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Formulation and Evaluation of Dabigatran Solid Self-Nano Emulsifying Drug Delivery System

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Abstract

Dabigatran Etexilate (DE), a prodrug of dabigatran, is a strong oral, reversible, and direct thrombin inhibitor with low oral bioavailability because of active efflux via intestinal P-glycoprotein receptors. By creating a self-emulsifying drug delivery system, the current work largely focused on improving the solubility of dabigatran. Dabigatran is a BCS class II medication with high permeability and poor water solubility. UV-spectroscopy was used to determine Dabigatran's saturated solubility in different oils, surfactants, and co-surfactants. Based on their maximum solubility and compatibility with Dabigatran, the excipients were chosen. Different oils, surfactants, and co-surfactant combinations were used to create SEDDS formulations of dabigatran (4:1 and 3:1). Pseudo ternary phase diagrams were created, and the nano emulsification area was assessed using these. Formulations were created utilising different ratios of oil (Capmul MCM NF), surfactant (Labrasol ALF), and co-surfactant (Transcutol HP) based on the pseudo ternary phase diagram. The produced formulations were chosen, and the 4:1 formulation underwent optimization and was subjected to additional tests, including self-emulsification time, phase separation and stability tests, thermodynamic stability studies, droplet size and zeta potential, and in vitro drug release investigations. According to the report's results, Dabigatran SEDDS are a viable system to increase Dabigatran's solubility.

Keywords: Dabigatran Etexilate (DE), dabigatran, thermodynamic, microenvironment, UV-spectroscopy.

1. INTRODUCTION

In cognitive and cooperative patients, oral administration is the most practical and preferred method of drug administration since it is more convenient, allows for self-administration, and increases patient safety, greater compliance, too. However, new chemical entities make up more than 40%. Due to undesirable physicochemical properties show limited oral bioavailability, pharmacokinetic attributes [1, 2].

Drugs administered orally can be absorbed and bioavailable only to a certain extent due to P-glycoprotein (P-gp) efflux and first-pass cytochrome P450 (CYP3A) metabolism. P-gp is a transmembrane receptor protein that naturally overexpresses in numerous organs, including the small intestine and blood-brain barrier, for balance. By aggressively expelling drugs from the enterocytes, intestinal P-gp reduces intracellular drug accumulation. Enhancing the bioavailability of such medication may be achieved by inhibiting P-gp in the intestinal lumen [9, 10].

A number of pharmaceutical methodologies aim to address the poor solubility, dissolution rate, and bioavailability of insoluble drugs, including micronization, salt form, lipid-based systems, pH-alteration of the microenvironment, use of metastable polymorphs, formation of solute-solvent complexes, solvent deposition, solid dispersion, and molecular encapsulation with cyclodextrins, among others [5-8]. A promising method is the lipid-based system, which includes Self- Emulsifying Drug Delivery Systems (SEDDS), Nano-emulsion, Microemulsion, etc.

The lipid component improves lymphatic transport to a greater extent and, either directly or indirectly, enhances bioavailability by lowering first pass metabolism. Some surfactants, which are typically present in these systems and include Labrasol ALF, Polysorbates etc., have the capacity to reduce the function of intestinal efflux transporters such the P-gp efflux pump [15].

SEDDS are mixtures of oils and surfactants that emulsify with gentle agitation, ideally isotropic and

occasionally with co-solvents, in the GIT. A droplet's typical size ranges around 2 and 200 nm. Drugs which are hydrophobic can be converted into SEDDS, allowing them to be encapsulated into unit dosage forms for oral delivery. Such a formulation disperses after being delivered into the GI lumen. Therein to create a delicate emulsion with a medication that has been solubilized avoiding the dissolving stage, which typically restricts the pace of hydrophobic drug absorption [3, 4]. By modifying the fluidity of the membrane and inhibiting transport activity, incorporation of a P-gp inhibitor (surfactant like Labrasol ALF) may limit drug efflux. The disruption of the hydrophobic environment by the surfactant molecules, which enhances bioavailability, is determined to be the cause of the loss of P-gp function. In general, this can result in greater bioavailability and a more regular temporal profile of absorption from the stomach, enabling dose reduction, selective targeting of drug towards specific absorption window in GI, and protection of drug from the unreceptive environment in gut [11, 12].

Dabigatran is a potent, synthetic, non-peptide competitive thrombin inhibitor belonging to BCS class II. It is supplied in the form of a prodrug because it is poorly absorbed after oral administration. Dabigatran Etexilate (DE), which lacks an anticoagulant activity. After oral administration, this prodrug is activated by non-specific DAB esterases in the liver and plasma. Dabigatran Etexilate is a swiftly acting, low-molecular-weight, reversible chemical, thrombin inhibitor and is the first direct thrombin inhibitor to be FDA-approved treatment for stroke and systemic embolism in individuals with atrial fibrillation, as well as well as for the avoidance of venous thromboembolism (VTE) following Knee and hip surgery [1, 2].

Solubility is highly dependent on pH, increasing with acidic pH. DE's low solubility and P-gp efflux are to blame for its low bioavailability (7.2%) upon oral dosing. Different formulation strategies have been reported by various researchers to increase the oral bioavailability of dabigatran etexilate, including the solid self-nanoemulsifying drug delivery system, the Soluplus®-TPGS binary mixed micelles system, and the drug-phospholipid complex nano-emulsion [1, 2].

The current study's goal was to create a self-micro emulsifying drug delivery system for DE to stop P-gp efflux from the small intestine and to increase its oral bioavailability [9, 10].

2. MATERIALS AND MATHODS

Oils like captex 200, Capmul MCM NF, Capmul MCM C8, Captex 355 EP/NF, Capryol 90 (propylene glycol monocaprylate, type II), Masine CC, Labrafac lipophile WL 1349 (medium-chain triglycerides), Labrafac PG (medium- chain triglycerides), and Labrafil M 1944 CS.

Surfactants like TWEEN 80 (polyoxyethylene sorbitan monooleate), TWEEN 20 (polyoxyethylene sorbitan monolaurate), Koliphor RH 40, Cremophor EL, Labrasol (caprylocaproyl macrogol-8 glycerides), Labrasol ALF and Gelucire.

Co-Surfactants like Lauroglycol 90 (propylene glycol monolaurate type II), Lauroglycol FCC (propylene glycol monolaurate type I), PEG 400 (polyethylene glycol 400), Trancutol HP (diethylene glycol monoethyl) and Simulsol were kindly provided by Gattefossé and Distilled water was used throughout the experiments.

3. SPECTROSCOPIC ANALYSIS

3.1. UV- SPECTROSCOPIC ANALYSIS OF DABIGATRAN

3.1.1. Preparation of Standard Stock Solution Using Methanol

The standard stock solution of the Dabigatran sample was made by placing 10 mg of the medication into a 10 ml volumetric flask and adding methanol to fill the remaining space. The medication was then dissolved in the solution using a sonicator for two to three minutes.

3.1.2 Preparation of Working Standard Solution

Pipette 1 ml of stock solution into a 10 ml volumetric flask to create the working standard solution, then add methanol to dilute it to the proper concentration.

3.1.3 Determination of Absorption Maxima (λmax) of Dabigatran in Methanol

From the working standard solution, a range of concentrations of 5, 10, 15, 20, 25 µg/ml were prepared and scanned in double beam spectrophotometer against respective blank by using spectrophotometric method.

The absorption maxima of Dabigatran in methanol were deliberate in range of 700-200nm.

3.1.4. CALIBRATION CURVE OF DABIGATRAN IN METHANOL

Methanol was used as the solvent to plot the Dabigatran calibration curve. In order to achieve a concentration of 1000 µg/ml, 10 mg of the medication were weighed and diluted with methanol in a 10 ml volumetric flask. To obtain a concentration of 100 µg/ml, 1 ml of this reserve solution was taken and diluted to 10 ml. A range of concentrations of 5, 10, 15, 20, and 25 µg/ml were made from the aforementioned solution, and the absorbance was measured at 263 nm in comparison to a blank using a UV spectrophotometer.

3.2. FT-IR SPECTROPHOTOMETRY

FTIR studies are carried out to determine the drug excipient compatibility. Using potassium bromide, it was completely mixed to create the samples. We were

able to obtain dabigatran in both pure and combined IR spectra. A scan range of 400 to 4000 cm-1 was used for the samples.

4. SOLUBILITY STUDIES

Different oils, surfactants, and co-surfactants were mixed with too much Dabigatran and then mixed in a cyclo- mixer. After 72 hours, the combination had reached equilibrium after being left at room temperature. The insoluble drug was removed from the equilibriated sample by centrifuging it at 100 rpm for 10 min. The concentration of Dabigatran in a sample of the supernatant was determined using a UV spectrophotometer after being diluted with methanol.

5. PSEUDOTERNARY PHASE DIAGRAM

Capmul MCM NF (oil), Labrasol ALF (surfactant), and Transcutol HP (co-surfactant) are components from the solubility studies that were used to generate the phase diagram. To identify self-emulsifying regions and choose the proper amounts of oils, surfactants, and co-surfactants for the formulation of SEDDS, pseudo ternary phase diagrams were created using the water titration method at room temperature. Each group's weight-ratio-mixed surfactant-to-co-surfactant ratio (S mix) (1:3, 3:1, 4:1). Different weight ratios, such as 9:1, 8:2, 7:3, 6:4,5:5, 4:6, 3:7, 2:8, and 1:9, are used to thoroughly mix oil and particular S mix ratios. Each mixture was titrated with water, vortexed for two minutes, and then allowed to equilibrate. The three component ternary phase diagram, where each axis indicates oil, S mix, and water, was used to visually examine and mark the shift in the physical condition from transparent to turbid phase diagrams were drawn.

6. FORMULATION OF LIQUID SEDDS OF DABIGATRAN

The ternary phase diagram was used to determine the various ratios of oil, surfactant, and co-surfactant. Different ratios of the excipients Capmul MCM NF, Labrasol ALF, and Transcutol HP were used to create a range of SEDDS formulations. By combining the necessary amount of surfactant and co-surfactant, S mix was created separately. In every formulation, the medicine dosage (110 mg of Dabigatran) remained the same. Smaller amounts of Dabigatran were added to the oily phase while stirring constantly until a clear solution was attained. To the S mix, Dabigatran-containing oil phase was added, and the mixture was vigorously agitated until it became homogeneous. Finally, the developed formulations were held at room temperature.

7. EVALUATION OF DABIGATRAN LIQUID SEDDS

7.1. GLOBULE SIZE AND ZETA POTENTIAL

The liquid SEDDS of dabigatran formulations are made and diluted with distilled water at a ratio of 1:100. They are then mixed on a cyclomixer for one minute and then set aside for an hour. DLS spectroscopy at a 90-degree angle using a Zeta sizer ZS 90 is used to measure the globule size and zeta potential of the resulting formulation (Malvern instruments). An electrophoretic cell was used to analyse the zeta potential of the diluted solution of the manufactured liquid SEDDS formulation. By applying the diluted solution on disposable blankets at 25 0 c, the size of the liquid SEDDS formulation of dabigatran was evaluated.

7.2. THERMAL STABILITY STUDIES

Thermodynamic stability studies were performed for the selected formulations to determine the effect of temperature.

7.2.1. Heating Cooling Cycle

Between refrigerator cold (4°C) and increased temperature (45°C), six cycles of cooling and heating are carried out, with exposure to each temperature lasting no longer than 48 hours. The centrifugation test is then performed on those formulations that pass.

7.2.2. Freeze-Thaw Stress Cycle

Three freeze-thaw stress cycles between -20°C and 25°C with storage at each temperature for not less than 48 hours. The formulations that pass this test exhibit good stability with no phase separation, cracking, or creaming. The formulations that pass this test are then subjected to a dispersibility test to determine their ability to self-emulsify.

7.3. Self-Emulsifying Efficiency Test- Visual Assessment Test

0.1 ml of each formulation was added to 250 ml of distilled water kept at 37 0.5°C and gently stirred using a magnetic stirrer revolving at a constant speed.

By witnessing the disappearance of SEDDS and the ultimate appearance of the nano emulsion, the emulsification time the length of time needed for a pre-concentrate to create a homogeneous mixture upon dilution was visually determined.

7.3.1. Emulsification Time: This is the amount of time it takes for the formulation to go from a pre-concentrated state to a homogeneous mixture after dilution.

Pre-concentration of the emulsion liquid SEDDS To the beaker holding the distilled water, the dabigatran formulation was introduced drop by drop. The beaker was then continuously stirred on the magnetic stirrer at 100 rpm, and the time it took for the self-emulsion to form was visually measured.

The likelihood that an emulsion will form was identified as:

A clean, bluish-transparent emulsion that forms in less than a minute is considered good. If the emulsion is not transparent, that's bad.

7.4. Dispersibility Test

250 ml of distilled water kept at 37 0.5°C and 0.1 ml of each formulation added were gently stirred with a magnetic stirrer revolving at a constant speed (100 rpm).

By witnessing the ultimate emergence of nano-emulsion and the disappearance of SEDDS, the dispersibility was evaluated visually.

Evaluating a drug's ability to disperse into an emulsion and classifying the size of the globules that form are the goals of the dispersibility test for SEDDS. A 250 ml volume of distilled water was mixed with 0.1 ml of pre-concentrated SEDDS while being swirled with a magnetic stirrer at a speed of about 100 rpm. The time it took for the emulsion to form is recorded. The SEDDS formulation creates a variety of mixtures when titrated with water. Depending on which mixtures are produced, a grading system can be used to evaluate the formulation's in vitro performance.

GRADE A: Developing rapidly (less than 1 minute), appearing clear or bluish.
GRADE B: A rapidly developing, slightly less transparent emulsion with a blue white appearance.
GRADE C: A fine milky emulsion that produced in less than two minutes.
GRADE D: Slow-emulsifying, dull, greyish-white emulsion with a faint greasy looks (longer than 2mins).
GRADE E: Formulations with little to no emulsification and visible surface oil globules.

7.5. Phase Separation and Stability Test

20 ml of distilled water is taken in a beaker, and the temperature is kept at 37 °C for the phase separation and stability test. SEDDS 1ml was added to this dabigatran liquid formulation in distilled water and diluted by agitation before being set aside for 24 hours. The formulation is next checked visually for any evidence of phase separation.

7.6. Effect of Dilution

Formulas were held for 24 hours after being diluted with excess water, 0.1 N HCl, and phosphate buffer (pH 6.8). All of the formulations were stable on dilution, as there was no evidence of precipitation or phase separation.

7.7. Centrifugation

Dabigatran SEDDS formulation and distilled water are mixed in a ratio of 1:10. The formulations are then spun at 3000 rpm for 30 minutes while being witnessed for any physical changes, such as precipitation or phase separation. Formulations that remain stable after centrifugation are chosen for further testing.

7.8. Percentage transmittance

To these three 10 ml volumetric flasks, 0.1 ml of the liquid Dabigatran SEDDS formulation was introduced. 0.1NHCL, distilled water, and 6.8 phosphate buffers were separately added to each flask, gently mixed, and then examined using a UV spectrophotometer to measure the % transmittance at a specific point. API is screened to a maximum.

7.9. Drug Loading Efficiency

UV Spectrophotometry was used to determine the drug content in the formulation. Each formulation's 50 mg dosage was precisely measured out and diluted with 100 mL of methanol. After the proper dilution, the resulting solutions were examined spectroscopically. Equation used to calculate drug loading efficiency.

Drug loading efficiency = Amount of drug in known amount of formulation x 100
Initial drug load

7.10. PH Determination Test

pH of the Dabigatran SEDDS formulation is measured by using pH meter.

7.11. In-Vitro Drug Release Studies

The USP II dissolution test apparatus is used for the in-vitro drug release studies. The 900ml of buffer medium that contains 0.1N HCL is where the capsules containing the liquid SEDDS formulation of Dabigatran are put. Temperature 37+5 c, PH 1.2, and 5 rpm 50 are kept constant. The samples (5ml) are removed and filtered via a 0.45um filter before being subjected to UV spectrophotometer analysis at regular intervals of 5, 10, 15, 30, 45, 60, 90, and 120 minutes. The calibration curve is used to calculate medication release.

8. Formulation of S–SEDDS

The formulation CNFL4T1 with good stability, good self-nano emulsification property, and showing reduced particle size and fewer PDI was chosen to formulate as solid SEDDS from the evaluation studies done on several Dabigatran SEDDS. S-SEDDS was made by combining liquid SEDDS containing Dabigatran in a 1:2 ratio with nuselin as a carrier. Over the nuselin that was enclosed in the porcelain dish, liquid SEDDS was applied drop by drop. For a consistent dispersion of the formulation, the ingredients were stirred using a glass rod after each addition. The resulting damp bulk was put through sieve 120, dried at room temperature, and then put away for later use.

9. Characterization of S-SEDDS
9.1. Flow Properties of S-SEDDS
9.1.1. Angle of Repose

The funnel method was used to calculate the S-SNEDDS' angle of repose. The funnel's height was modified such that its tip just touches the highest point of the powder heap. It was permitted for the accurately

weighed sample to freely flow down the funnel and onto the surface. The formula:

tan = h/r

Where h and r are the height and radius of the powder cone, was used to determine the diameter of the powder cone and the angle of repose.

9.1.2. Bulk Density and Tapped Density

The 10ml measuring cylinder was filled with 2gm of S-SEDDS. At intervals of two seconds, the cylinder was allowed to fall from a height of 2.5 cm onto a hard surface while the initial volume was recorded. Until there was no longer any loudness change, tapping was continued. Using the following equations, bulk density and tapped density were calculated:

Bulk density (BD) = Weight of powder blend
Volume of the packing

Tapped density (TD) = Weight of powder blend
Tapped Volume of the packing

9.1.3. Compressibility Index

Using the calculation for Carr's compressibility index, the compressibility index of the mix was calculated.

The formula for Carr's compressibility index is (Tapped Density – Bulk Density)/Tapped Density X 100.

9.1.4. Hausner's Ratio

The Hausner's Ratio is a number that is related to a powder's or granular material's ability to flow.

Hausner's Ratio = Tapped Density/Bulk Density is the formula for calculating Hausner's ratio.

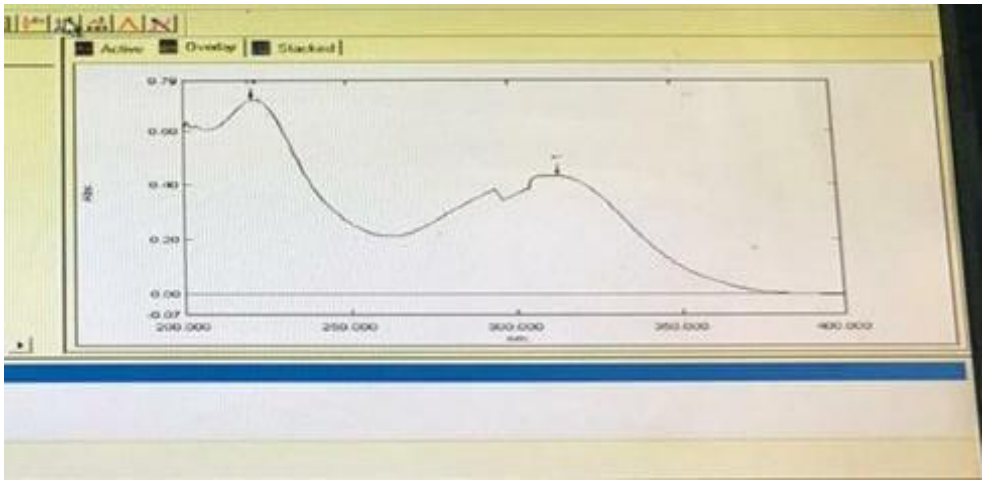
9.2. Drug content

Accurately weighing out 10 mg of Dabigatran S-SEDDS, they were then thoroughly dissolved in methanol. The solution was sonicated for 10 minutes to extract the medication from the methanol, and then it was filtered. Using a UV-Visible Spectrophotometer, the filtrate's absorbance was calculated at 263 nm.

10. RESULTS AND DISCUSSION

10.1. Determination OF λmax of Dabigatran

Observation: The spectrum of Dabigatran showed maximum absorption at wavelength 263nm in methanol.



Graph 1: SPECTRUM OF DABIGATRAN

10.1.1. CALIBRATION CURVE OF TICAGRELOR IN METHANOL

Observation: The values in the table were used to plot the standard graph. The standard plot of dabigatran in methanol was created by plotting absorbance on the x-axis and concentration on the y-axis. The regression coefficient R2 was found to be 0.9981.

Table 1: calibration curve of Dabigatran

SAMPLE ID	TYPE	CONC	WL 263.0	Wgt. Factor
5ppm	STD	5	0.005	1
10ppm	STD	10	0.121	1
15ppm	STD	15	0.222	1
20ppm	STD	20	0.322	1
25ppm	STD	25	0.419	1

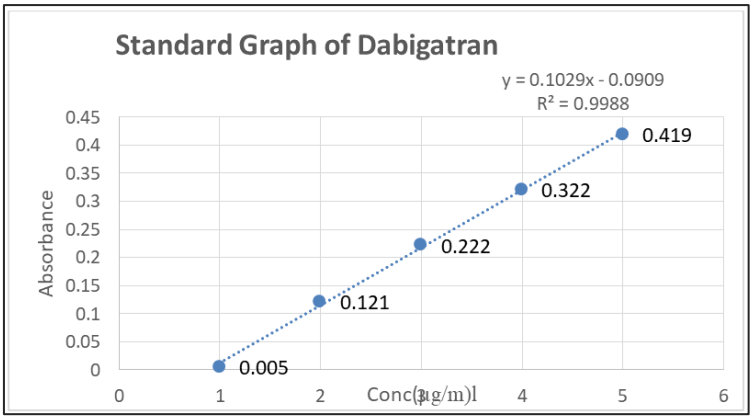


Fig-1: standard graph of Dabigatran

10.2. FTIR STUDIES

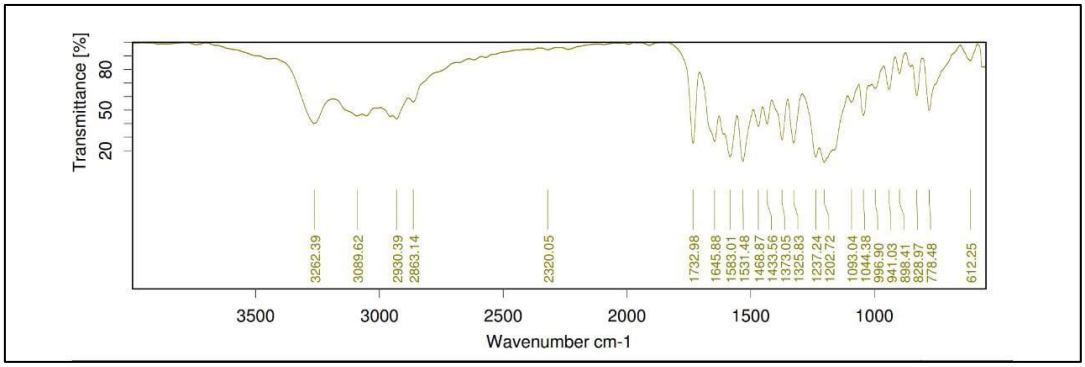


Fig-2: Dabigatran pure drug FTIR

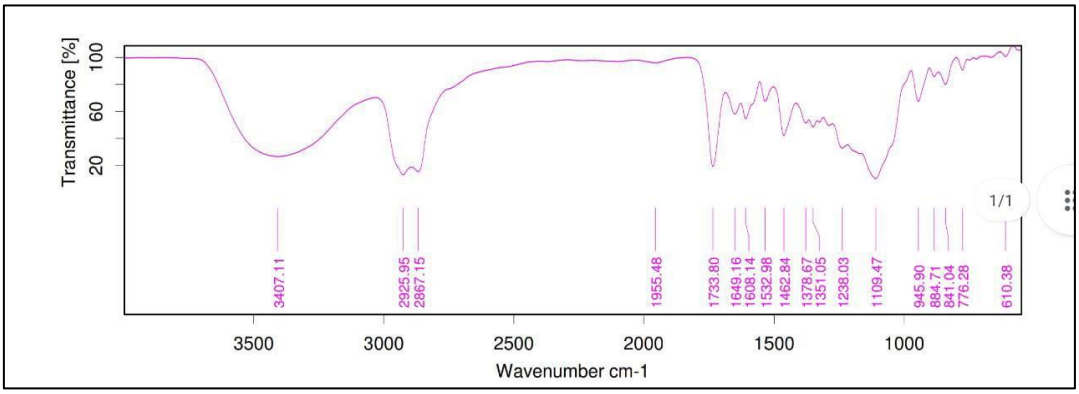


Fig-3: Dabigatran SNEDDS FTIR

Table 2: FTIR Comparative studies of Dabigatran pure drug and Formulation

Wave number (cm^{-1}) of Formulation	Wave number (cm^{-1}) of pure drug	Group	Compound class
1608.14	1645.88	C-N Stretching	Imine/Oxime
2925.95	3089.62	O-H Stretching	Carboxylic acid
3407.11	2930.39	N-H Stretching	Amine salt/ primary amine
1649.19	1732.98	C-H Bending	Aromatic compound

10.3. SOLUBILITY STUDIES

The excipients used in the SEDDS should have the highest solubility for the drug in order to ensure the drug's maximum solubilization and avoid drug precipitation in the gut lumen. In the figures 1, 2, and 3, it is shown how well dabigatran dissolves in different lipid vehicles, surfactants, and co-surfactants. Dabigatran's maximum solubility in oils was discovered to be in Capmul MCM NF. In surfactants, Labrasol ALF had the highest solubility, and in co-surfactants, Transcutol HP had the highest solubility.

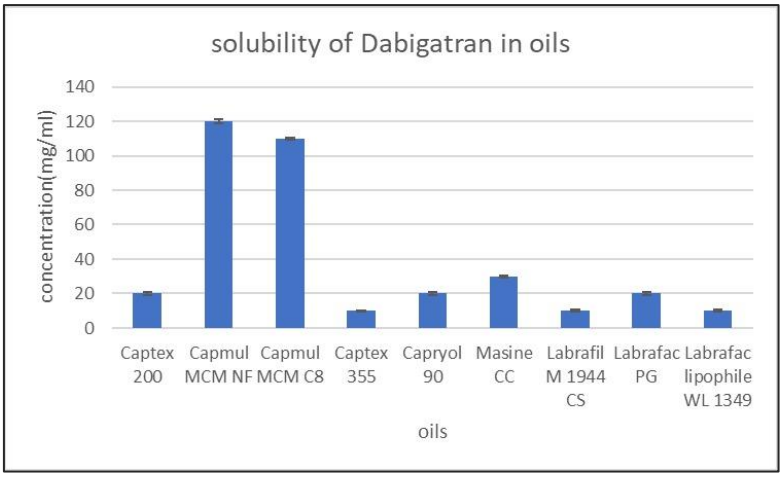


Fig-4: Solubility of Dabigatran in different oils

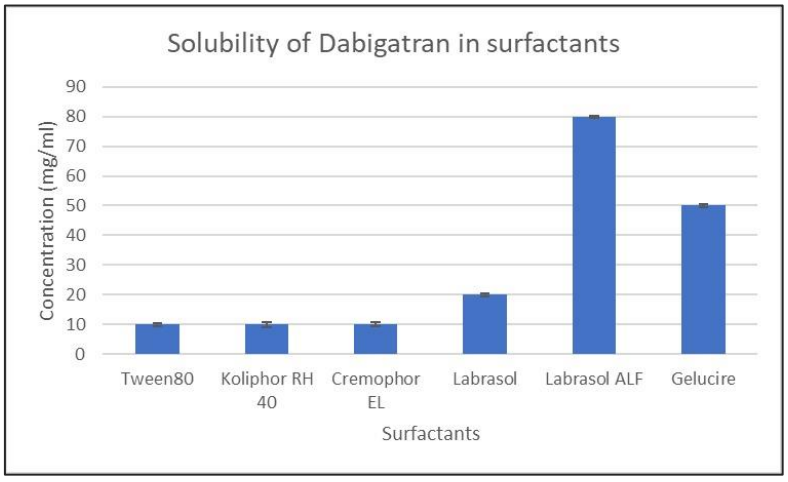


Fig-5: Solubility of Dabigatran in different Surfactants

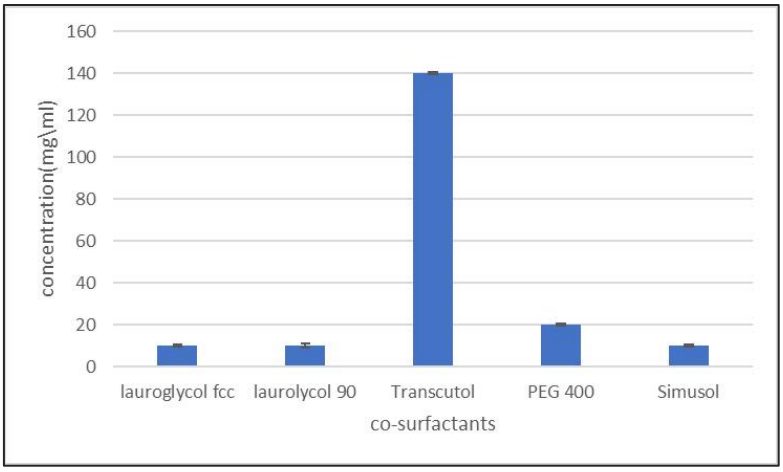


Fig-6: Solubility of Dabigatran in different Co-Surfactants

10.4. Composition of Dabigatran liquid SEDDS formulation

Table 4: Composition of Dabigatran SEDDS formulations

s.no	Formulation	API(mg)	CAMPUL MCM NF (mg)	Smix(mg)	Total(mg)
1	CNFL3T1 **F1**	1100	500	4500	6100
2	CNFL4T1 **F2**	1100	500	4500	6100

10.5. PSEUDOTERNARY PHASE DIAGRAM

Using water titration techniques, pseudo ternary phase diagrams were built in the current work for oil, water, and surfactant/co-surfactant. Figures 5 and 6 display the findings.

Pseudo ternary phase diagram of Capmul MCM NF, Labrasol ALF, Trancutol HP (1:4 S mix).

Table 5: Aqueous titration of Capmul MCM NF, Labrasol ALF, Transcutol HP

Oil : Smix	Oil	Smix	Water	Total	%Oil	%Smix	%Water	Remarks
1:9	50	450	1122	1622	3.082	27.74	69.17	Stable
2:8	100	400	511	1011	9.89	39.56	50.54	Stable
3:7	150	350	506	1003	14.91	34.79	50.29	Unstable
4:6	200	300	383	883	22.65	33.97	43.37	Unstable
5:5	250	250	264	764	32.72	32.72	34.55	Unstable
6:4	300	200	265	765	39.21	26.14	34.64	Unstable
7:3	350	150	258	758	46.17	19.78	34.03	Unstable
8:2	400	100	253	753	53.12	13.28	33.59	Unstable
9:1	450	50	257	757	59.44	6.60	33.94	Unstable

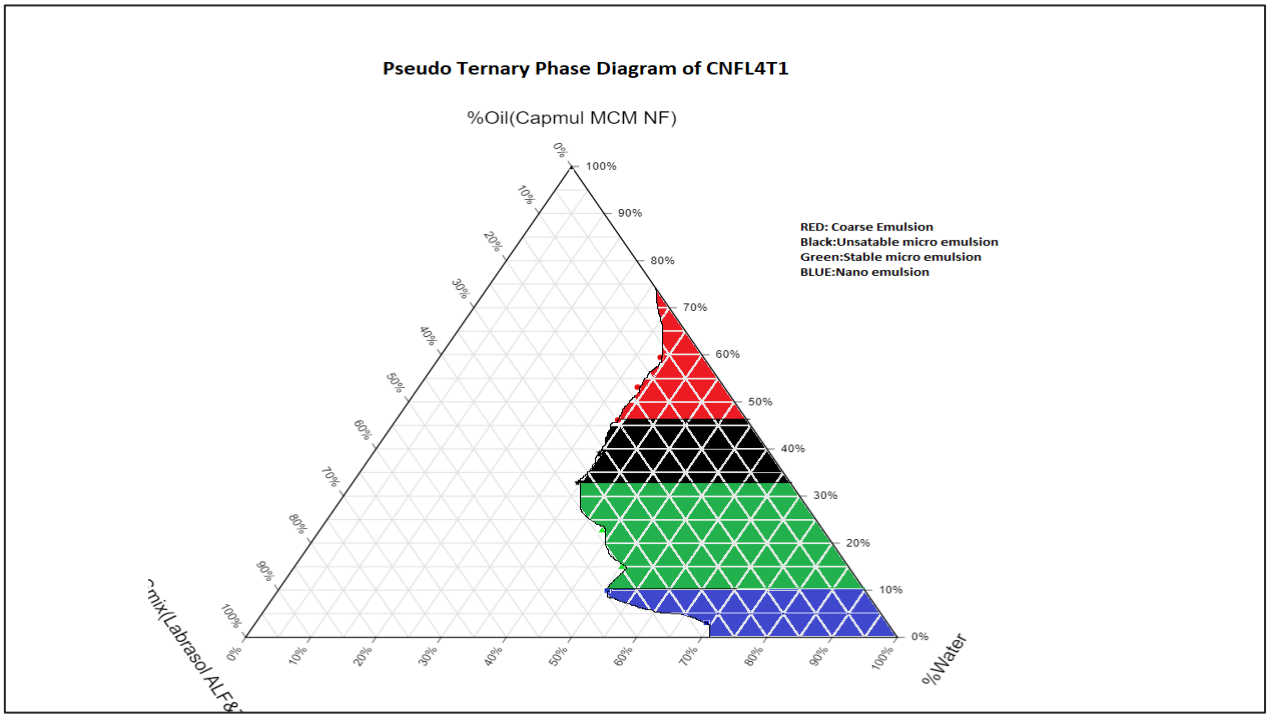


Fig-7: **Pseudo ternary phase diagram of CNFL4T1**

Fig-8: **SELECTED CAPMUL MCM NF OIL: SMIX RATIO**

Pseudo ternary phase diagram of Capmul MCM NF, Labrasol ALF, Trancutol HP (1:3 S mix).

Table 6: Aqueous titration of Capmul MCM NF, Labrasol ALF, Transcutol HP

Oil : Smix	Oils	Smix	Water	Total	%Oil	%Smix	%Water	Remarks
1:9	50	450	752	1252	0.399	35.94	60.06	Stable
2:8	100	400	389	889	11.24	44.99	43.75	Stable
3:7	150	350	511	1011	14.83	34.61	50.54	Unstable
4:6	200	300	320	820	24.39	36.58	39.02	Unstable
5:5	250	250	384	884	28.28	28.28	43.43	Unstable
6:4	300	200	420	920	32.60	21.73	45.65	Unstable
7:3	350	150	256	756	46.29	19.84	33.86	Unstable
8:2	400	100	212	712	56.17	14.04	29.77	Unstable
9:1	450	50	311	811	55.48	6.16	38.34	Unstable

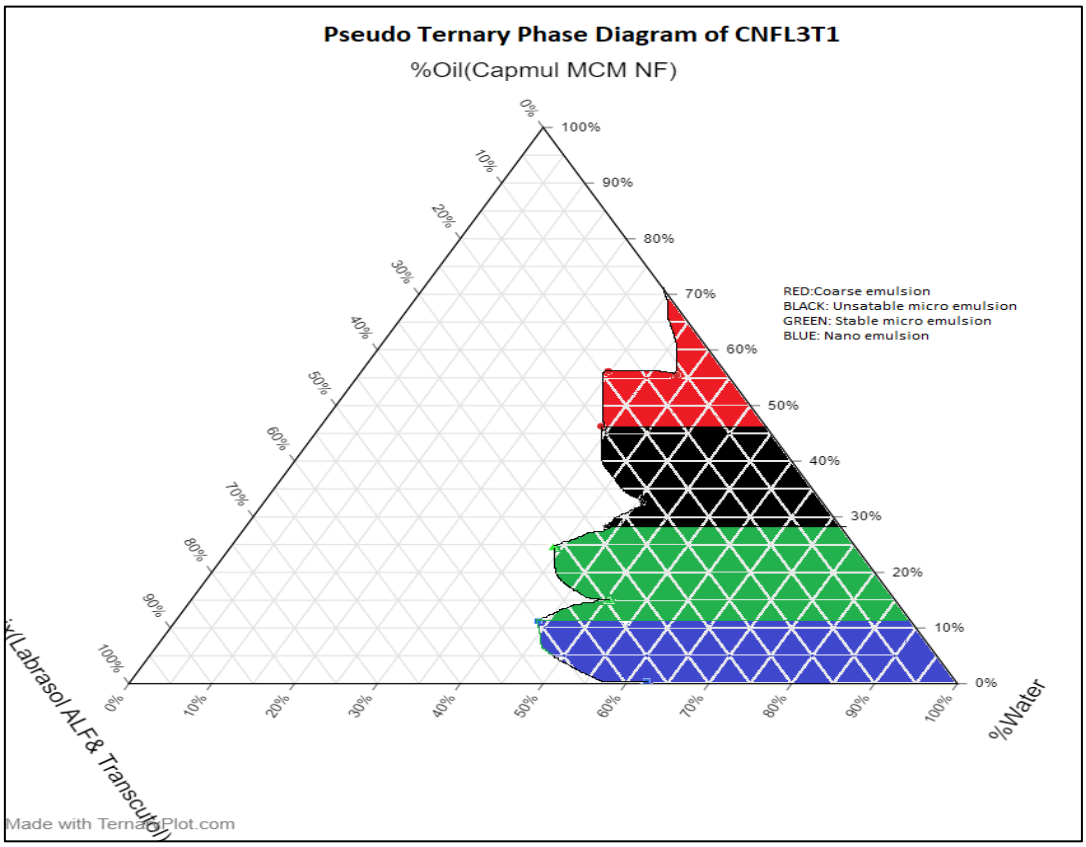


Fig-9: Pseudo Ternary Phase diagram of CNFL3T1

Fig-10: SELECTED CAPMUL MCM NF OIL: SMIX RATIO

10.6. Zeta Potential, Globule Size and PDI

10.6.1. Zeta Potential of CNFL4T1 without Drug

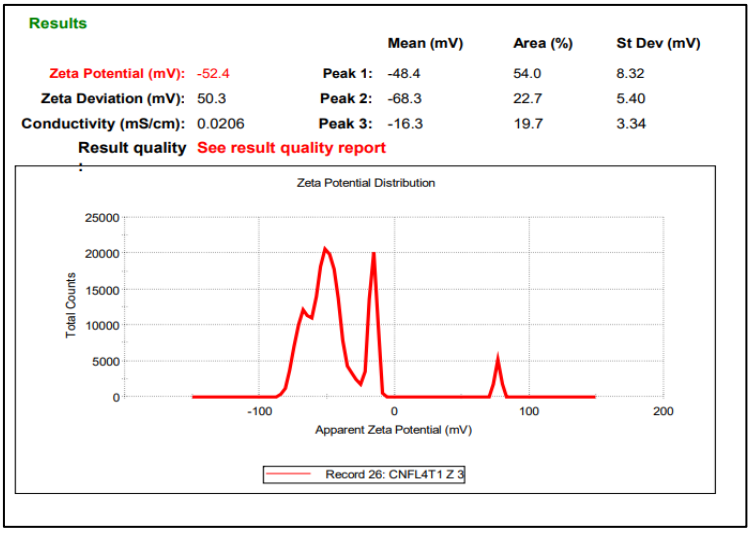


Fig-11: Zeta potential of CNFL4T1 without drug

10.6.2. GLOBULE SIZE & PDI of CNFL4T1 with Dabigatran

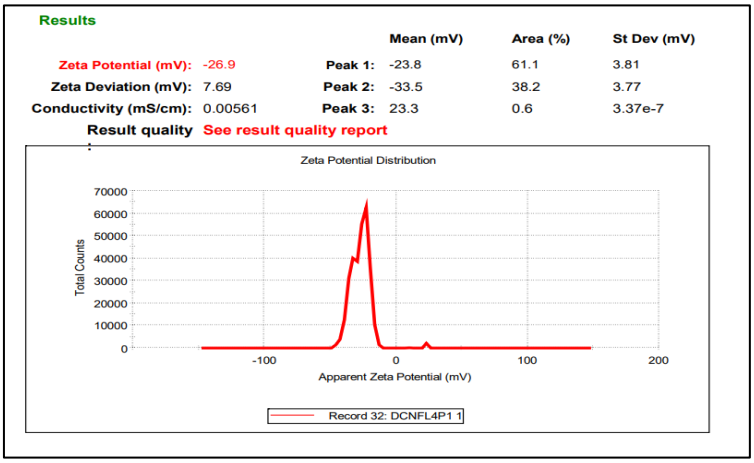


Fig-12: Globule size & PDI of CNFL4T1 with Dabigatran

10.6.3. Globule size of CNFL3T1 without drug

Fig-13: Globule size of CNFL3T1 without drug

10.6.4. Globule size of CNFL4T1 with Dabigatran

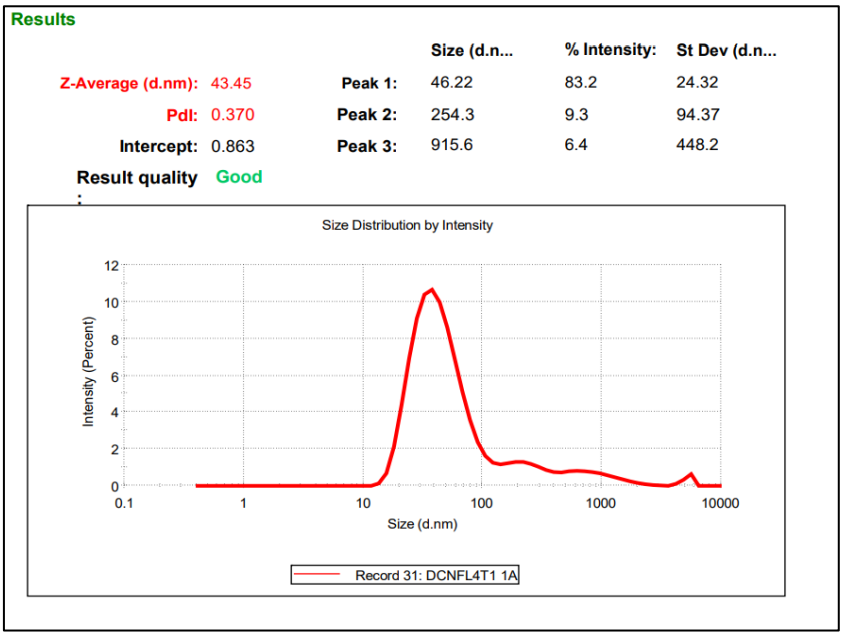


Fig-14: Globule size of CNFL4T1 with Dabigatran

10.6.5. Globule size of CNFL4T1 without Drug

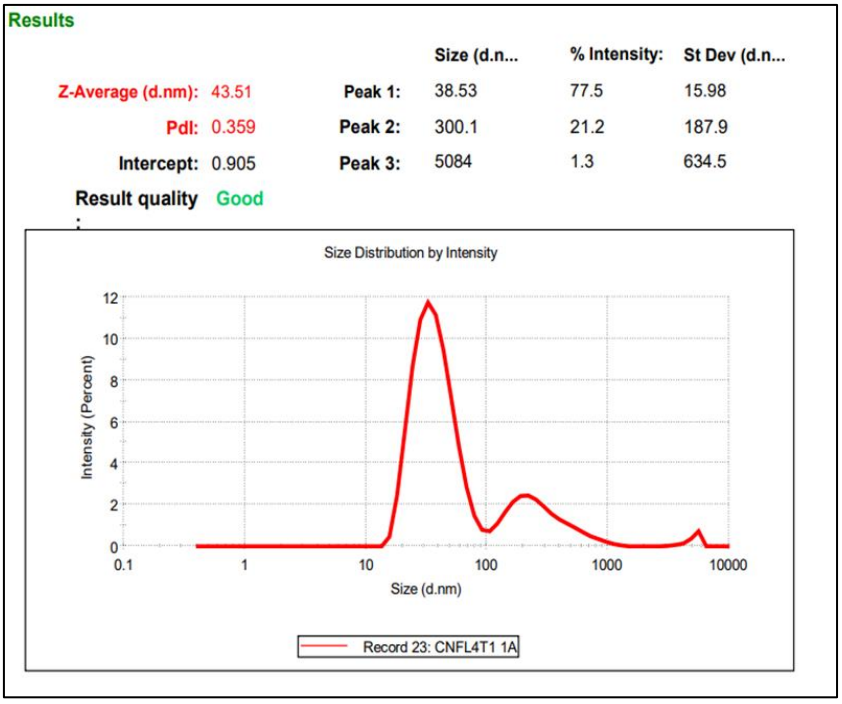


Fig-15: Globule size of CNFL4T1 without Drug

10.7. Thermodynamic Stability Studies

No phase separation or precipitation observed for formulations CNFL3T1 (1:9) & CNFL4T1 (1:9) and indicates stable formulations under effect of temperature.

Table 7: thermodynamic stability studies of Dabigatran SEDDS

Formulation	Freeze thaw cycle (2 cycles NLT 48hrs)	Heating and cooling cycle
CNFL3T1(1:9)	Passed	Passed
CNFL4T1(1:9)	Passed	Passed

10.8. Self-emulsification time

- The emulsification time (time required for a pre-concentrate to form a homogenous mixture upon dilution) was assessed visually by observing disappearance of SEDDS and final appearance of nanoemulsion.

Table 8: Results of self-emulsification time

SNO	FORMUALTION	SELF EMULSIFICATION TIME (sec)	Result
1.	CNFL3T1	34sec	Good
2.	CNFL4T1	21sec	Good

The SEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. It was clear that the formulation was self-emulsified within 27 ±1.05seconds and indicates ability for easy and rapid emulsification.

Fig-16: disappearance of SEDDS after magnetic stirring

10.9. Dispersibility Test

- The dispersibilty was assessed visually by observing disappearance of SEDDS and final appearance of Nano-emulsion.
- Visual observation showed that optimized SEDDS formulation (CNFL4T1) & (CNFL3T1) were found to be grade B& C. The rapid self-emulsification of the investigated systems can be attributed to their low oil content.

Fig-17: dispersed SEDDS upon magnetic stirring

Table 9: dispersibility test results

SNO	FORMULATION	OBSERVATION	GRADE
1.	CNFL4T1	Rapidly forming slightly less clear emulsion with bluish appearance	B
2.	CNFL3T1	BRIGHT MILKY EMULSION	C

10.10. Phase Separation

Table 10: results of phase separation test formulation of Dabigatran and they are stable after 24hrs obseravtion

Sno	Formulation	Observation	Result
1.	CNFL3T1	No phase separation was observed after 24hrs	Stable
2.	CNFL4T1	No phase separation was observed after 24hrs	Stable

10.11. PH Determination Test

The formulation of Dabigatran Liquid SNEDDS (CNFL4T1) has shown pH 6.86.

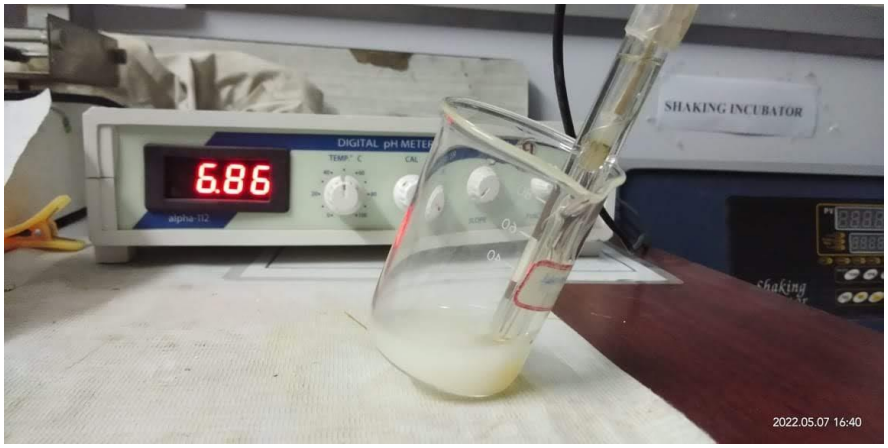


Fig-18: pH of Dabigatran SEDDS

10.12. Characterization of Solid SNEDDS

10.12.1. Micrometric Studies of Solid SNEDDS

Table 11: **Micrometric studies of Solid SNEDDS**

Batch No	Angle of Repose(ɵ)	Bulk Density(g/ml)	Tapped Density(g/ml)	Husner's Ratio
S-CAP 1	23.84±0.05	0.683±0.04	0.671±0.04	1.15±0.03
S-CAP 2	24.99±0.04	0.598±0.05	0.596±0.05	1.12±0.03
S-CAP 3	23.56±0.05	0.645±0.03	0.635±0.04	1.17±0.05

Remarks: The solid SNEDDS flow properties from the aforementioned micromeritic measurements are excellent. Justified by the Hausner's Ratio and Angle of Repose standard values.

10.13. Dissolution Studies

10.13.1. Dissolution kinetics of liquid SEDDS

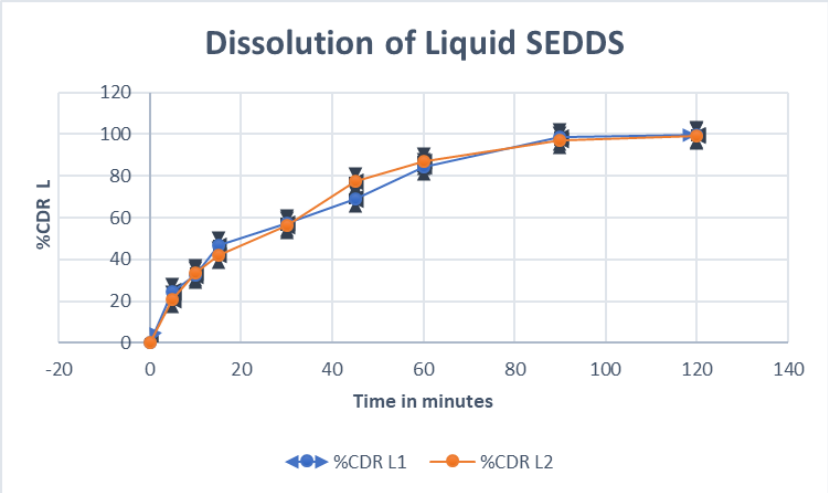


Fig-19: **Dissolution of Liquid SEDDS**

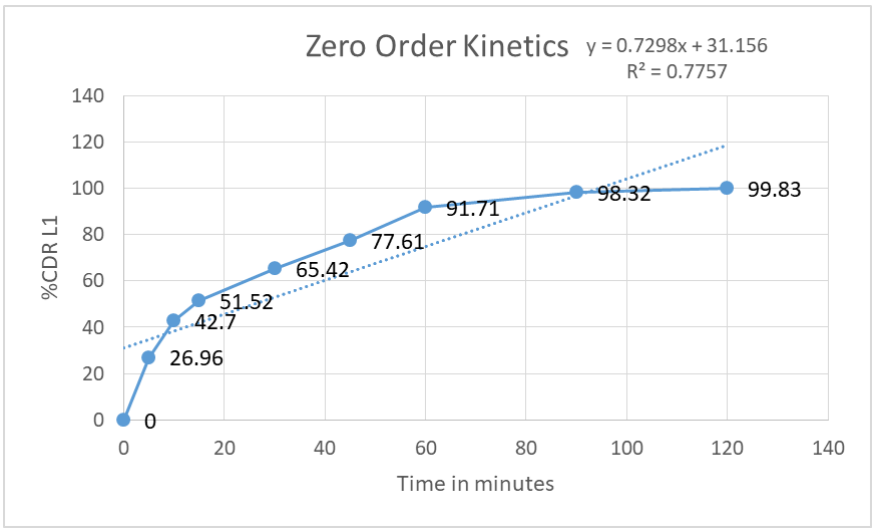


Fig-20: Zero order kinetics of L-SEDDS

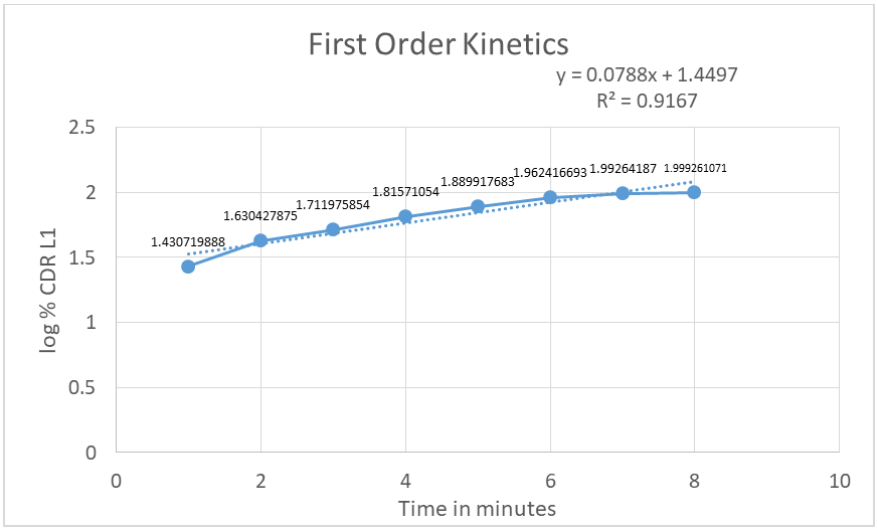


Fig-21: First order kinetics of L-SEDDS

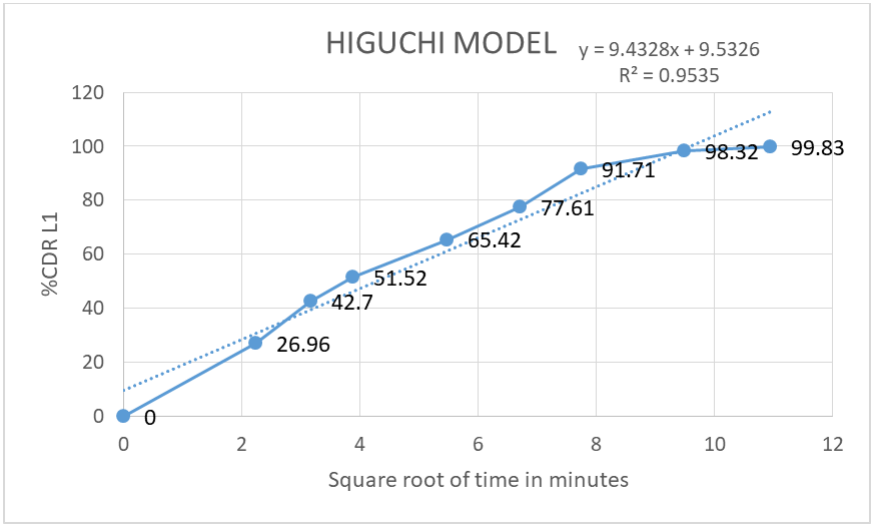


Fig-22: Higuchi model of L-SEDDS

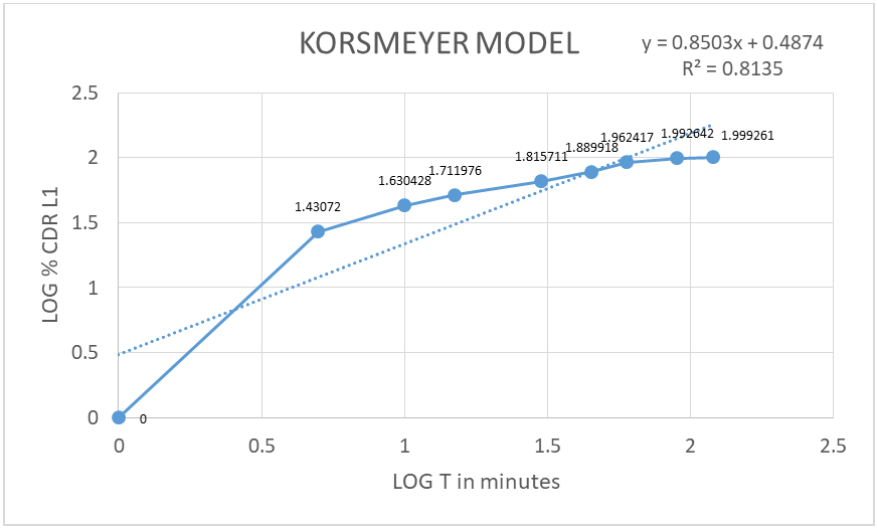


Fig-23: Korsmeyer model of L-SEDDS

Observation: From the above graphs it shows that liquid SEDDS doesn't follow drug release kinetics.

10.13.2. Dissolution Kinetics of Solid SEDDS

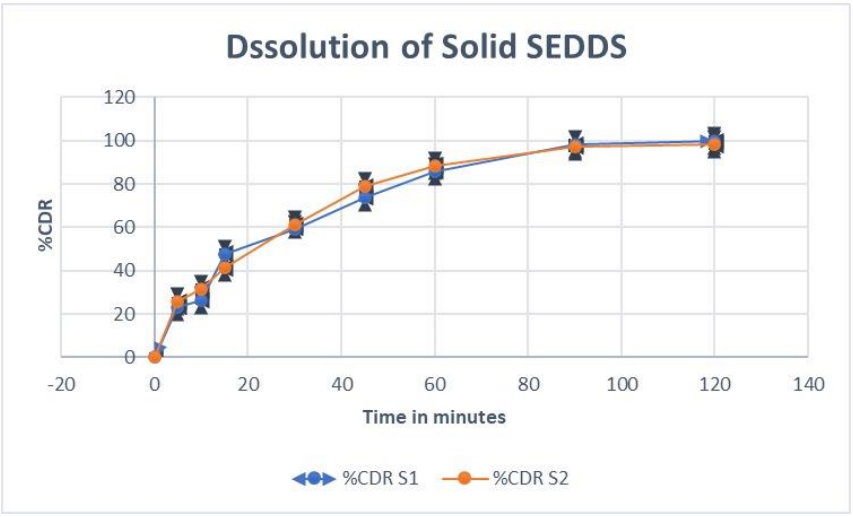


Fig-24: **Dissolution of Solid SEDDS**

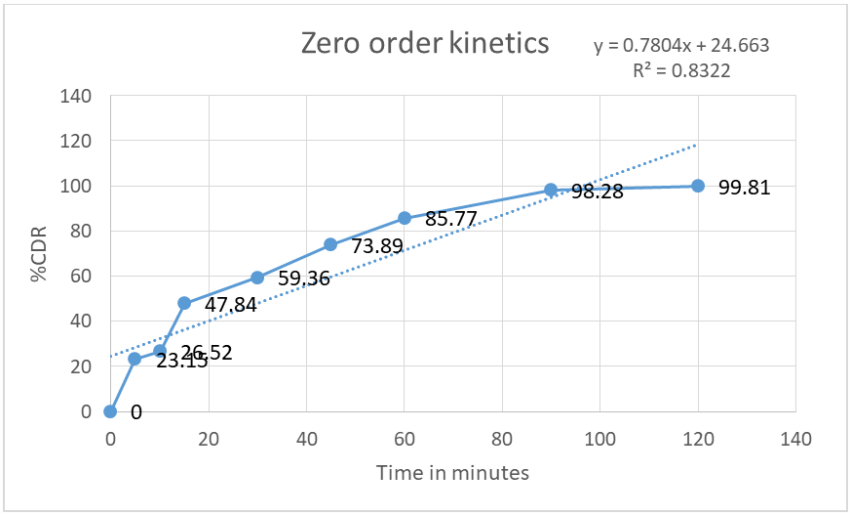


Fig-25: Zero order kinetics of S-SEDDS

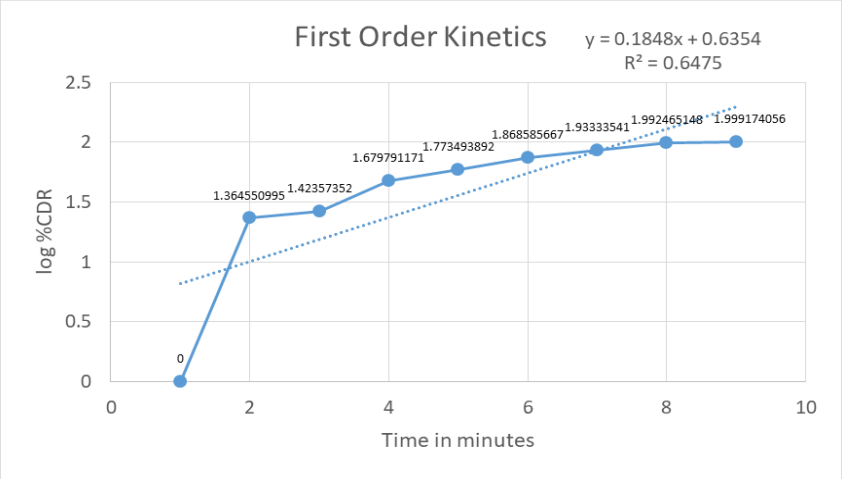


Fig-26: First order kinetics of S-SEDDS

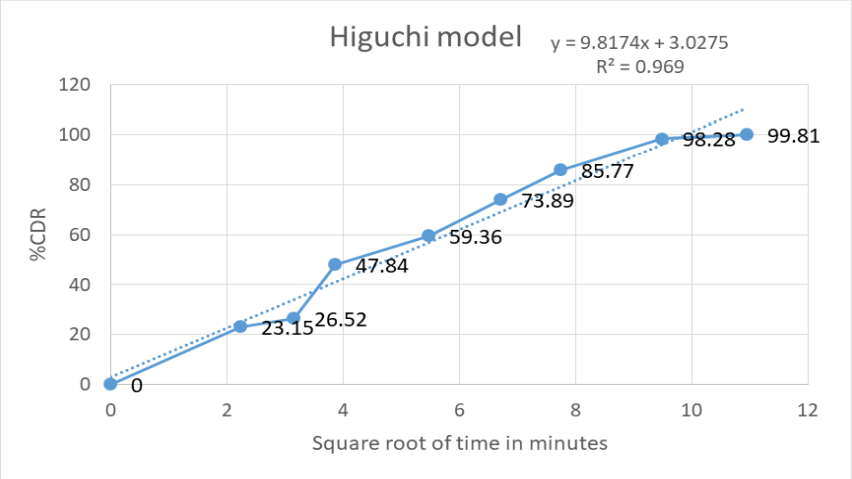
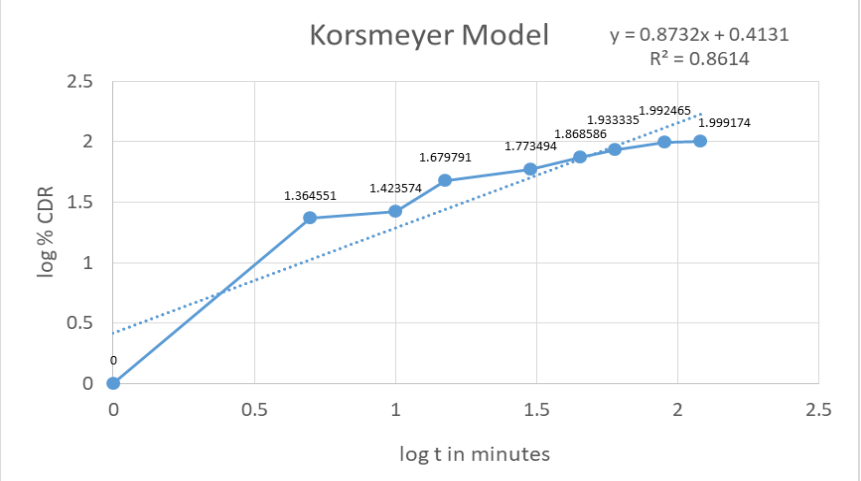


Fig-27: Higuchi model of S-SEDDS



Graph 2: Korsmeyer model of S-SEDDS

Observation: From the above graphs 2 it shows that solid SEDDS doesn't follow drug release kinetics.

11. CONCLUSION

A solid self-nanoemulsifying drug delivery system is required for overcoming formulation challenges and enhancing the oral bioavailability of hydrophobic/lipophilic medicines. Dabigatran, a medication with poor water solubility, was successfully produced for oral administration in this study using SNEDDS and solid-SNEDDS formulations. They were also evaluated for their in vitro performance. F2 in SNEDDS and SF2 in solid-SNEDDS, among other formulations, demonstrated promising findings in terms

of globule size analysis, self-emulsification time, zeta potential, drug content, and in vitro drug release. It might be said that SNEDDS, which was created from Capmul MCM NF, Labrasol ALF, and Transcutol HP as oil, surfactant, and co-surfactant, is a potential method to increase the solubility, dissolving rate, and consequently bioavailability of Dabigatran. In comparison to the pure medication, the optimised formulations demonstrated noticeably better drug release. When looking for a steady dose form, solid-SNEDDS were favoured over SNEDDS. It can be said that Dabigatran solid-SNEDDS offer more predictable and extensive drug release/absorption than the similar conventional formulations. The study's findings demonstrated the value of solid-SNEDDS for improving the solubility and bioavailability of sparingly soluble substances like dabigatran, which can help to lower dosage and minimise associated side effects. The current exploratory work effectively demonstrates the possible utility of solid-SNEDDS for the delivery of poor water-soluble compounds.

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