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Original Article

Super-Saturated SNEDDS with Vegetable Oils: Formulation and Evaluation

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ABSTRACT

Background: Solubility is the most vital parameter in the formulation of different drug delivery systems and one of the core concepts of the formulations. More than 50% of the new drug molecules are facing poor solubility issues. Poor solubility leads to limited bioavailability. Dabigatran Etexilate (DBE) is an anti-coagulant drug belonging to BCS class II drug having low solubility and high permeability and its oral bioavailability is 30%. Self-Nano-Emulsifying Drug Delivery System (SNEDDS) is used for the enhancement of solubility and bioavailability of the drug. However, SNEDDS has some major disadvantages such as less drug loading and precipitation of the drug in the GI. Therefore, a Supersaturated Self Nano Emulsifying Drug Delivery System (S-SNEDDS) is prepared. **Materials and Methods:** A ternary phase diagram was constructed to determine the nano-emulsion region. Liquid S-SNEDDS was prepared by mixing castor oil, Transcutol HP and Cremophor EL with DBE including Sodium taurocholate as a precipitate inhibitor The Liquid S-SNEEDS was further converted to Solid S-SNEDDS by using Aerosil 200 as an adsorbent to form a more stable dosage form. A higher amount of Aerosil 200 was used which exhibits good flow properties and preserved the self-emulsifying properties of Liquid SNEDDS. **Results and Conclusion:** The final formulation was characterized using DSC and SEM and evaluated for *in vitro* dissolution. All the evaluations demonstrated that S-SNEDDS had particle size less than 200 nm, PDI was less than 0.5 and zeta potential was between -25 and -45. *In vitro* dissolution demonstrated that higher drug release was found in capsules incorporated with S-SNEDDS as compared to SNEDDS capsules.

Keywords: Dabigatran Etexilate, Nano-Emulsion, Solubility, Super-Saturated Self Nano-Emulsifying Drug Delivery System.

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INTRODUCTION

Approximately 70% of the new drug entities are lipophilic by nature so they are poorly soluble in water. Drugs that do not dissolve or do not absorb well may be enhanced via lipid-based formulations that increase a drugs solubility as well as absorption (Chai *et al*., 2016). One of the most appealing technologies among this lipophilic formulation has been self-nano-emulsifying drug delivery systems in recent years for improving the solubility and bioavailability of poorly water-soluble drugs (Villar *et al*., 2012).

Self-Nano-Emulsifying Drug Delivery Systems (SNEDDS) are self-emulsifying nanoparticles that are phospholipid-like nanoparticles that are being developed for the delivery of oral drugs because they have the property of enhancing the solubility of the drug and improving the rate and extent of absorption of poorly hydrophilic drugs. (Kuruvila *et al*., 2017; Subramanian *et al*., 2020). This form of drug delivery is a colloidal mixture of lipophilic drugs, oils, surfactants and co-surfactants which forms a clear nano-emulsion after dilution. SNEDDS are pigmented emulsions with a globule size less than 200 nm. SNEDDS consist of oil, surfactant and co-surfactant. It get emulsified when SNEDDS come in contact with an aqueous solution in the GIT under mild agitation. Self-emulsification is one of many ways SNEDDS improves oral absorption of poorly soluble drugs by using different dosage forms such as capsules, tablets, beads, nanospheres, etc (Nazlı *et al*., 2021; Park *et al*., 2020; Michaelsen *et al*., 2019). The main advantage of this is that the pre-dissolving compound overcomes the initial rate-limiting step of dissolution in the aqueous environment within the GI tract (Thomas *et al*., 2012).

Dabigatran etexilate is a BCS class II drug with challenging biopharmaceutical properties such as poor solubility and slow dissolution rate. These properties have lain the ground for the

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development and optimization of the lipid-based formulation of DBE (Singh and Pai, 2015; Bandyopadhyay *et al.*, 2014). The solubilizing capacity of SNEDDS diminishes *in vivo* as the drugs oil content decreases during absorption, resulting in the precipitation of drug. Drugs contained in SNEDDS are less soluble than their equilibrium solubility (i.e. drugs that should be given at a higher dose) (Kumar and Sureshkumar, 2020). As precipitates form on a drug nucleus, precipitate inhibitor slows down the process. Supersaturated self-nano emulsifying drug delivery systems consist of a Polymeric Precipitation Inhibitor (PPI) which is blended into the formulation of SNEDDS. During the process of crystallization, it inhibits the process of nucleation by absorbing onto the hydrophobic surface of the crystal (ElKasabgy, 2014; Patel *et al.*, 2016; Singh *et al.*, 2021). Hydroxypropyl Methylcellulose (HPMC) is the most common PPI used in S-SNEDDS. Other common PPI which is used are 4- Bromo benzene boronic acid, polyvinyl pyrrolidone (Savjani *et al.*, 2012).

MATERIALS AND METHODS

Materials

Dabigatran etexilate was purchased from Yarrow Chem. Castor oil, Transcutol HP and Cremophor EL was obtained from lobachemie. Aerosil 200 and sodium taurocolate was purchased from CDH. All other reagents were of analytical grade and used without further purification.

Determination of DBE solubility in the oil, surfactant and co-surfactant

The Solubility tests were carried out on various oils, surfactants and co-surfactants. One mL of each oil, surfactant and co-surfactant was added in glass vial containing excess amount of DBE. These vials are then sonicated for 15 min and then kept in water bath shaker for 24 hr. After 24 hr these vials are centrifuged at 15,000 rpm for 15 min (Jindal, 2017; Lalwani *et al.*, 2013). After centrifugation at 4000 rpm for 25 min the supernatant liquid was diluted using methanol and was analyzed in UV-spectrometer at 223 nm (Dash *et al.*, 2015). The materials used in the study included olive oil, castor oil, arachis oil, Cremophor EL, Tween 80, Cremophor RH40, Transcutol HP, 1-2,propendiol. Results from each experiment were expressed as values in µg/mL.

Construction of Ternary Phase Diagram

For Construction of Ternary Phase Diagram oil, surfactant and co-surfactant (S_{mix}) were mixed in different ratios (1:1, 1:2 and 1:3) with water at room temperature. The liquid mixtures were then titrated with dropwise addition of water in the magnetic stirrer (200-400 rpm) and the solution was monitored visually until the solution turned clear. In order to determine the percent transmittance of the clear solution, we measured it using a UV spectrophotometer at 638.2 nm and distilled water as a blank (Alothaid *et al.*, 2021). If the solution formed is clear and transparent emulsion, then the emulsion is considered as good emulsion (% transmittance$^{>}$85) and if the solution is turbid or formed coalescence then this emulsion is considered as bad emulsion (% transmittance$^{<}$85). The values are then plotted in Chemix software to find the emulsification region (Parmar *et al.*, 2015; Abo Enin and Abdel-Bar, 2016).

Characterization of prepared Super-saturated SNEDDS

In terms of globule size analysis, the self-emulsifying system with the larger nano-emulsion region (oil phase-castor oil, surfactant-Cremophor EL, co-surfactant-Transcutol HP) was chosen for further evaluation as seen in Table 1.

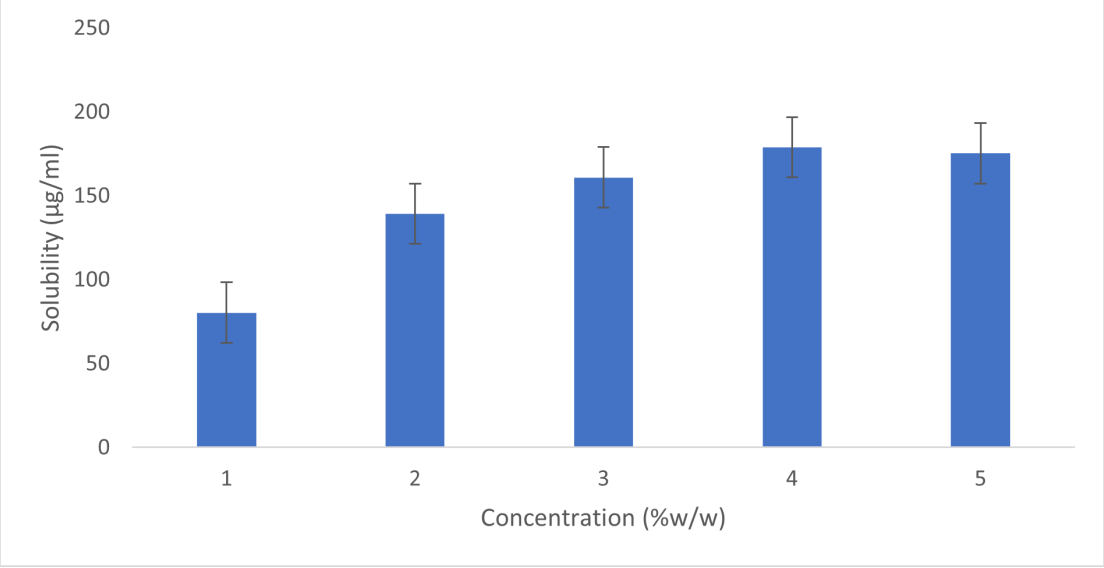

Figure 1: Solubility data in different concentration of PPI.

Table 1: Composition of selected SNEDDS.

Sl. No.	Oil (Castor oil) %v/v	Surfactant (Cremophor EL) %v/v	Co-surfactant (Transcutol HP) %v/v	Remarks
1.	50	25	25	Turbid
2.	45	25	30	Clear
3.	40	30	30	Clear
4.	35	30	35	Clear
5.	30	35	35	Clear
6.	25	35	40	Clear
7.	20	40	40	Clear
8.	15	40	45	Clear
9.	10	45	45	Clear
10.	60	20	20	Turbid
11.	65	20	15	Turbid
12.	70	15	15	Turbid
13.	75	15	10	Bluish
14.	80	10	10	Turbid
15.	85	10	5	Turbid
16.	90	5	5	Turbid

Table 2: Composition of S-SNEDDS.

Sodium taurocholate (PI)	S%
0	50
0.5	50
1	50
2	100
5	100

Saturated solubility of Liquid supersaturated SNEDDS

An excess amount of the drug was added to 1 mL of the formulation (Data from the overlay plot) in the selected system (Castor oil/ Cremophor EL/Transcutol HP) and put in a water bath shaker for 12 hr (Kim *et al.*, 2018). Then they are centrifuged at 5000 rpm for 15 min. The supernatant was diluted with methanol and filtered and was determined spectrophotometrically at 223 nm (Thomas *et al.*, 2012).

Preparation of Super-saturated SNEDDS

The liquid super-saturated SNEDDS was prepared in two continuous steps. First, an amount of drug equivalent to its saturated solubility was added to a mixture of oil, surfactant and co-surfactant by using a magnetic stirrer at a speed of 200- 400 rpm at room temperature to produce a clear, isotropic solution (Thomas *et al.*, 2013; Singh and Pai, 2016). Then the precipitation inhibitor was added to the above solution in different concentrations, i.e., 0.5%, 1%, 2% and 5%, to increase their equilibrium solubility as seen in Table 2 and (Figure 1). The super-saturated liquid SNEDDS will be mixed with aerosol 200 adsorbents until the adsorbents form a free-flowing powder (Dash *et al.*, 2015). The prepared powder will be sieved to get a uniform size and stored in a desiccator for further evaluation. The solid granules or powder of Solid Super-saturated SNEDDS will be filled into the hard-shell gelatin capsules (Radha *et al.*, 2019). Characterization of the prepared S-SNEDDS formulation.

Determination of percentage transmittance

1 mL of the formulation was taken to this 0.1 mL SNEDDS formulation and was titrated with 100 mL of distilled water. The percentage transmittance was measured using distilled water as the blank in a UV spectrophotometer at 638.2 nm (Albaidhani and Hussein, 2019).

Visual observation

Liquid SNEDDS was diluted to 100 mL of distilled water and made to stand for 24 hr. They are observed for phase separation and turbidity (Chen *et al.*, 2021).

Self-emulsification time

To determine the emulsification time, 1 mL of liquid SNEDDS was titrated with 100 mL of distilled water at 37°C using a magnetic stirrer at 100 rpm. The time required for the formation of clear or milky emulsion was noted visually (Nazlı *et al.*, 2021).

Table 3: Solubility of the drug in various oils, surfactants and co-surfactants.

Components	Observed Solubility (mg/mL)
Water	1.72±0.013
OILS	
Castor oil	75.6±1.048
Olive oil	16.19±0.0854
Arachis oil	3.92±1.608
SURFACTANTS	
Cremophor EL	93.98±0.0347
Tween 80	58.92±0.184
CO-SURFACTANTS	
1-2,propendiol	261.68±0.2406
Transcutol HP	368.96±0.235
PEG 400	152.03±0.122

Droplet size and zeta potential

1 mL of the formulation was taken, to this 0.1 mL SNEDDS and supersaturated SNEDDS formulation was titrated with 100 mL of distilled water and sonicated for 10 min. The resulting nano-emulsion was checked for droplet size and zeta potential in a particle size analyzer (Malvern zetasizer) (Cai *et al.*, 2016; Faltas, 2010). The Zeta and droplet size values were determined.

Drug Content

1mL of formulations was taken and diluted with 10 mL methanol. The solution was then filtered, and dilutions was made and then analyzed in the UV spectrophotometer at 223 nm (Sharif *et al.*, 2017).

Characterization of prepared SS-SNEDDS formulation

Angle of repose (θ)

The angle of repose was done using funnel method. The accurate weigh sample was pour in a funnel at a fixed height, onto the base. The powder was allowed to flow through funnel freely onto the surface (Nantsupawat *et al.*, 2018). The powder cone's diameter was measured, and angle of repose was calculated by using below equation:

$$\tan \theta = h/r$$

Where, h=height of heap, r=radius of heap.

Bulk density

A quantity of 2 g of S-SNEDDS was placed in a graduated cylinder 10 mL to measure occupied volume by the powder (Redondo *et al.*, 2011). Bulk density was determined by using equation:

$$\text{Bulk density} = \text{Weight of powder} / \text{Bulk volume}$$

Tapped density

Several taps of the same powder were made from a height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted (Sarah, 2013). Tapped density was calculated using equation:

$$\text{Tapped density} = \text{Weight of powder} / \text{Tapped volume}$$

Compressibility index

The compressibility of the S-SNEDDS granules was determined by Carr's compressibility index as follows (Ge *et al.*, 2018).

$$\text{Carr's compressibility index}(\%) = [TD-BD)/TD] \times 100$$

Hausner's ratio

It is the ratio of tapped density to bulk density. It is used to indicated powder flow properties and can be calculated as:

$$\text{Hausner's ratio} = TD/BD$$

Drug entrapment efficiency

The entrapment efficiency of formulated S-SNEDDS DBE was determined by checking the amount of unentrapped drug by centrifugation method. The samples were centrifuged at 1000 rpm for 15 min and the supernatant was collected, diluted with methanol and analyzed in UV spectroscopy at 223 nm (Deshmane *et al.*, 2024; Mundada and Sawant, 2018). % EE was calculated by following equation:

$$\%EE = \text{Total amount of DBE-Amount of free DBE} / \text{Total amount of DBE} \times 10$$

Differential Scanning Calorimetry (DSC)

In pharmaceutics, it is important to deliver a drug in the amorphous form, to check the drug temperatures below which crystallization occur. So Differential Scanning Calorimetry (DSC) is used for the identification of various physical properties and thermal transitions. Drug loaded-SDs are examined using differential scanning calorimeter equipped with auto sampler (Abed and Hussein, 2019; Cho *et al.*, 2017).

Scanning electron microscopy

SEM pictures were captured at 15 KeV accelerating voltage to observe the morphology and size of the prepared SNEDDS. Samples were attached on a brass stub using double sided adhesive tape and made electrically conductive by covering with a thin layer of gold (Nagadeep *et al.*, 2019).

Table 4: Physical observations for one month compatibility study between drug and excipient.

Components	Quantity (1:1) mg	First week	Second week	Third week	Fourth week
DBE-Castor oil (A)	100:100	Yellowish light colour	No change	No change	No change
DBE-Cremophor EL (B)	100:100	Yellowish to slight orange colour	No change	No change	No change
DBE-Transcutol HP (C)	100:100	Whitish fine light colour	No change	No change	No change

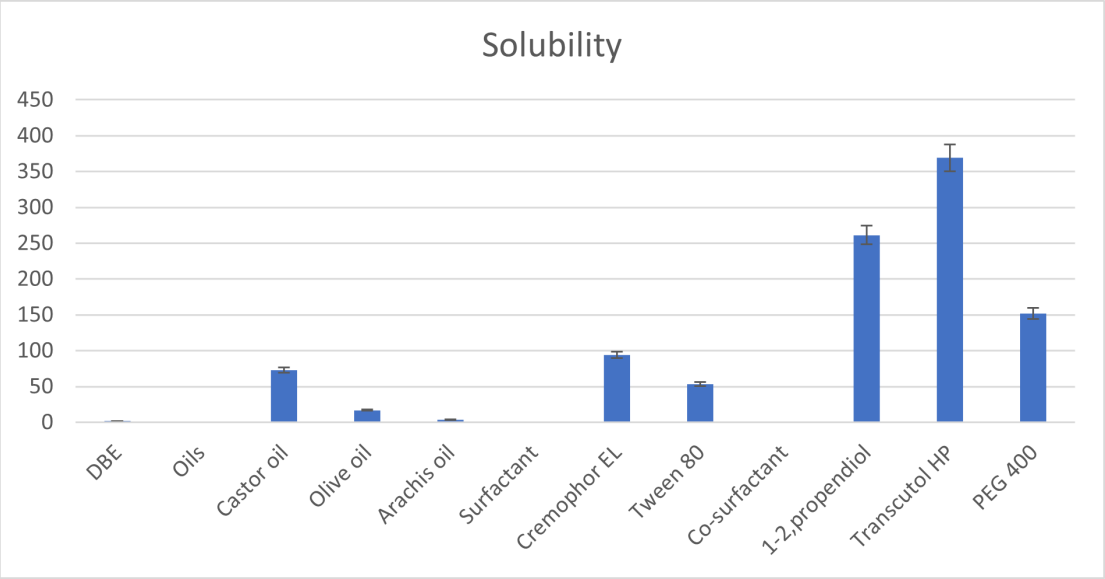

Figure 2: Solubility of drug, oil, surfactant and co-surfactant.

In vitro dissolution test

In vitro dissolution studies were carried out using USP apparatus II electrolab, rotating paddle. Pure drug, SNEDDS and S-SNEDDS were filled in the three different capsules. Then, these capsules were placed in 750 mL of SGF at 37±0.5°C in different baskets for 2 hr followed by exposure to SIF by the addition of 250 mL of a sodium phosphate solution (0.2 mol/L). An aliquot of 5mL was withdrawn at predetermined time intervals with the replacement of an equal volume and filtered through Whatman filter paper. The concentration of DBE was measured by UV spectrophotometry (Scioli *et al.*, 2020; Poorani *et al.*, 2016).

RESULTS

Determination of Drug Solubility in water, Oils, Surfactants and Co-surfactants

The method of determination of solubility of DBE in various oils is mentioned in Table 3. The equilibrium solubility of DBE in oils, surfactants and co-surfactants is shown in Figure 2.

Firstly, DBE solubility was tested in various vegetable oils. Vegetable oils are the most common lipid phases used in lipid-based delivery systems to solubilize lipophilic/hydrophobic drugs owing to their safety, digestibility and absorption. Among the selected oils, castor oil exhibited the highest and good solubility for DBE compared to all other oils, it was selected as the oil phase for S-SNEDDS formulation. Hence, castor oil was chosen as an oil phase for formulating DBE-loaded SNEDDS. In several studies, castor oil was used as an oil phase in micro/nano-emulsion formulations of quercetin (Kaziazi *et al.*, 2020). The highest solubility of DBE at 75.6±1.048 mg/mL was found in castor oil. Among the selected surfactants, cremophor EL exhibited the highest and best solubility for DBE compared to all other surfactants. Cremophor RH 40 has less solubilization capacity, but it shows good emulsification ability (transmittance above 90%) as compared to Cremophor RH 40 and Tween 80. Hence, Cremophor EL was used as a surfactant in the present study. Cremophor EL was studied for its emulsification ability with Castor oil. Co-surfactants screened for improving the nano-emulsification ability of the selected surfactant were found to increase the spontaneity of nano-emulsion formation which was monitored by several inversions required to produce nano-emulsion. Among the selected co-surfactants, transcutol HP exhibited the highest and best solubility for DBE compared to all other co-surfactants.

Drug-Excipient compatibility study

The study was conducted at room temperature as described in Table 4 and (Figure 3). It was observed that the physical interaction

was seen after one month of storage at room temperature. Before any excipients are used in the preparation of formulation, the compatibility between the drug and excipients must be ensured. Therefore, it is essential to conduct drug excipient interaction studies during pre-formulation.

The FTIR spectra of castor oil with drug (A) showed characteristic peaks of castor oil and drug at 3418.82, 2854.27, 2727.56 and 1746.23 cm^{-1} respectively. It indicates that there was no interaction between the drug and castor oil and they both were compatible with each other.

The FTIR spectra of Cremophor EL with drug (B) showed characteristic peaks at 3449.05, 2921.00, 1967.25 and 1735.02 cm^{-1} which confirms the compatibility between Cremophor EL and drug.

The FTIR spectra of the physical mixture of Transcutol HP and drug (C) showed characteristic peaks at 3452.51, 2928.43, 2346.06 and 1733.31 cm^{-1} which confirms the compatibility between Transcutol HP and drug. No change in peaks showed there was no physical interaction between the drug and Transcutol HP.

Table 5: **Solid S-SNEDDS formulation study data.**

Parameters	Range	Remarks
Bulk density	0.52	Within limits
Tapped density	0.62	Within limits
Hausner's ratio	1.2	Excellent
Angle of repose	28.34	Excellent
Compressibility index	15.8	Excellent

Construction of Ternary Phase Diagram

A ternary phase diagram was used to identify the self-emulsifying regions and to optimize the percentages of different liquid SNEDDS components as shown in Figure 4. Based on the data obtained from solubility studies, Castor oil was used as the oil phase and S_{mix} (Cremophor EL: Transcutol HP) was used as a surfactant and co-surfactant to construct the ternary phase diagram. Different ratios of surfactant/co-surfactant were used to prepare different ternary systems. The results suggested that the emulsification ability was good when the surfactant/co-surfactant concentration increased demonstrated by the wide clear nano-emulsification region and the emulsification ability was bad/turbid as shown when the oil concentration increased. The maximum concentration of oil that was solubilized by this ratio in the phase diagram was found to be 22% w/w by incorporating S_{mix} around 52% w/w, itself showed the domination of surfactant (Cremophor-EL) along with co-surfactant in nanosizing. The data indicated that the larger the shaded area, the more the self-emulsification ability. All experiments were done in triplicates.

Characterization of the prepared SNEDDS

Determination of percentage transmittance

The formulation selected was subjected to percent transmittance. Percentage transmittance is a crucial factor in determining if a system is isotropic. By utilizing a visible spectrophotometer with a wavelength of less than 650 nm to measure the turbidity of an emulsion produced from SNEDDS in aqueous media, the percentage of transmittance was determined. The value of the formulation was found to be 99.5%. The value above 90% shows that the particles are nano size. It showed that the formulation was clear and transparent. The formulation's percent transmittance

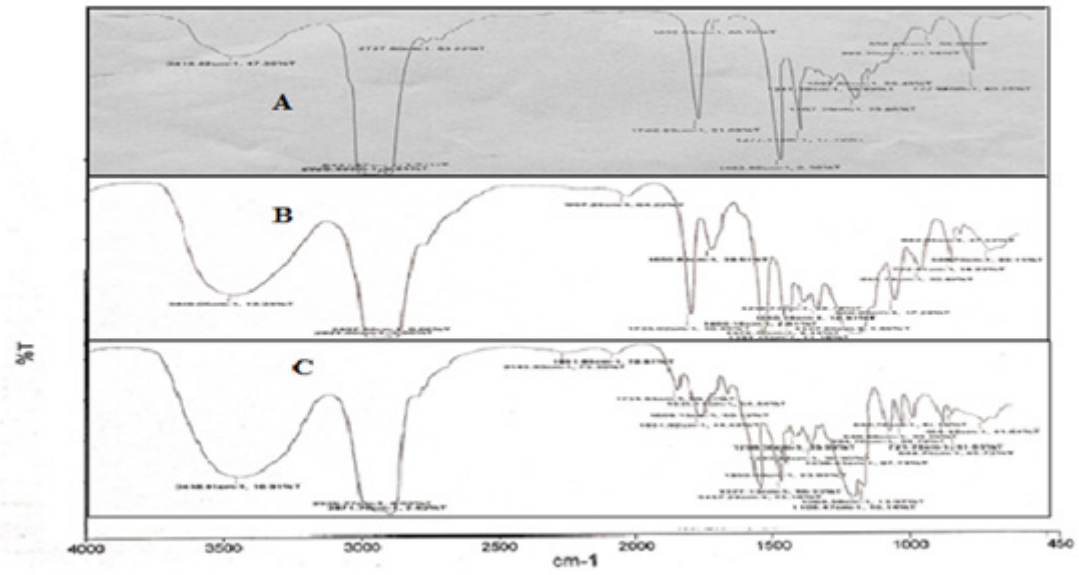

Figure 3: FTIR spectra of DBE with components.

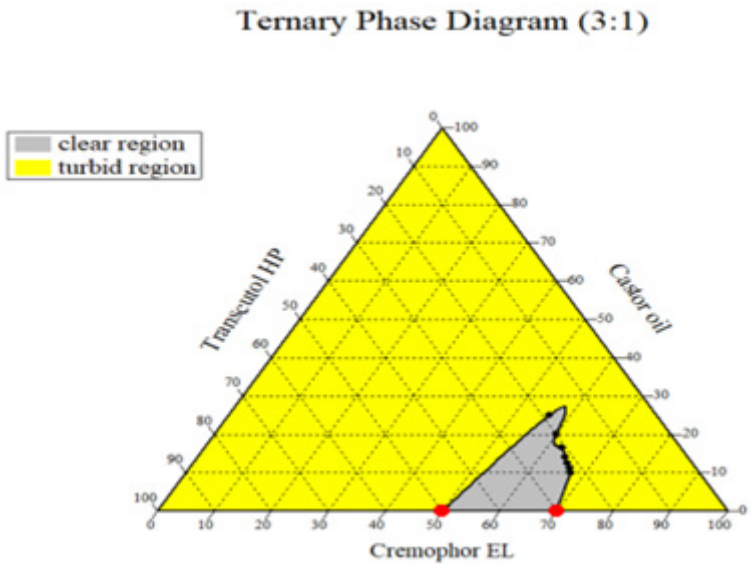

Figure 4: Ternary phase diagram showing the effect of oil (castor oil), surfactant (Cremophor EL) and co-surfactant (Transcutol HP). Nano-emulsion regions are shaded.

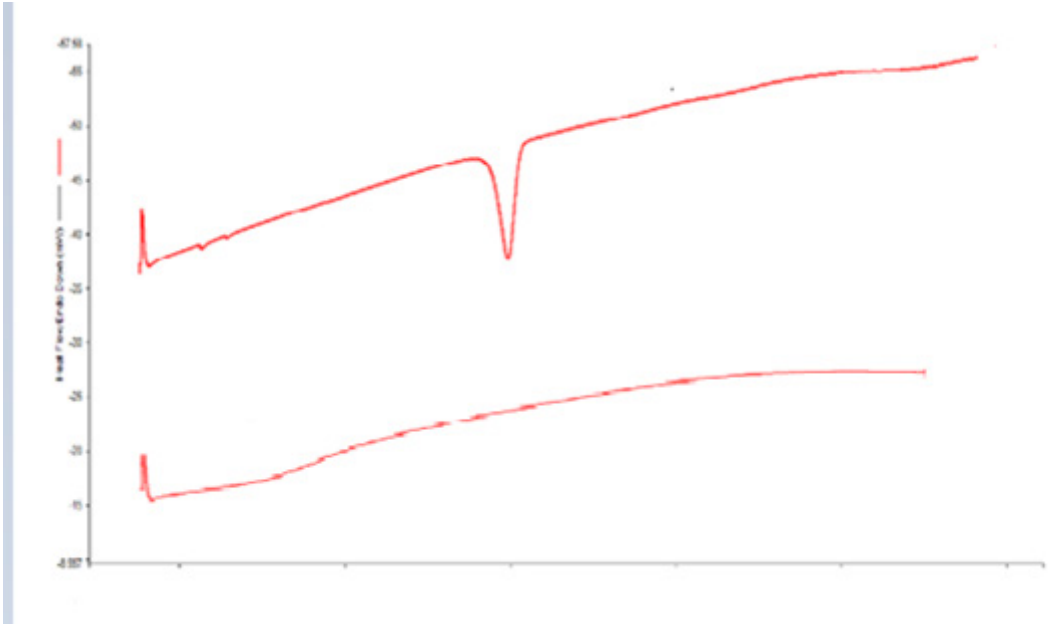

Figure 5: DSC curve of a) Dabigatran etexilate b) S-SNEDDS Formulation.

showed that it was transparent. Because the droplets in the dispersed phase were no larger than 1/4 of the wavelength of visible light, the system was transparent (Chenhen *et al.*, 2015). The nano-emulsion appears translucent or transparent because it scatters light. On increasing the concentration of oil, the percentage transmittance was more turbid due to the presence of the lyophilic group.

Phase Separation

The formulation was visually observed for any phase separation, creaming and cracking. There was no phase separation of the formulation checked for 24 hr. Phase separation was not observed in formulations with oil concentrations less than 30% and surfactant concentrations greater than 60%.

Self-emulsification time

The time at which the formulation emulsifies is an important parameter to check the efficiency of self-emulsification because SNEDDS should dissolve quickly and completely when subjected to dilution under mild agitation. When diluted with gentle agitation, the ideal SNEDDS formulation should be able to disperse instantly and fully. The rate and depth of water penetration into the various phases (liquid crystalline or gel phase) generated on the surface of the droplet are connected to the rate and depth of emulsification. When the energy needed to

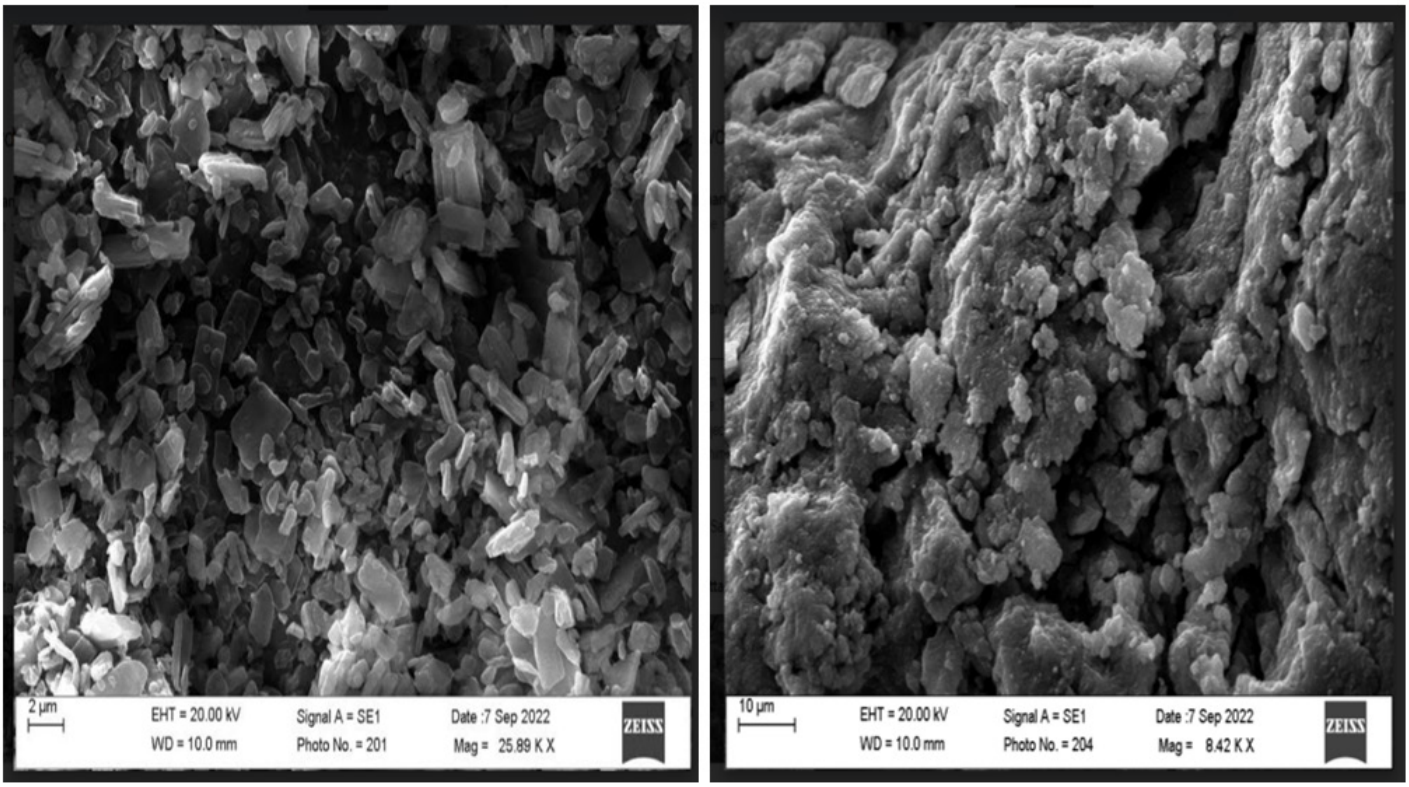

Figure 6: SEM of DBE and SEM of Solid S-SNEDDS.

expand the surface area between the oil and aqueous phases of the dispersion is larger than the entropy changes favoring dispersion, self-emulsification occurs. When the oil phase is added to the aqueous phase of a self-emulsifying system with gentle stirring, the aqueous phase will permeate through the oil phase's interface until the two phases' interfaces are broken. As a result, oil droplets are created, which causes emulsification (Basalious *et al.*, 2010). The time of emulsification for the formulation was found to be 42±2.5 sec.

Zeta potential and PDI

The size of droplets after nano-emulsion is the most important parameter as it affects the absorption of the drug as well as drug release. Small droplets have more surface area, hence enhancing the absorption. Zeta potential is an indicator of the physical stability of the emulsion. From the ternary phase diagram, it is estimated that when increasing the concentration of oil resulted in turbidity while increasing the S_{mix}. concentration resulting in clear formulation. From the ternary phase diagram, the droplet size, PDI and Zeta potential were found to be 114.9, 0.463 and -55.7 which was similar to the optimized formulation. Smaller particles were recorded with high zeta potential conferring to the higher stability of the product (Singh *et al.*, 2011). It was also reported that an increase in surfactant concentration to 60% increased mean droplet size (Alghananim *et al.*, 2020).

Drug content

The drug content of the prepared S-SNEDDS was calculated. The drug content of the formulation was found to be 94.3±0.5%.

Characterization of the prepared Solid supersaturated-SNEDDS formulation

Flow properties of solid S-SNEDDS powder were determined from bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose was mentioned in Table 5. The bulk density of the powder was determined which shows the density as well as arrangement of the powder particles. Tapped density shows that the void spaces decrease when the powder is tapped many times.

This study shows that the bulk density was found to be 0.52±0.05 and the tapped density was found to be 0.62±0.09. The powder has good flow when the Hausner's ratio is lower than 1.2 and if it is more than 1.2 it is considered as bad. From the above bulk and tapped density Hausner's ratio and Carr's index were determined and were found to be 1.2±0.12 and 15.8±0.699. The angle of repose was found to be 28.34±0.02. The flow property of powder was in the range and was considered excellent.

Differential Scanning Colorimetry

The thermal behavior and physical state of a drug within a formulation can be determined by DSC studies. DSC of the drug (DBE) and supersaturated SNEDDS formulation of DBE are shown in Figure 5. Pure DBE exhibited a sharp endothermic peak corresponding to its melting point of 159.8°C, indicating

that the drug is present in a crystalline form. The supersaturated SNEDDS formulation did not show an obvious endothermic peak corresponding to the melting point of crystalline DBE. Therefore, the formulation probably contains an amorphous component of the drug in the formulation. Amorphous substances require less energy for their dissolution, resulting in increased dissolution rates and thus, higher apparent solubility (Kimim *et al.*, 2021). This might explain the reason for the higher solubility of the SNEDDS observed in this study.

Scanning Electron Microscopy

The surface morphology and globule size of the formulated SNEDDS were also determined microscopically using SEM. The SEM image shows rough and spherical shapes with a size smaller than 50 nm. It is clear that the globules were well dispersed, and no aggregation occurred. The image of the solid SNEDDS of powdered medication and the formulation containing DBE shows that the particles had the same exterior macroscopic

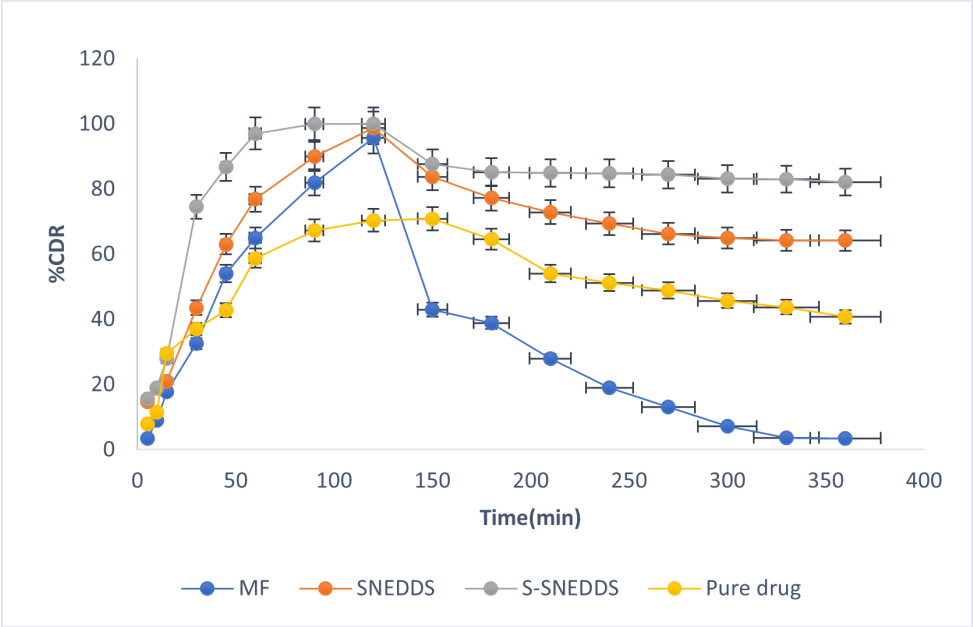

Figure 7: *In vitro* drug release profile comparison between marketed formulation, the capsule containing SNEDDS and the capsule containing S-SNEDDS in 0.1N HCl and pH 6.8 phosphate buffer.

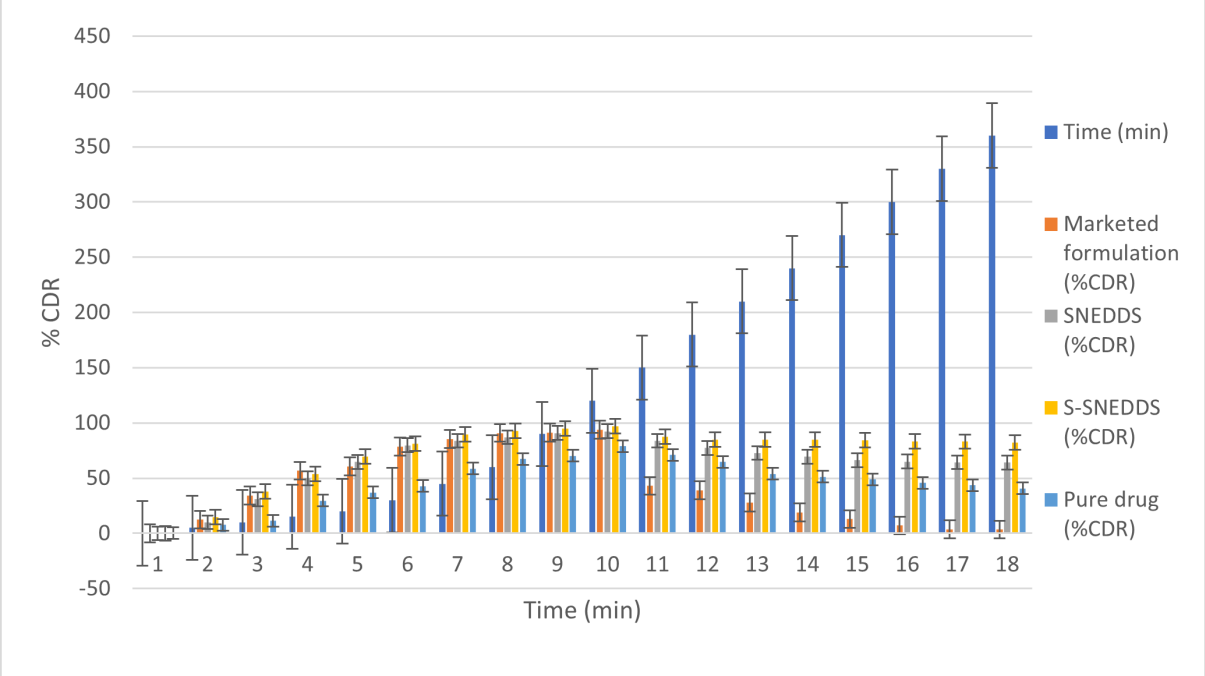

Figure 8: Percentage CDR release with respect to time (min).

morphology, which consisted of well-separated spherical particles with moderately deep dents and similar sizes (Figure 6).

In vitro Drug Release of SNEDDS

In vitro drug release studies of marketed formulation and capsule containing SNEDDS formulation without and with the incorporation of PI were carried out in 0.1N HCl and 6.8 pH phosphate buffer and were done using "USP type II apparatus". The dissolution was carried out in 0.1N HCl and in pH 6.8 phosphate buffer (Figure 7). The marketed formulation of DBE, SNEDDS and S-SNEEDS shows greater drug release of 90% in SGF in about 60 min and there was approximately 67% dissolution of DBE when switching to SIF. This is because SNEDDS can rapidly form oil-in-water nano-emulsions when subjected to aqueous dilution under gentle agitation. The marketed formulation of DBE was highly dissolved in SGF (93%) but precipitated immediately in SIF (3%); the precipitation in the small intestine delays the oral absorption and the bioavailability of poorly water-soluble drugs. For this S-SNEDDS was formulated and inhibited the precipitation in SIF and showed drug release of about 82% in 6 hrs. A capsule containing S-SNEDDS shows a greater drug release of 96% in 60 min as compared to a capsule containing SNEDDS which shows a drug release of 92% in 0.1N HCl. Whereas 6.8 pH buffer capsules containing S-SNEDDS showed faster drug dissolution (82%) as compared to SNEDDS (64%) which is due to low surface free energy (Figure 8).

DISCUSSION

Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) are advanced formulations designed to improve the bioavailability of poorly water-soluble drugs. These systems offer a unique solution for delivering lipophilic drugs that struggle with low solubility and poor absorption in the Gastrointestinal (GI) tract. SNEDDS are isotropic mixtures of oils, surfactants and co-surfactants or solvents that spontaneously form oil-in-water nano-emulsions upon contact with aqueous environments such as the GI fluids, without the need for external energy like mechanical stirring.

SNEDDS was prepared using oil, surfactant and co-surfactant. Castor oil (triglyceride) is a Ricinoleic acid, a C18:1 carbon fatty acid with a hydroxyl group. Cremophor EL is used as a medium-chain triglyceride. Transcutol HP is used as a co-surfactant. To formulate supersaturated SNEDDS; Castor oil, Cremophor EL and Transcutol HP was used in the most appropriate ratio to produce a stable nano-emulsion. Sixteen SNEDDS formulations of these components were prepared using different amounts of oil, surfactant and co-surfactant. Then from the Ternary phase diagram formulation is selected. From the formulation Dabigatran Etexilate (150 mg) and Sodium taurocholate (2%) were incorporated and Liquid supersaturated SNEDDS formulation was prepared.

The FTIR spectra of castor oil with the drug showed characteristic peaks of castor oil and drug at 3418.82, 2854.27, 2727.56 and 1746.23 cm^{-1}[11]. The FTIR spectra of Cremophor EL with the drug showed characteristic peaks at 3449.05, 2921.00, 1967.25 and 1735.02 cm^{-1} which confirms the compatibility between Cremophor EL and the drug. The FTIR spectra of the physical mixture of Transcutol HP and the drug showed characteristic peaks at 3452.51, 2928.43, 2346.06 and 1733.31 cm^{-1} which confirms the compatibility between Transcutol HP and the drug. PDI, Zeta and globule size of Liquid supersaturated SNEDDS were found to be 114.9, 0.463 and -45.7. The drug content of the formulation was found to be 94.3±0.5%.

supersaturated SNEDDS formulation is achieved by adsorbing liquid supersaturated SNEDDS in aerosil 200 to fill the solid granules in capsules. Pure DBE exhibited a sharp endothermic peak, that corresponds to its melting point 159.8°C and this indicates that the drug is present in a crystalline form. The SEM image shows rough and spherical shapes with a size smaller than 50 nm. S-SNEDDS was formulated and inhibit the precipitation in SIF and show drug release of about 82% in 6 hr. *In vitro* drug release studies showed greater drug release in supersaturated SNEDDS as compared to marketed formulation and SNEDDS formulation.

CONCLUSION

In this study supersaturated SNEDDS formulation was prepared. To formulate supersaturated SNEDDS; Castor oil, Cremophor EL and Transcutol HP was used in the most appropriate ratio to produce a stable nano-emulsion. From the ternary phase diagram sixth formulation was selected that shows significant zeta potential and PDI index. In this preparation Sodium taurocholate as a precipitation inhibitor at different concentrations was added to the best formulation whose zeta potential and PDI were determined. The Zeta potential and PDI of the formulation were found to be -45.7 and 0.46. The drug content of the formulation was found to be 94.3±0.5% with increased oral bioavailability. Overall, this study showed that employing HPMC as a precipitation inhibitor might stabilize and enhance the *in vitro* performance of Super-saturated SNEDDS of Dabigatran etexilate.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SNEEDS: Self Nano-Emulsifying Drug Delivery System; **HPMC:** Hydroxypropyl methylcellulose; **PPI:** Polymeric Precipitation Inhibitor; **DSC:** Differential Scanning Calorimetry; **DBE:** Dabigatran Etexilate; **SEM:** Scanning Electron Microscopy.

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