



# Formulation and *in-vitro* Characterization of Solid Self Nanoemulsifying Drug Delivery System (s-SNEDDS) Of Simvastatin

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## Abstract

The Aim Of The Present Work Is To Prepare Solid Self Nanoemulsifying Drug Delivery System (S-Snedds) Of A Poorly Water Soluble Drug Simvastatin With Crospovidone As Carrier To Enhance Dissolution Rate Of Simvastatin. Based On Solubility Studies And Pseudo Ternary Phase Diagrams Five Liquid Snedds Were Prepared With Selected Systems In Various Proportions And Evaluated For Self Emulsification Time, Phase Separation And Precipitation Of The Drug, Robustness To Dilution, Percentage Transmittance, Thermodynamic Stability Studies, Droplet Size, Pdi And Zeta Potential. From The Evaluation Studies It Was Found That Formulation Consisting Of Capryol90(18%W/W) , Cremophore Rh40(57.6%W/W), Transcutol – Hp(14.4%W/W) And Drug(10%W/W) Was Stable And Optimum And Selected For Preparation Of S-Snedds. With Selected Optimum Formulation S-Snedds Are Prepared Using Crospovidone As Carrier In 1:2 Ratio By Adsorption Technique And Evaluated For Flow Properties, Drug Content, Effect Of Dilution, Droplet Size Determination, Ft–Ir Studies, In–Vitro Drug Release Study And Accelerated Stability Study For 6 Months. Prepared S-Snedds Showed “Good” Flow Properties And 94.192±1.39% Drug Content. Reconstitution Properties Showed Spontaneous Nano Emulsification With Droplet Size 16.27 Nm And Pdi 0.276. Results Of In-Vitro Dissolution Revealed That % Drug Released Form S-Snedds Is Higher Than That Of Pure Drug And Marketed Tablet. Results Of Accelerated Stability Study For 6 Months Showed That Formulation Was Stable And Does Not Alter The Dissolution Rate Of Simvastatin. The Results Of Present Study Have Proved The Potential Use Of Snedds To Improve Solubility And Dissolution Rate Of Poorly Water Soluble Drug Simvastatin.

**Keywords:** Accelerated Stability Study, Crospovidone, Solid-Self Nanoemulsifying Drug Delivery System (S-Snedds), Simvastatin

## INTRODUCTION

Oral route is most preferred route of drug delivery for treatment of number of diseases as the oral route is patient convenient and most preferred route for treatment of number of chronic diseases. If we go for oral route one of the most important criteria is aqueous solubility. But more than 40% new chemical entities are poorly soluble in water resulting in unsatisfactory oral delivery of drugs due to low and inconsistent bio availability which in turn effect the pharmacological response of the drug [1]. For successful oral delivery of such poorly water soluble drugs it is necessary to improve their solubility. Different technological strategies are developed to increase solubility of poorly soluble drugs like Particle size reduction, Salt formation, Hydrotrophy, Solid dispersions, pH Adjustment, Use of surfactants, Complexation, Super critical fluid process, Co-solvency etc [2, 3]. Each strategy has its own limitations owing to development of other formulation strategies like Self Emulsifying Drug Delivery Systems (SEDDS). Self nano emulsifying drug delivery systems(SNEDDS) are member to SEDDS family. SNEDDS are isotropic mixtures of oil, hydrophilic surfactant, co surfactant / co solvent and drug that form fine o/w nano emulsion when introduced into aqueous phase under mild agitation with globule size less than 100nm. The advantages of these systems include Enhanced oral bioavailability enabling reduction in dose, Fine oil droplets would pass rapidly and promote wide distribution of the drug throughout the GIT, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall, as compared

with oily solutions they provide a large interfacial area for partitioning of the drug between oil and water [4].

Conventionally SNEDDS are prepared as liquid dosage forms and filled in hard or soft gelatin capsules which may have some disadvantages like stability, handling problems, incompatibility with gelatin shells, potential of leaching. To overcome these difficulties Solid SNEDDS were developed for potential commercial use and patient comfort [5]. Many solidification techniques are used to transform liquid SNEDDS to s-SNEDDS such as Adsorption onto solid carrier, Spray drying, Melt granulation, Melt extrusion [6]. Among all these Adsorption onto solid carrier in simple technique involving addition of liquid SNEDDS to carrier followed by simple blending. Then the resultant powder may filled into capsule shell or compressed into tablets by mixing with suitable excipients [7]. The drug Simvastatin an Anti-Hyperlipidaemic drug belonging to BCS Class II which has poor aqueous solubility of 30µg/mL [8], high partition coefficient (log p=4.5) and low bio availability (<5%) [9]. Thus there is need to overcome the problems associated with poorly soluble drug to produce reproducible and better dissolution profile for Simvastatin. To enhance solubility, dissolution, stability, absorption and bio availability of drug, SNEDDS are one of the most promising technique. The selected SNEDDS formulations overcome the problems associated with poorly soluble drug and are more capable to produce reproducible and better dissolution profile for Simvastatin. Present study aimed to Prepare and characterize s-SNEDDS of Simvastatin using Crospovidone by adsorption technique to enhance dissolution rate of Simvastatin.

## MATERIALS AND METHODS

### Materials:

Simvastatin was obtained as gift sample from Hetero Drugs Pvt. Ltd. (Hyderabad, India). Capryol 90, Cremophore RH40, Transcutol HP, Labrasol, Labrafac PG, Labrafac Lipophile WL 1349, Peceol, Lauroglycol 90 were donated by Gattefosse (Mumbai, India). Oleic acid was purchased from SD Fine chemicals (Mumbai, India). UV Spectrophotometric grade Methanol was purchased from Merck (Mumbai, India). Crospovidone was obtained as gift sample from Hetero Drugs Pvt. Ltd. (Hyderabad, India).

### Methods:

#### Solubility studies

The saturation solubility of Simvastatin was determined in selected vehicles such as oils, surfactants and co-surfactants. 1g of vehicle has been taken in screw capped glass vial to this excess amount of drug is added. The resultant drug-vehicle mixtures were cyclomixed using cyclomixer (CM 101, Remi, India) to simplify a process of Solubilization. Then the mixtures were heated in thermostatic water bath at 40°C for 10 minutes further to facilitate Solubilization. Then, the mixtures were shaken in rotary shaker for 48hrs at 25 °C and kept for equilibration for 24hrs. After reaching equilibrium each vial was centrifuged at a speed of 3500rpm for 15minutes. The supernatant was separated by filtration using 0.45µ filters and then suitably diluted with methanol. Samples were analyzed UV Spectrophotometrically<sup>[10, 11]</sup> at 237.8nm. Concentration of Simvastatin in each vehicle was calculated using regression equation that was given along with previously constructed calibration curve.

#### Construction of pseudo-Ternary Phase Diagrams

Pseudo-ternary phase diagrams were constructed for selected oil, surfactant, co-surfactant with water at room temperature by water titration method. From solubility studies oleic acid, capryol90 were selected as oil phase; labrasol, cremophor RH40 were selected as surfactants; Transcutol P was selected as co-surfactant. The surfactant was mixed with co-surfactant in ratio 4:1, 3:1, 2:1, 1:1 respectively. Aliquots of surfactant/co-surfactant mixture were then mixed with oil at ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 in different vials and then titrated with water at room temperature<sup>[12]</sup>. The samples were then equilibrated for 30seconds and visually observed after each addition. Based on visual observation the systems were classified as nanoemulsion, micro emulsion, coarse dispersion and gel phases<sup>[13]</sup>. Pseudo ternary phase diagrams were then constructed using Triplot software version 4.1.2. The samples which were clear (or) bluish transparent in appearance were considered as nanoemulsions.

#### Preparation of liquid SNEDDS

Five different Simvastatin SNEDDS were made using Capryol 90 as oil Cremophor RH 40 as surfactant and Transcutol P as co-surfactant. Concentration of Simvastatin was kept constant (10mg) in all formulations. Surfactant/co-surfactant mixture ( $S_{mix}$ ) was prepared by mixing in suitable proportions and cyclomixed. Simvastatin was accurately weighed and dissolved in oil and then  $S_{mix}$

was added to above oil-drug mixture. The components were cyclomixed until transparent preparations were obtained. Finally prepared SNEDDS of Simvastatin were kept aside at room temperature to examine for signs of turbidity (or) phase separation prior to characterization.

#### Characterization of liquid SNEDDS

##### Self emulsification and visual assessment<sup>[14]</sup>

Self emulsification property of SNEDDS formulations was evaluated by visual assessment. Time taken for the formation of nano emulsion was determined by drop wise addition of formulation to 250mL of distilled water, simulated gastric fluid and phosphate buffer of pH 6.8 in separate glass beakers at 37 °C and the contents were gently stirred using magnetic stirrer at 100rpm. The tendency to form an emulsion is assessed as “good” when emulsification occurs rapidly in less than 1 minute with clear (or) transparent appearance. The tendency to form an emulsion is assessed as “bad” when there is less clear emulsion formation. Depending on visual appearance and time taken for self emulsification, formulations are graded as<sup>[15]</sup>,

- Grade A: Rapidly forming (within 1min) nano emulsion having a clear (or) bluish appearance.
- Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
- Grade C: Fine milky emulsion that formed within 2 minutes.
- Grade D: Dull, grayish white emulsion with a slight oily appearance that is slow to emulsify (more than 2 minutes).
- Grade E: Formulation Exhibiting either poor or minimal emulsification with large oil globules present on the surface.

##### Phase separation and stability study of emulsions

Each SNEDDS formulation (50µL) was added to a vials containing 5mL of double distilled water, simulated gastric fluid at room temperature and cyclomixed for 1 minute then each mixture was stored and observed for phase separation and precipitation of drug at intervals 2, 4, 6, 8, 12, 24 hours period of time.

##### Robustness to dilution<sup>[16]</sup>

Prepared SNEDDS formulations were subjected to dilution in ratios 1:100 & 1:1000 folds with distilled water, 0.1 N HCl and phosphate buffer of pH 6.8. the diluted nano emulsions were stored for 24 hrs and visually observed for any signs of phase separation (or) precipitation of drug.

##### Percentage Transmittance

Each SNEDDS formulation (100µL) was added to a vial containing 10mL of double distilled water, 0.1 N HCl and phosphate buffer of pH 6.8 at room temperature and cyclomixed for 1minute<sup>[17]</sup>. Each sample was observed for %Transmittance at 238nm.

##### Drug loading efficiency<sup>[18]</sup>

Drug content in formulation was determined UV-Spectrophotometrically. 50mg of each formulation was accurately weighed and dilute to 100mL with methanol. Resultant solutions were analyzed spectroscopically following suitable dilution.

Drug loading efficiency was calculated by equation

Drug loading efficiency

$$= \frac{\text{Amount of drug in known amount of formulation}}{\text{Initial drug load}} \times 100$$

#### **Thermodynamic stability studies**

The prepared SNEDDS formulations were subjected to thermodynamic stability studies to study the effect of centrifugation and temperature on stability of nano emulsions.

#### **Centrifugation study<sup>[19]</sup>**

The formulations were added to deionized water in ratio 1:20 and centrifuged at 3500 rpm for 30minute and observed for phase separation (or) precipitation.

#### **Freeze thaw cycle<sup>[19]</sup>**

The formulations which are stable under centrifugation were subjected to freeze thaw cycle. In this study , SNEDDS formulations were diluted with deionized water in 1:20 ratio and subjected to two freeze thaw cycles between -20 °C and +25 °C by storing at each temperature for 48hrs and after 48hrs samples were observed for phase separation (or) precipitation.

#### **Droplet size and Zeta potential determination**

Prepared SNEDDS formulations were added to distilled water in ratio 1:1000 in test tube and mixed for 1 minute using a cyclo mixer. The droplet size, PDI of the emulsions were determined at 25°C by dynamic light scattering (DLS) technique at 90° angle and Zeta potential was determined by electrophoretic light scattering technique using a Malvern Zeta sizer nano ZS90.

#### **Formulation of Solid – SNEDDS<sup>[20,21]</sup>**

From the characterization studies done on five different Simvastatin SNEDDS , formulation C90C40T41-2 with good stability , good self nano emulsification property and showed less particle size and less PDI was selected to formulate as solid SNEDDS. S-SNEDDS was prepared by mixing liquid SNEDDS containing Simvastatin with Crospovidone as carrier in ratio 1:2. Liquid SNEDDS was added in drop wise manner over Crospovidone contained in porcelain dish. After each addition, contents were mixed using glass rod for uniform distribution of formulation. Resultant damp mass was passed through sieve no.120 and dried at room T °C and stored until further use.

#### **Characterization of S-SNEDDS**

##### **Flow properties of S-SNEDDS<sup>[22, 23]</sup>**

##### **Angle of repose<sup>[22]</sup>**

The angle of repose of S-SNEDDS was determined by funnel method. Height of funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of powder. Accurately weighed sample was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the equation

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

where h and r are height and radius of powder cone.

##### **Bulk density and tapped density**

A quantity of 2gm of S-SNEDDS was introduced into 10mL measuring cylinder. Initial volume was noted and cylinder was allowed to fall under its own weight into a hard surface from a height of 2.5 cm at 2 second intervals. Tapping was continued until no further change in volume

was noted. Bulk density and Tapped density were calculated using the following equations<sup>[22]</sup>;

$$\text{Bulk density (BD)} = \frac{\text{Weight of powder blend}}{\text{Volume of the packing}}$$

$$\text{Tapped density (TD)} = \frac{\text{Weight of powder blend}}{\text{Tapped Volume of the packing}}$$

##### **Compressibility index**

The compressibility index of the blend was determined by Carr's compressibility index given by the equation.

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

##### **Hausner's Ratio**

Hausner's Ratio is a number that is correlated to the flowability of a powder (or) granular material. Hausner's ratio can be calculated by the equation

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

##### **Drug content<sup>[24]</sup>**

S-SNEDDS of Simvastatin was accurately weighed equivalent to 10mg and dissolved in sufficient quantity of methanol. The solution was sonicated for 10min in order to extract the drug in methanol and filtered. The absorbance of filtrate was measured at 237.8 nm using UV-Visible Spectrophotometer.

#### **Reconstitution properties of S-SNEDDS**

##### **Effect of dilution on S-SNEDDS<sup>[25]</sup>**

100 mg S-SNEDDS was accurately weighed and introduced into 100mL double distilled water in a beaker at 37°C and mixed gently using magnetic stirrer at 100rpm. The property of rapid emulsification was observed. The tendency to form an emulsion is assessed as “good” when emulsification occurs rapidly in less than 1 minute with clear (or) transparent appearance. The tendency to form an emulsion is assessed as “bad” when there is less clear emulsion formation.

##### **Droplet size determination**

100 mg of S-SNEDDS formulation was diluted with 100 mL distilled water in a test tube and cyclomixed. The droplet size and poly dispersibility index of emulsion was determined at 25 °C by dynamic light scattering (DSC) technique at 90° angle using a Malvern zeta sizer Nano ZS90.

##### **FT-IR studies**

FT-IR Spectrum of pure drug , Crospovidone and Formulation were obtained by FT-IR Spectrophotometer. The spectrums were taken with the accumulation 24 scans and a resolution of 4cm<sup>-1</sup> over the range of 400-4000 cm<sup>-1</sup>. The spectrum of formulation so obtained was compared with spectrum of pure drug for any interactions.

##### **In-Vitro drug release study**

The in-vitro dissolution study of S-SNEDDS which were filled into 0 size capsule, API and marketed drug were carried out using USP-Type II dissolution test apparatus (DS1800 Lab India) in 500mL buffer of pH 1.2 containing 0.3%w/w SLS at 37±0.5 °C with 100rpm rotating speed. Samples were withdrawn at 5, 10, 15, 30, 45, 60 minutes time intervals and filtered through 0.45µ filter. An equal volume of dissolution medium was replenished after every sampling to maintain constant volume. Samples were analyzed using a double beam UV-Spectrophotometer at

238.8nm. The cumulative percentage drug released was calculated and graph was plotted against time.

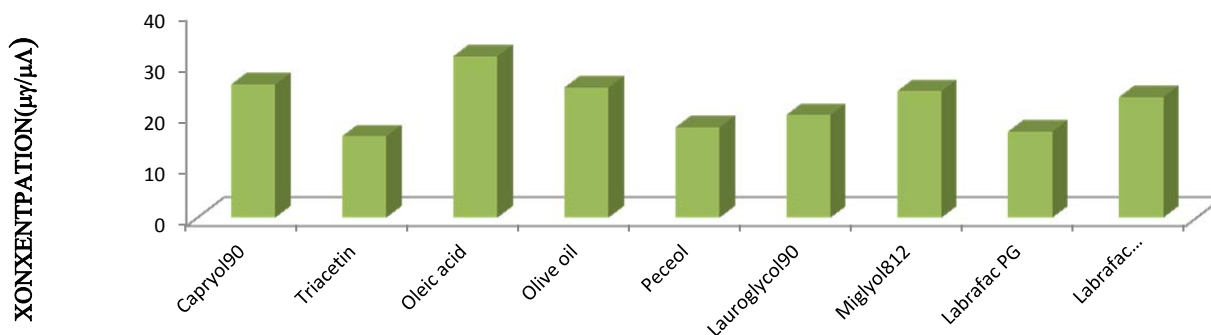
**Accelerated stability Testing**

Accelerated stability studies of S-SNEDDS formulations was carried out according to ICH guidelines. The formulation was stored at 40 °C and 75%RH for 6 months in stability chamber. Later the formulation was evaluated for parameters such as effect of dilution, droplet size, PDI and in vitro drug release.

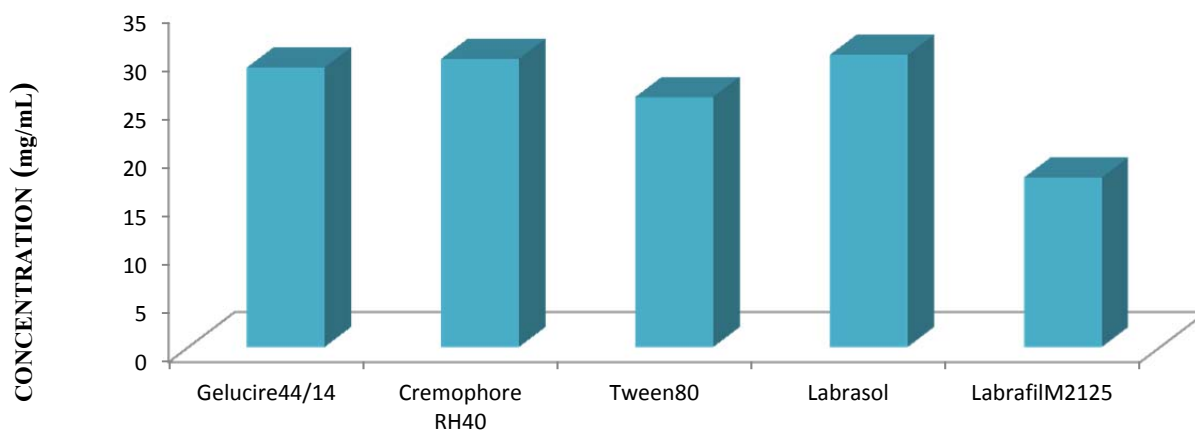
**RESULTS AND DISCUSSION**

**Solubility studies**

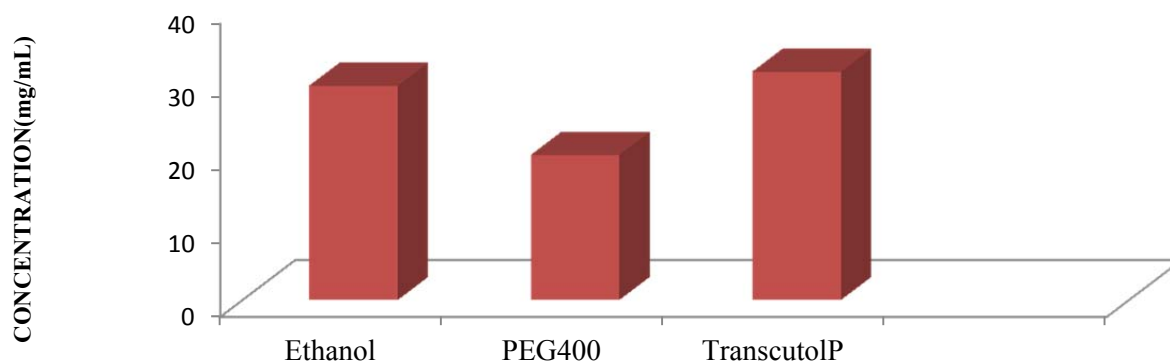
Solubility of Simvastatin is determined in various Oils, Surfactants, Co-surfactants by UV-Spectrophotometric method. Simvastatin has been shown maximum solubility in oils Oleic acid & Capryol 90; in surfactants & Cremophore RH40 and in co-surfactant Transcutol HP. Results of solubility studies are given in **Figure 1** to **Figure 3**.



**Figure 1: Solubility of Simvastatin in various Oils**



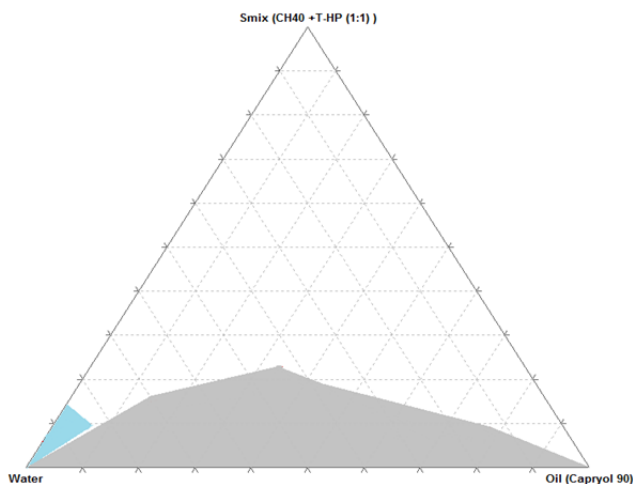
**Figure 2: Solubility of Simvastatin in various Surfactants**



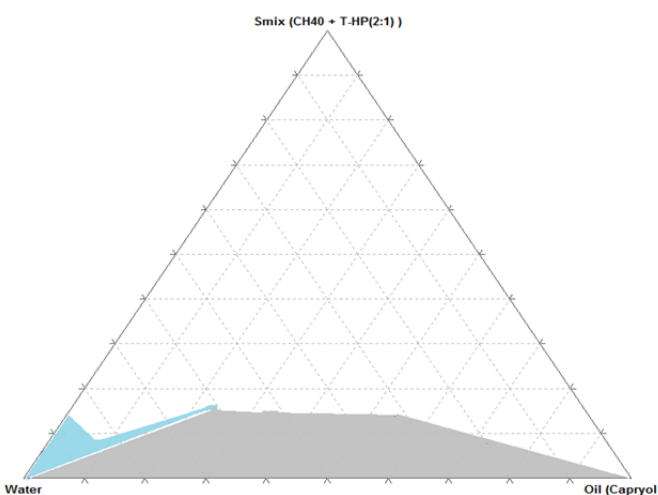
**Figure 3: Solubility of Simvastatin in various Co-surfactants**

**Construction of Pseudo-ternary Phase Diagrams**

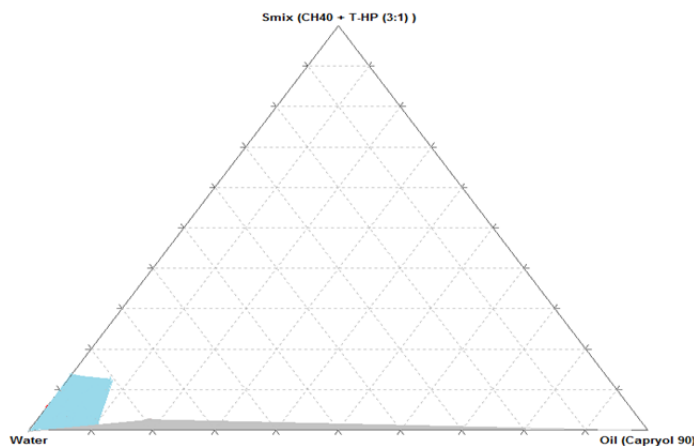
Pseudo – ternary Phase Diagrams are constructed to identify the nano emulsion regions and to identify suitable composition of oil , surfactant and co-surfactant for formulation of SNEDDS. From Pseudo – ternary phase diagrams it has been found that the systems consisting of Capryol 90 as oily phase, Cremophore RH40 as surfactant and Transcutol HP as co-surfactant showed good nano emulsifying property though drug has been shown more solubility in Oleic acid and Labrasol based on solubility studies. It was also found that by increasing oil content systems showing appearance of coarse emulsion. It was also found that for systems consisting of Capryol 90, Cremophore RH40, Transcutol HP by increasing co-surfactant proportion in  $S_{mix}$  systems had been shown decreasing property of spontaneous nano emulsion formation. From this observation it is also clear that Surfactant is playing role to form nano emulsion in a proper range spontaneously. Pseudo-ternary phase diagrams of C90C40T systems are shown in **Figure 4** to **Figure 7**.



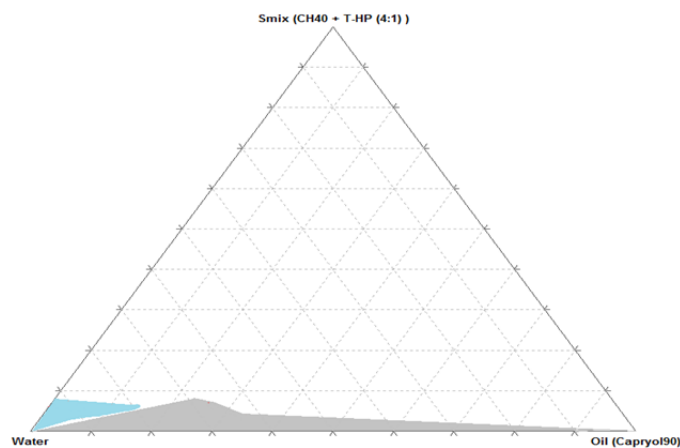
**Figure 4: Pseudo ternary phase diagram of C90C40T 1:1**



**Figure 5: Pseudo ternary phase diagram of C90C40T 2:1**



**Figure 6: Pseudo ternary phase diagram of C90C40T 3:1**



**Figure 7: Pseudo ternary phase diagram of C90C40T 4:1**

◆ NANO EMULSION  
 ◆ COARSE EMULSION

**Preparation of selected SNEDDS formulations**

Five different SNEDDS formulations are prepared with varying ratios of Oil , Surfactant, Co-surfactant. In all formulations the amount of Simvastatin is constant(10mg). Composition of prepared SNEDDS formulations was given in **Table 1**.

**Table 1 : Composition of prepared SNEDDS formulations**

Formulation name	Drug (mg)	Capryol 90 (mg)	Cremophore RH40(mg)	Transcutol-HP(mg)
C90C40T41-2	10	18	57.6	14.4
C90C40T41-3	10	27	50.4	12.6
C90C40T31-2	10	18	54	18
C90C40T21-3	10	27	42	21
C90C40T11-2	10	18	36	36

**Evaluation of Simvastatin liquid SNEDDS**

*Self emulsification and visual assessment*

According to visual assessment formulations are graded for self-emulsification time. Self emulsifying mixtures should disperse rapidly in aqueous medium with mild shaking. Self emulsification time that was determined for prepared SNEDDS are given in **Table 2**. It was found that all

formulations are emulsified in 30 to 42 seconds i.e. performance of all formulations was said to be good.

**Table 2 : Self emulsification time (Seconds) (n=3)**

Formulation name	Self emulsification time (Seconds)	Performance of emulsion
C90C40T41-2	30.33 ± 2.52	Good
C90C40T41-3	39 ± 3	Good
C90C40T31-2	35.33 ± 1.53	Good
C90C40T21-3	42.67 ± 2.082	Good
C90C40T11-2	42 ± 2	Good

#### Phase separation and stability study of emulsions

Prepared SNEDDS formulations are observed for precipitation and phase separation of drug at intervals 2, 4, 6, 8, 12, 24 hrs period of time and it was found that all formulations showed neither precipitation nor phase separation of the drug. Results are given in **Table 3**.

**Table 3: Phase separation and precipitation of the drug (n = 3)**

Formulation name	Precipitation	Phase separation
C90C40T41-2	NO	NO
C90C40T41-3	NO	NO
C90C40T31-2	NO	NO
C90C40T21-3	NO	NO
C90C40T11-2	NO	NO

#### Robustness to Dilution

Formulations are diluted with excess of Water, 0.1N HCl and Phosphate buffer of pH 6.8 and the diluted samples are stored for 24hrs and visually observed for precipitation (or) phase separation of drug. No precipitation (or) phase separation is found which indicates all formulations are robust to dilution. Results are given in **Table 4**.

**Table 4 : Robustness to dilution (n = 3)**

Formulation name	Distilled Water	0.1N HCl	Phosphate buffer pH 6.8
C90C40T41-2	*P	*P	*P
C90C40T41-3	*P	*P	*P
C90C40T31-2	*P	*P	*P
C90C40T21-3	*P	*P	*P
C90C40T11-2	*P	*P	*P

#### Percentage Transmittance

All formulations showed %Transmittance more than 95% indicating clear emulsions. Results are given in **Table 5**.

**Table 5: Percentage Transmittance (n=3)**

Formulation name	Distilled Water	0.1N HCl	Phosphate buffer pH 6.8
C90C40T41-2	97.53 ± 0.53	98.064 ± 0.32	97.87 ± 0.242
C90C40T41-3	96.842 ± 0.4	98.067 ± 0.4	96.13 ± 0.4
C90C40T31-2	96.93 ± 0.394	96.96 ± 0.32	97.2 ± 0.571
C90C40T21-3	97.152 ± 0.214	97.253 ± 0.31	97.035 ± 0.2
C90C40T11-2	98.313 ± 0.322	97 ± 0.264	97.12 ± 0.274

#### Drug loading efficiency

It was found that all formulations have drug loading efficiency more than 90% except the formulation C90C40T21-3 which contain 87.4% loading. Results are given in **Table 6**.

**Table 6: Drug loading efficiency of formulations (n=3)**

Formulation name	Drug loading efficiency
C90C40T41-2	96.25 ± 0.31
C90C40T41-3	98.163 ± 0.65
C90C40T31-2	91.7 ± 0.342
C90C40T21-3	87.85 ± 0.412
C90C40T11-2	95.82 ± 0.55

#### Thermodynamic stability studies

Thermodynamic stability study is designed to identify Metastable formulation. The SNEDDS are subjected to Centrifugation study and Freeze thaw cycle. The emulsions are stable during centrifugation at 3,500rpm and alternative temperature cycles of -20 °C and +25 °C .

There is no precipitation and phase separation of formulations. The results are given in **Table 7**

**Table 7 : Thermodynamic stability studies**

Formulation name	Centrifugation (3,500rpm for 30min)	Freeze thaw cycle (-20 °C and +25 °C)
C90C40T41-2	*P	*P
C90C40T41-3	*P	*P
C90C40T31-2	*P	*P
C90C40T21-3	*P	*P
C90C40T11-2	*P	*P

#### Droplet size and Zeta potential determination

Droplet size , PDI and Zeta potential of the prepared formulations were determined. Droplet size was found to be in between 15.20 to 206.2 nm and PDI of all formulations was found to be below 0.5 i.e. there is distribution of uniform size particles. Zeta potential was found to be in between - 8.48 to - 19.3 mV. The results are given in **Table 8** and **Figures 8** to **9**. From the results it was found that formulation C90C40T41-2 showed less droplet size than other formulations.

**Table 8 : Results of Droplet size , PDI and Zeta potential(n=3)**

Formulation name	Average Droplet size (d.nm)	PDI	Zeta potential (mV)
C90C40T41-2	15.20	0.303	- 19.3
C90C40T41-3	151.8	0.386	- 8.48
C90C40T31-2	73.48	0.469	- 17.0
C90C40T21-3	77.3	0.463	- 15.7
C90C40T11-2	206.2	0.474	- 11.1

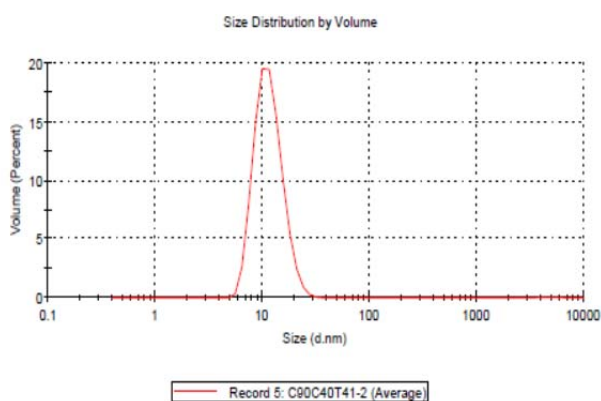


Figure 8 : Droplet size distribution of C90C40T41-2

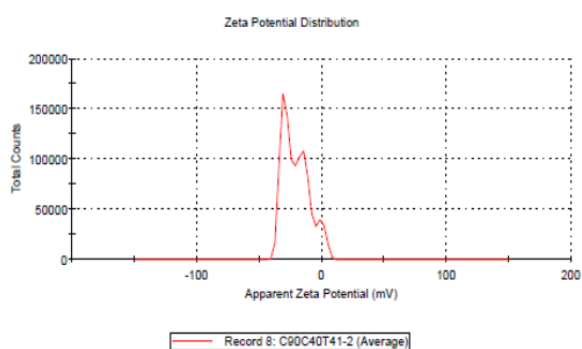


Figure 9: Zeta potential of C90C40T41-2

**Preparation of Solid SNEDDS of Simvastatin**

Based on evaluation tests done for five liquid SNEDDS formulations the formulation C90C40T41-2 is selected for preparation of solid SNEDDS of Simvastatin. Compared to other formulations C90C40T41-2 showed good self emulsification property which was emulsified spontaneously in  $30.33 \pm 2.52$  sec and also droplet size (15.20 nm) was less than other formulations with more uniform distribution of particles (PDI = 0.303). Hence the optimum composition for preparation of s-SNEDDS was found to be Capryol90 (18%w/w) , Cremophore RH40 (57.6%w/w), Transcutol – HP (14.4%w/w) and Drug (10%w/w). With selected optimum formulation s-SNEDDS are prepared using Croscopovidone as carrier in 1:2 ratio by adsorption technique.

**EVALUATION OF SOLID SNEDDS OF SIMVASTATIN**

**Flow properties of s-SNEDDS**

Flow properties such as Angle of Repose, Bulk density, Tapped density, Compressibility Index and Hausner’s Ratio are determined and it was found that Prepared s-SNEDDS showed “Good” flow properties. Results are given in Table 9.

Table 9 : Flow properties of s-SNEDDS of Simvastatin (n=3)

FLOW PROPERTIES	RESULTS
Angle of repose	$27.998 \pm 1.302$
Bulk density (g/mL)	$0.367 \pm 0.015$
Tapped density (g/mL)	$0.41 \pm 0.015$
Compressibility index (%)	$9.85 \pm 0.38$
Hausner’s ratio	$1.11 \pm 0.006$

**Drug Content**

Amount of drug present in prepared s-SNEDDS was determined. Drug content of the s-SNEDDS was found to be  $94.192 \pm 1.39$  %.

**Reconstitution properties of s-SNEDDS**

**Effect of dilution on s-SNEDDS**

Effect of dilution on s-SNEDDS was studied and it was found that prepared s-SNEDDS showed spontaneous emulsification i.e. in less than 1min and it was also found that there is no phase separation (or) phase inversion of nano emulsion after 24hrs storage of diluted sample.

**Droplet size Determination**

Mean droplet size and Poly dispersibility index of reconstituted s-SNEDDS were found to be 16.27nm and 0.276 . The s-SNEDDS showed PDI less than 0.3 i.e. there is distribution of uniform size particles. Results are shown in Figure 10.

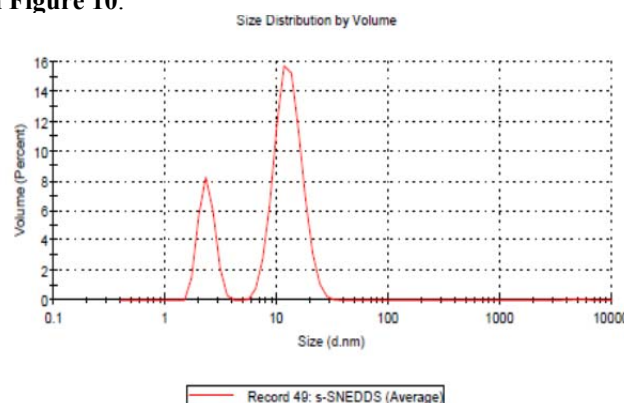


Figure 10: Droplet size distribution of s-SNEDDS

**FT – IR Studies**

FT-IR Spectrum of pure drug , Croscopovidone and the s-SNEDDS were obtained by FT-IR Spectrophotometer. The spectrum of s-SNEDDS so obtained was compared with spectrum of pure drug for any interactions. Characteristic peaks observed at  $3550.62, 2960.48, 1701.42 \text{ cm}^{-1}$  for O-H stretching vibration, C-H vibration, ester stretching vibration . FT-IR spectrum of pure drug and s-SNEDDS were almost similar because of same functional groups. It indicates there was no interaction between Simvastatin and excipients used in formulation. FT-IR spectrums of pure drug, Cross copovidone and s-SNEDDS are shown in Figures 11 to 13.

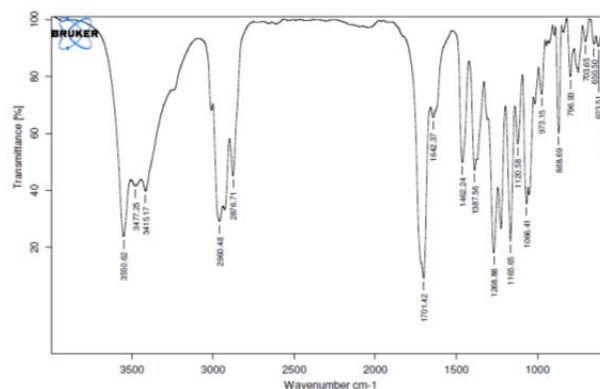


Figure 11 : FT-IR Spectrum of pure drug (Simvastatin)

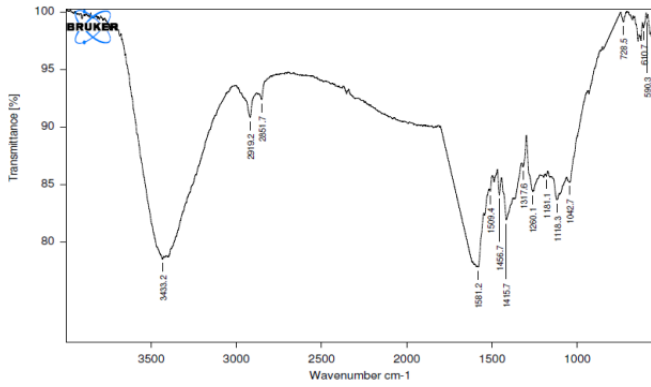


Figure 12 : FT – IR Spectrum of Crospovidone

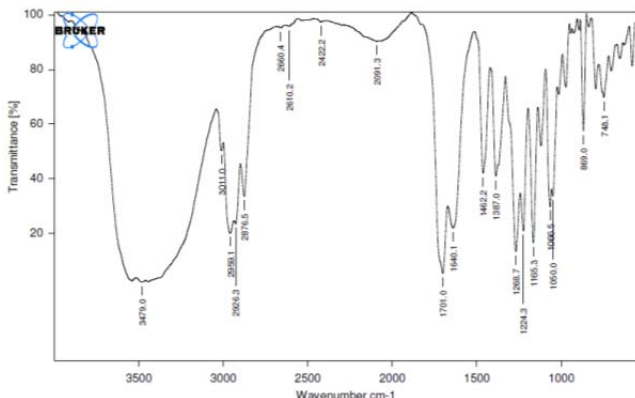


Figure 13 : FT – IR Spectrum of s-SNEDDS

**In – Vitro drug release study**

In – Vitro drug release study was done for pure drug, marketed tablet and s-SNEDDS of Simvastatin. The percentage drug release from s-SNEDDS was found to be higher than that of pure drug and marketed tablet. Cumulative Percentage drug release from prepared s-SNEDDS at 60min was found to be  $84.86 \pm 2.08 \%$  whereas for pure drug and marketed tablet Cumulative percentage drug release was found to be  $14.53 \pm 2.88 \%$  and  $48.42 \pm 2.32 \%$ . From this it was clear that prepared s-SNEDDS increased solubility of poorly water soluble drug Simvastatin thereby increased its percentage drug release. Results are shown in Figure 14.

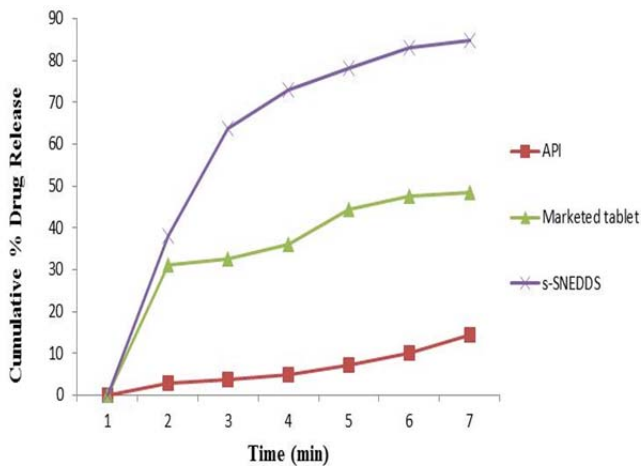


Figure 14: In – Vitro dissolution profile of s-SNEDDS, API and Marketed tablet

**Accelerated Stability Testing**

After 6 months Accelerated stability study formulation was evaluated for parameters such as effect of Dilution, Droplet size, PDI and In-Vitro drug release. s-SNEDDS passed the test of Effect of Dilution. Droplet size was found to be 15.37 nm with PDI 0.252 indicating no effect on Droplet size after 6 months stability study. Cumulative percentage of Simvastatin from s-SNEDDS was  $84.081 \pm 2.21 \%$  at the end of 6 months indicating no change in % drug release after 6 months stability study. Results are given in Table 10 and Figure 15, results of drug release are shown in Figure 16. From the results it was clear that formulation was stable for 6 months accelerated stability study.

Table 10: Accelerated stability study of s-SNEDDS after 6 months

Formulation	Effect of dilution	Droplet size (d.nm)	PDI	Drug release (AM $\pm$ SD for n=3)
s-SNEDDS	Passed	15.37	0.252	$84.081 \pm 2.21$

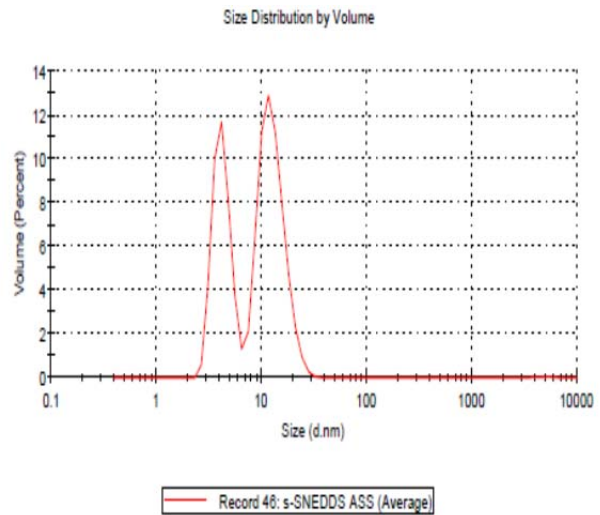


Figure 15 : Droplet size distribution of s-SNEDDS after 6 months

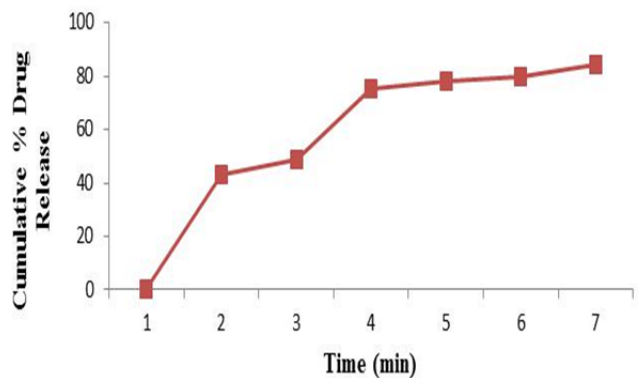


Figure 16: In – Vitro dissolution profile of s-SNEDDS at the end of 6 months accelerated stability study



### CONCLUSION

A SNEDDS formulation of a poorly water-soluble drug, Simvastatin was formulated. The formula composition of SNEDDS for preparation of s-SNEDDS was identified based on solubility evaluation, pseudo ternary phase diagram, and droplet size analysis. The optimized formulation showed rapid self nano emulsification in an aqueous media with droplet size 15.20 nm and PDI 0.303. The SNEDDS formulation converted into s-SNEDDS using Crospovidone as carrier in 1:2 ratio by adsorption technique. Prepared s-SNEDDS showed "Good" flow properties. Prepared s-SNEDDS showed spontaneous emulsification i.e. in less than 1min with Droplet size 16.27nm and PDI 0.276. From In-Vitro drug release profile it was clear that the percentage drug release from s-SNEDDS is 5.8 times and 1.7 times higher than that of pure drug and marketed tablet. Accelerated stability testing at 40°C and 75%RH for s-SNEDDS of Simvastatin showed formulation was stable for 6 months accelerated stability study. Hence the present study concluded that the s-SNEDDS formulation clearly shown improved and increased dissolution of Simvastatin.

### ACKNOWLEDGMENTS:

I would like to thank Gattefosse, Mumbai for providing gift samples of vehicles. Gift samples of Simvastatin and Crospovidone by Hetero Drugs Pvt.Ltd, Hyderabad is duly acknowledged.

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