharmacy- Erbil, Kurdistan region, approved this research (HMUE1ph 01/06/2025-633).

Author Contributions:

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work, with the concept and design contributed by A.B.Q., the acquisition, analysis, or interpretation of data carried out by S.T.R., and A.B. Q., and the drafting of the manuscript completed by S.T.R., and A.B.Q.

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