

## Development and Evaluation of Telmisartan Self Nano Emulsifying System

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### Abstract

Self nano-emulsifying system drug delivery system (SNEDDS) is promising for drugs of BCS class II. The objective of present study to develop self nano-emulsifying drug delivery system for Lipophilic drug Telmisartan (TEL) to enhance the oral bioavailability of poorly water-soluble drug. TEL is an angiotensin II receptor blocker (ARB) and antihypertensive drug. Screening of Surfactant, Co-surfactant is done by percent transmittance and is also observed for turbidity or phase separation visually. Pseudo ternary phase diagram are constructed to identify the self-emulsifying regions and also to establish the optimum concentration of oil, surfactant and co-surfactant. For prepared formulation further characterization studies are done. Various studies like FTIR, SEM, Particle size, zeta potential is carried out for prepared SNEDDS. Further they are formulated into tablets and evaluated. All the results obtained are found to be in limits. From the present study it is clear that SNEDDS can be formulated to improve the dissolution and oral bioavailability of poorly water-soluble drug Telmisartan.

**Keywords:** Bioavailability; poor water solubility; self-nanoemulsifying drug delivery system; telmisartan.

### Introduction

Around forty percent of new chemical entities developed by the pharmaceutical industry are poorly soluble or lipophilic compounds, which result poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality<sup>1</sup>. Oral delivery route is the most convenient route for drug administration to achieve desired therapeutic effects and the greatest degree of patient compliance, especially

for chronic condition diseases. Despite some clinical oral formulations have been developed, their low oral bioavailability is still a major hurdle, leading to challenges for pharmaceutical manufacturers to design delivery systems that can provide improved pharmacokinetic profiles and therapeutic responses<sup>2</sup>. Currently, many efforts such as efflux pump inhibitors, permeation enhancers and drug nanonization, have been

made to overcome the challenges of low oral bioavailability resulting from low drug solubility, poor permeation and enzymatic degradation, which limiting drug effective delivery<sup>3</sup>.

Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that rapidly form fine oil-in-water (o/w) nanoemulsions when introduced into aqueous medium under mild agitation<sup>4</sup>. In the human body, the agitation required for formation of nanoemulsions is provided by digestive motility of the gastrointestinal tract<sup>3</sup>. In comparison with the ready to use nanoemulsions or nanosuspensions, SNEDDS have shown many advantages such as: physical or chemical stability profile improvement in long term storage; possibility of filling into soft/hard gelatin capsules, which results in attractive commercial viability and patient acceptability; no palatability-related issues. In recent years, Self-emulsifying drug delivery systems (SNEDDS) is used to improve the oral bioavailability of poorly water-soluble drugs<sup>5</sup>.

In recent years, SNEDDS have attracted more and more attention as the mean to enhance the oral bioavailability of poorly soluble and highly metabolized drugs<sup>6</sup>. Never the less, conventional SNEDDS also require a relatively large number of surfactants, which may induce GI irritation and side-effects<sup>7</sup>. In order to achieve a safe and efficient delivery system for the poor oral bioavailability drugs, we have designed a novel self-nanoemulsifying drug delivery system with high proportion lemon essential oil as carrier for lipophilic drugs<sup>7</sup>.

Self-emulsifying drug delivery systems (SEDDS) are emulsion pre-concentrates or anhydrous forms of emulsion. These systems (SEDDS) are ideally isotropic mixtures of drugs, oils and surfactants, sometimes containing co-surfactant or co-solvents<sup>8</sup>. Upon mild agitation

followed by dilution with aqueous media, SEDDS can form fine oil-in-water emulsions spontaneously<sup>9</sup>. In gastrointestinal tract of human body, the agitation required for formation of emulsions is provided by gastric mobility, the aqueous media are gastrointestinal fluids. In comparison with ready-to-use emulsions, which are metastable dispersed forms, SEDDS possess improved physical and/or chemical stability profile upon long-term storage, and also easy manufacture property<sup>9,10</sup>. Thus, for the lipophilic drugs that exhibit poor water solubility and rate-limited dissolution, SEDDS may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles<sup>11</sup>.

## **Materials and methods:**

### **Materials:**

Telmisartan was gifted from Octavius, India. Cinnamon oil and lactose LR were obtained from S.D. Fine chemicals, India. PEG 400, Pluronic F 127, Dicalcium Phosphate and MCC were obtained from Sigma Aldrich, India.

### **Preparation of SNEDDS:**

The drug was weighed to 80mg and was mixed with the specified amount of oil. To this the specified amount of the surfactant and co surfactant were added. It was heated to 40°C and sonicated for 15 mins, after which it was stored at room temperature. The composition chart of Telmisartan SNEDDS formulation was tabulated in Table 1 below. Brij – 72 was not used as surfactant because brij – 72 forms insoluble aggregates when preparing formulations. T2, T4&T9 are selected based on formation of emulsion. After few days emulsion goes to instability due to improper selection of surfactants. Due to instability of emulsion cosurfactant was changed and replaced with pluronic F 127 because it has higher percentage of transmittance after propylene glycol<sup>12</sup>.

**Table 1: Composition of Telmisartan SNEDDS formulation**

Formulation code	Drug (mg)	Oil (cinnamon oil) (ml)	Surfactant (PEG-400) (ml)	Cosurfactant (propylene glycol) (ml)
FT 1	1	0.3	0.5	0.2
FT 2	1	0.2	0.3	0.5
FT 3	1	0.5	0.3	0.2
FT 4	1	0.2	0.4	0.4
FT 5	1	0.4	0.2	0.4
FT 6	1	0.3	0.5	0.2
FT 7	1	0.3	0.3	0.4
FT 8	1	0.5	0.2	0.3
FT 9	1	0.4	0.4	0.2
FT 10	1	0.2	0.5	0.3
FT 11	80	3	400	300
FT 12	80	2	400	400
FT 13	80	2	350	350

#### Conversion of liquid SNEDDS to solid SNEDDS:

Liquid SNEDDS was taken and mixed with adsorbents avicel pH 101 until free-flowing powder was obtained. The powder was then mixed with additives, dicalcium phosphate as binding agents in suitable proportions. 13 mm punch and die cavity were used for punching to yield self-nanoemulsifying tablets of telmisartan<sup>12</sup>.

#### Drug-Excipient Compatibility Study by Fourier Transform Infrared Spectroscopy (FTIR)<sup>13</sup>:

The FT-IR spectra of pure Telmisartan and prepared optimized formulation of chitosan loaded nanoparticles were recorded using FTIR (Bruker Alpha-T, Switzerland) to investigate any interaction between telmisartan and polymers in formulated nanoparticles. The samples were ground with KBr and pressed into a disk shape for measurement. The prepared pellets were scanned over a frequency range of 4000-400 cm<sup>-1</sup>

#### Evaluation parameters of liquid SNEDDS<sup>14,15</sup>:

##### Visual observation:

The formulation was diluted and made to stand for 24 hours at 37 °C. They were observed for phase separation and turbidity.

##### Self-emulsification time:

1ml of formulations was added to 100 ml of distilled water at 37 °C being agitated at 100 rpm. The time required for the formation of a milky emulsion was noted.

##### Droplet size and zeta potential:

1ml of formulation was diluted to 100 ml with distilled water and sonicated for 15 minutes. the resulting nano-emulsion was checked for droplet size and zeta potential in a particle size analyzer (Malvern zetasizer). The average droplet size and zeta potential was determined.

##### Drug content:

1ml of formulations were taken and diluted sufficiently. these solutions were then analyzed in the UV spectrophotometer. The drug concentration present was extrapolated from the

standard graph. The drug content was calculated using the below formula.

Drug content = concentration X dilution factor X correction factor X vol. of formulation.

#### **Robustness to dilution:**

The formulations were diluted to 10 ml, 50 ml, and 100 ml and were observed over a period of 24 hours for phase separation or signs of precipitation.

#### **Morphological studies<sup>16</sup>:**

##### **Scanning electron microscopy:**

The morphology and size of the prepared SNEDDS was observed by SEM. samples were fixed on a brass stub using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 15 KeV accelerating voltage.

#### **Evaluation of solid – SNEDDS<sup>17</sup>**

##### **Micrometrics properties of s-SNEDDS of telmisartan**

##### **Angle of repose ( $\theta$ ):**

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

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

Where; h = height of the heap, r = radius of the heap

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

Both bulk density (BD) and tapped density (TD) were determined. A quantity of 2 g of S-SNEDDS was introduced into a 10 mL measuring cylinder. Initial volume was observed, and then the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. Bulk density and tapped density were calculated using the following equations

$$BD = \text{Weight of powder} / \text{Bulk Volume}$$

$$TD = \text{Weight of powder} / \text{Tapped Volume}$$

#### **Compressibility Index:**

The compressibility of the S-SNEDDS granules was determined by Carr's Compressibility Index as follow

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

#### **Hausner ratio:**

It is the ratio of tapped density to bulk density. It gives an idea about the flow characters of powder particles and can be calculated as follow

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

#### **Evaluation of telmisartan SNE tablet<sup>18</sup>:**

##### **Weight variation:**

10 tablets were selected randomly and weighed. The average weight was also seen. The weight variation between the individual weight and average weight was calculated. The weight variation should conform to the limits. IP limits for weight variation is tabulated in Table 2.

**Table 2: IP limits for weight variation**

Average weight of the tablet (mg)	Maximum percentage deviation allowed (%)
<130 mg	10
130-324	7.5
>324	5

**Hardness:**

Tablet hardness is the force required for breaking the tablet in a diametric compression test. A tablet was placed between the anvils of the tester and the crushing strength is noted. normal hardness ranges from 4-6 kg/cm<sup>2</sup>

**Friability:**

10 tablets were weighed and placed in a friabilator. It was operated at 25rpm for 4 mins or 100 revolutions dropping the tablet from a 6-inch height during revolutions. The percentage friability was calculated by

Percentage friability = (initial weight – final weight) / initial weight X 100

**Disintegration:**

It is the time in which tablets will disintegrate into particles which will pass through a mesh screen size 10. The disintegration tester contains a basket a basket rack with 6 tube with 10 mesh screen at the bottom. The basket is immersed in a medium at 37 °C usually.

***In-vitro* dissolution studies:**

Instrument: USP II dissolution rate test apparatus

Type: paddle type

Medium: 0.1N HCL buffer pH 1.2 – 900 ml

Temperature: 37 ± 0.5°C

Testing time: 60 mins

Sample withdrawal volume: 5 ml at specified intervals

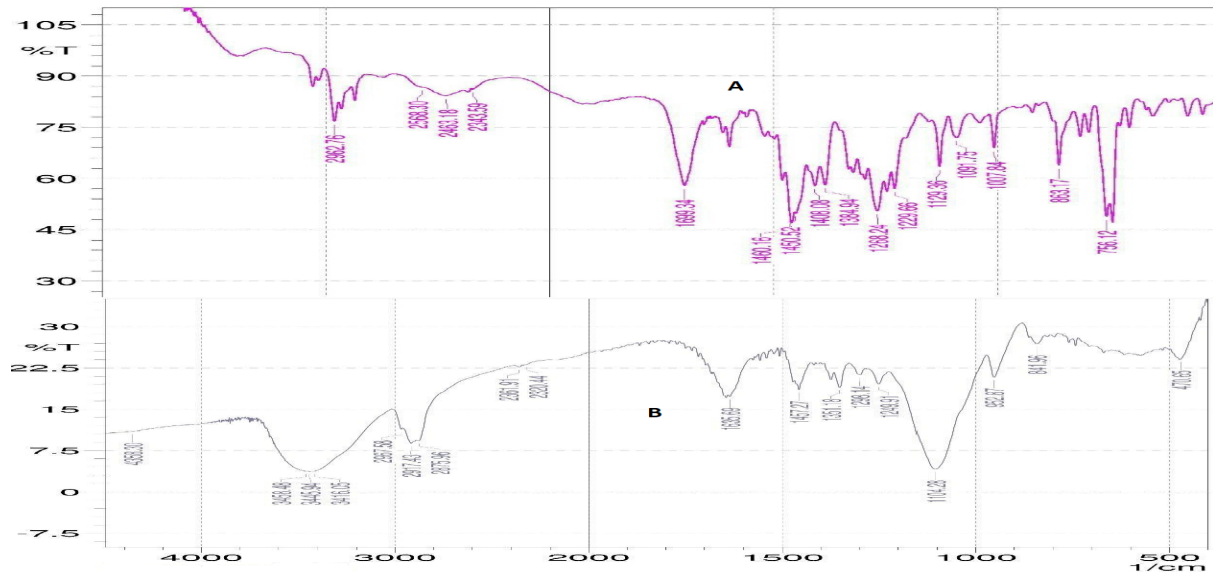
Sample: telmisartan S-SNE tablet

**USP 2 paddle instrument (Electro lab TDT – 06 P):**

The dissolution of the tablets was performed in 0.1N HCL buffer pH 1.2 at 37 °C at 75 rpm and a stirrer depth of 25mm. the sampling intervals were 5,10,15,30,45,60,75 and 90 minutes. 5 ml of fresh buffer solution was replaced after each withdrawal. The sample was then filtered and analyzed spectrophotometrically. The experiments were performed in triplicate and the mean values are reported.

**Results and discussion:****Drug-Excipient Compatibility Study by FTIR:**

Drug-Excipient compatibility study by FT-IR: The compatibility studies were performed using FTIR spectrophotometer. The characteristic absorption peaks of pure drug and optimized formulation were obtained at different wave numbers. The characteristic peaks were observed Methyl C-H asymmetric bond 1460 cm<sup>-1</sup>, Carboxylic acid stretching 1408 cm<sup>-1</sup>, Aliphatic nitro compounds Stretching 1384 cm<sup>-1</sup> obtained in pure drug and optimized formulation were used. The above results were indicating that there was no incompatibility between the drug and excipients used and the FTIR graph Showed in Figure 1.

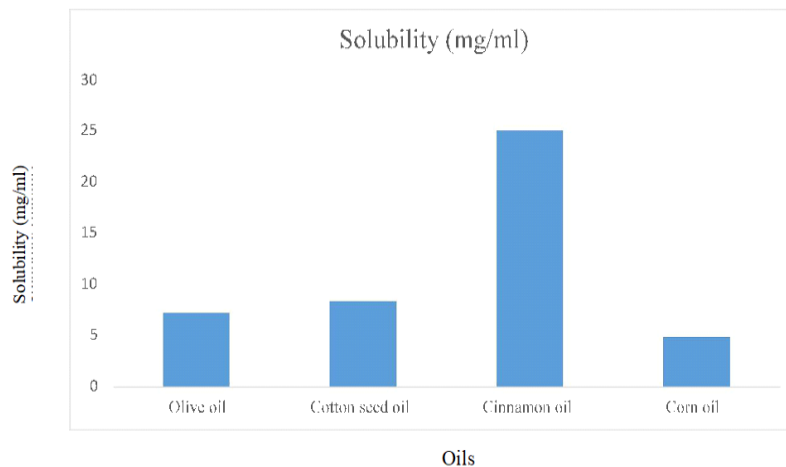


**Figure 1: FTIR spectra of A. pure drug and B. optimized formulation**

### FORMULATION OF S-SNEDDS:

The components of the SNEDDS have to be selected with care in order to avoid precipitation of the drug during the shelf life. Therefore, the solubility studies of Telmisartan in oils and

surfactants were carried out. The results are shown in the figure. Telmisartan was highly soluble in cinnamon oil among the lipids,  $25 \pm 1.43$  mg/ml. The various solubilities are depicted in the Figure 2 below.



**Figure 2: Solubility studies in oil**

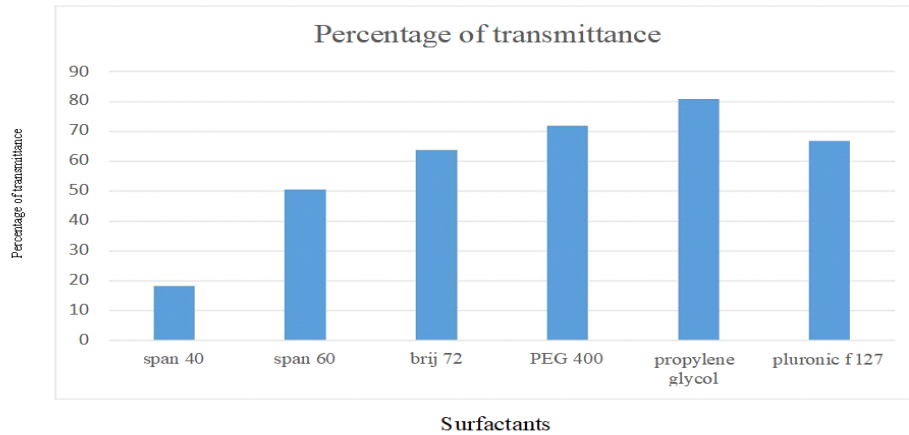
### Screening of Surfactants:

300 mg of the surfactant was mixed with 300 mg of the selected oil, heated to  $50^{\circ}\text{C}$  and diluted to 50 ml with water. The ease of emulsification was observed by the number of flask inversions required for the formation of an emulsion. The

prepared emulsions were analysed in the UV spectrophotometer for their percentage transmittance at 650 nm using distilled water as blank. They were also observed visually for any signs of phase separation or turbidity. Based on the percentage of transmittance surfactant has

selected for formulation. Brij 72 forms insoluble aggregates so we select the propylene glycol,

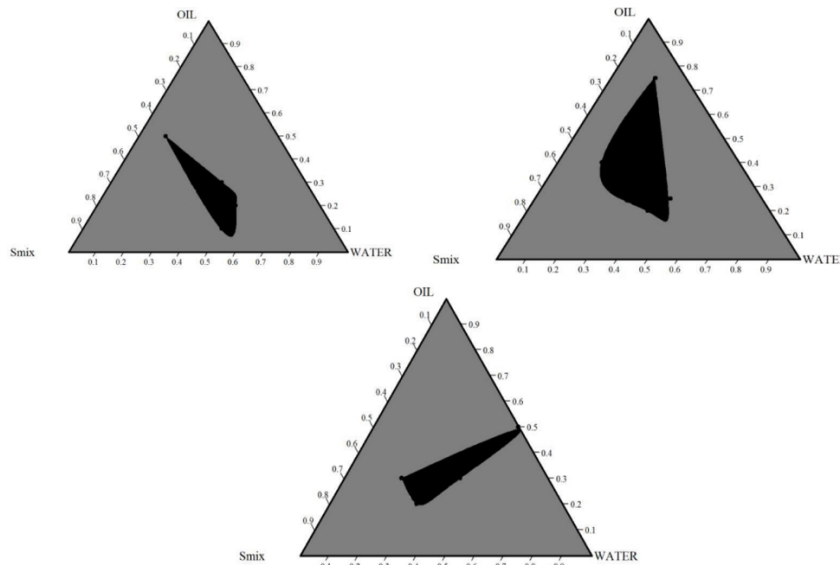
Span 60, PEG 400 and Pluronic f 127 results were depicted in Figure 3.



**Figure 3: Percentage Transmittance of surfactants**

Pseudoternary phase diagrams were constructed (Figure 4) for identifying the self-emulsifying regions. It gives us an idea of the changes a SNEDDS under goes when diluted with gastric fluids Larger the shaded area in the diagram, more the self-emulsification ability. From each phase diagram different concentrations of oil, at which nanoemulsions formed, were selected at a difference of 5% (10, 15, 20, 25 and 30) so that

maximum formulations could be selected for optimizing the best formulation. Another phase diagram was also plotted without water to give us an idea of the miscibility of the other 3 excipients. Better self-emulsification was seen with concentrations of surfactant above 50% and oil below 30%. Above these concentrations either phase separation or turbidity was seen.



**Figure 4: Pseudo Ternary phase diagram**

**Evaluation****Visual assessment and self-emulsification time:**

Formulations FT-11, FT-12 and FT-13 showed no phase separation or turbidity. Formulations with concentrations of oil below 30% and surfactant above 70% showed SNEDDS that have good clarity and No phase separation.

**Visual assessment and self-emulsification time:**

In nano-emulsion formulations only FT-11, FT-12 and FT-13 were clear. The rest of the formulations showed precipitation. Visual assessment and self-emulsification time of prepared SNEDDS formulations were tabulated in Table 3.

**Table 3: Visual assessment and self-emulsification time of SNEDDS formulations**

Formulation	Visibility Grade	Precipitation
FT 1	III	Yes
FT 2	III	No
FT 3	III	Yes
FT 4	III	No
FT 5	III	Yes
FT 6	III	Yes
FT 7	III	Yes
FT 8	III	Yes
FT 9	III	No
FT 10	III	Yes
FT 11	III	No
FT 12	III	No
FT 13	III	No

**Droplet size and Zeta potential:**

The size of droplets after nan emulsification is the most important factor as it affects the absorption of the drug as well as drug release. The smaller droplets have larger surface area thereby increasing the absorption. The size of droplets decreased with high concentration of either oil or surfactant. PDI is the ratio of standard deviation to the mean droplet size. It indicates the

uniformity of size range in the formulation. Zeta potential denotes the charge of repulsion among the particles. A high zeta potential for small particles is indicative of better stability. The particle size of FT11, FT12 & FT13 range from 277nm, 246nm & 220 nm with PDI from 0.159, 0.385 & 0.395. Characterization of S-SNEDDS formulations were tabulated in Table 4.

**Table 4: Characterization of S-SNEDDS formulations**

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)
FT11	181	0.199	-0.118
FT12	273	0.201	-4.44
FT13	220	0.395	-6.49

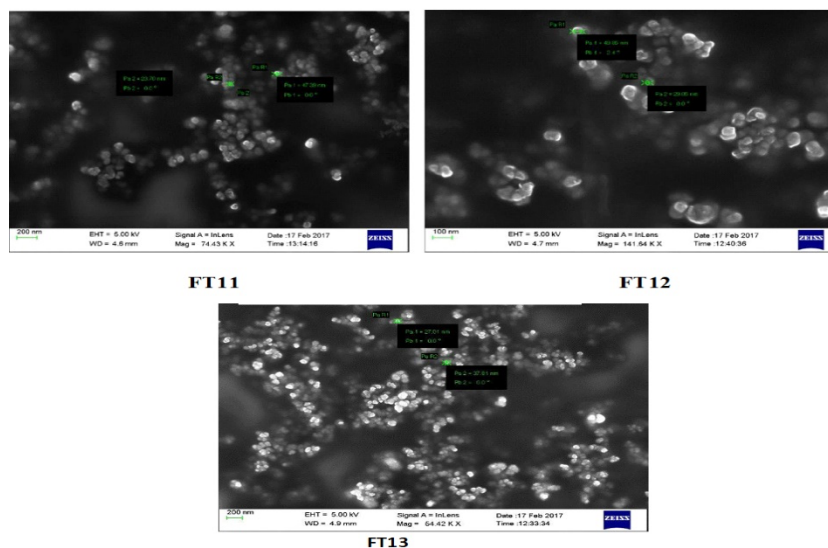


**Robustness to dilution:**

The formulations were diluted in various ratios to assess the performance of the S-SNEDDS in the body. The diluted S-SNEDDS showed no precipitation or phase separation indicating the stability of the nanoemulsions.

**Self-emulsification time:**

1ml of formulations was added to 100ml of distilled water at 37° C being agitated at 100rpm. The time required for the formation of a milky emulsion was noted for FT11, FT 12 & FT13 were 83secs, 94secs and 77secs.

**Morphological studies****Scanning electron microscopy**

**Figure 5: SEM image of FT11, FT12 and FT13**

**Conversion of liquid S-SNEDDS to solid form (SNE tablets):**

FT11, FT12 and FT13 were mixed with avicel PH 101 in varying amounts from 50mg – 500 mg, yielded a free-flowing powder that was further dried in the oven for 30 mins. For the tablet compression, the selected binders were Lactose and dicalcium phosphate. Tablets were punched with magnesium stearate and talc as lubricant.

**Drug content in S-SNEDDS:**

100mg of nano formulation was dissolved in 100ml of distilled water. From this 1ml was taken and made upto 10ml. further from this 1ml was taken and made upto 10ml and absorbance was taken at 294nm using UV-spectrophotometer.

From this the required amount of nano formulation to be made into tablet and it is being calculated.

**Characterization of telmisartan S-SNEDDS:****Micromeritic properties of S-SNEDDS:**

The values obtained for the angle of repose of the three formulae FT11, FT12 and FT13 after adding glidant were 32° $\theta$ , 33° $\theta$  and 35° $\theta$ . these values indicate that all formulae have good flowability. The bulk density of the three formulae FT11, FT12 and FT13 was found to be 0.29g/ml, 0.27g/ml and 0.24g/ml respectively. However, tapped density was 0.32g/ml, 0.33g/ml and 0.37g/ml. Carr's index of formulae FT11, FT12 and FT13 was found to be 9.37, 15 and 9

respectively which give an indication about the good flowability of the three S-SNEDDS formulae. This was further supported by the values of Hausner's ratio. The results of Hausner's ratio of formulae FT11, FT12 and

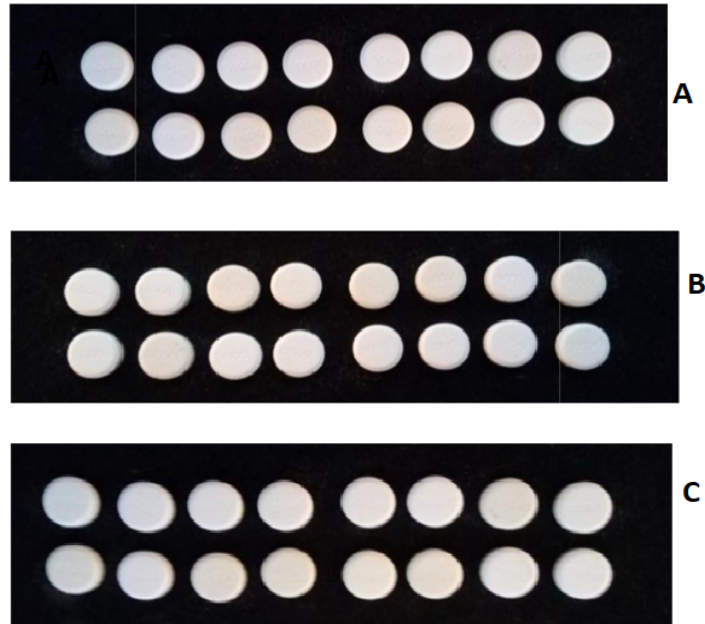
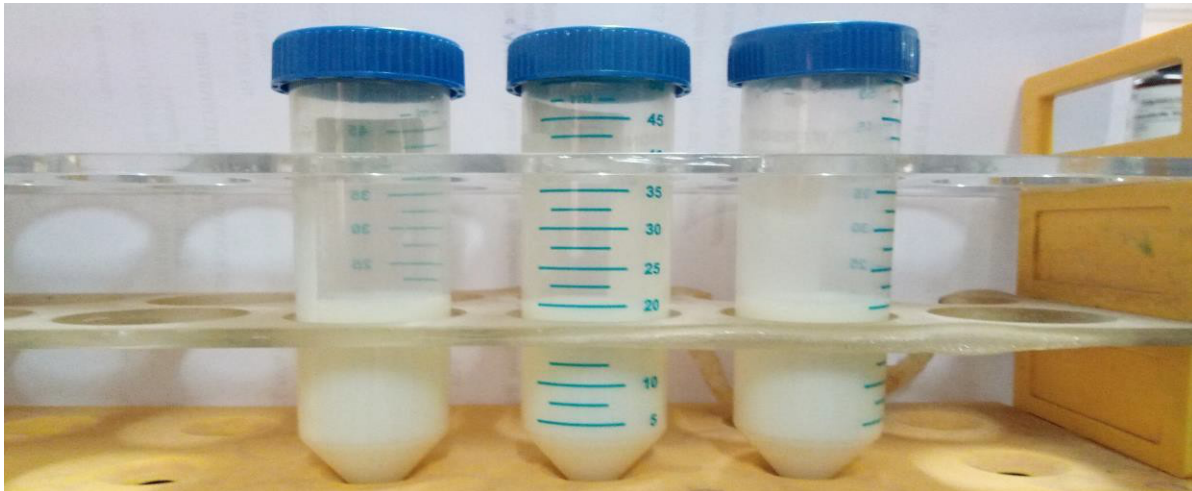
FT13 were 1.09, 1.18 and 1.1 respectively. The improved flowability of S-SNEDDS formulae may be due to good sphericity of particles these three formulae go for tablet compression. Results were tabulated in table 5.

**Table 5: Micromeritics properties of SNE powder formulation**

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio	Angle of repose( $\Theta$ )
<b>Before adding glidant</b>					
FT11	0.22	0.35	34	1.5	45
FT 12	0.23	0.33	30	1.4	45
FT13	0.24	0.34	28	1.4	46
<b>After adding Talc 2%</b>					
FT11	0.29	0.32	9.3	1.09	32
FT12	0.27	0.33	15	1.18	33
FT13	0.24	0.37	9	1.1	35

**Table 6: Compression of telmisartan SNE tablet**

Punching of telmisartan sne – tablet (FT 11)	Telmisartan 20mg (excipients- dicalcium phosphate/lactose / micro crystalline cellulose/magnesium stearate & talc	For 1 tablet: Drug – 20 mg Excipients- 113mg/100mg/190mg Magnesium stearate 2% Talc 1%
Punching of telmisartan sne – tablet (FT 12)	Telmisartan 20mg (excipients- dicalcium phosphate/ lactose / micro crystalline cellulose /magnesium stearate & talc	For 1 tablet: Drug – 20 mg Excipients- 102mg/110mg/170mg Magnesium stearate 2% Talc 1%
Punching of telmisartan sne – tablet (FT 13)	Telmisartan 20mg (excipients- dicalcium phosphate/ lactose /micro crystalline cellulose /magnesium stearate & talc	For 1 tablet: Drug – 20 mg Excipients- 123mg/100mg/190mg Magnesium stearate 2% Talc 1%
Formulation FT11 contains 87mg of telmisartan nano formulation equivalent to 20mg of telmisartan pure drug (with excipients)	Formulation FT12 contains 118mg of telmisartan nano formulation equivalent to 20mg of telmisartan pure drug (with excipients)	Formulation FT13 contains 77mg of telmisartan nano formulation equivalent to 20mg of telmisartan pure drug (with excipients)

**Telmisartan SNE tablets****Figure 6: Telmisartan SNE tablets A. F11, B. F12 & F13****Figure 7: Formulation of Telmisartan Liquid SNEDDS****Evaluation of Telmisartan SNE tablet: Weight variation test:****Table 7: Weight variation test**

Formulation code	Weight variation (%)
FT11	3.8
FT12	4.4
FT13	4.5

The percentage weight variation for all formulations was performed. All the formulations passed weight variation test as per the pharmacopeia limits of 5% as shown in the table 7 above

**Friability test:****Table 8: Friability test**

Formulation code	Friability (%)
FT11	0.28
FT12	0.24
FT13	0.26

The friability test for formulations was performed. All the formulations passed friability test as per the pharmacopeia limits as shown in the Table 8.

**Hardness test:****Table 9: Hardness test**

Formulation code	Hardness (Kg/cm <sup>2</sup> )
FT11	5
FT12	4
FT13	5

The hardness of formulations was carried out and found that it was 4 to 5 Kg/cm<sup>2</sup> for formulations FT11, FT12 and FT13 are passed and within these limits as shown in the Table 9 above.

**Disintegration test:****Table 10: Disintegration test**

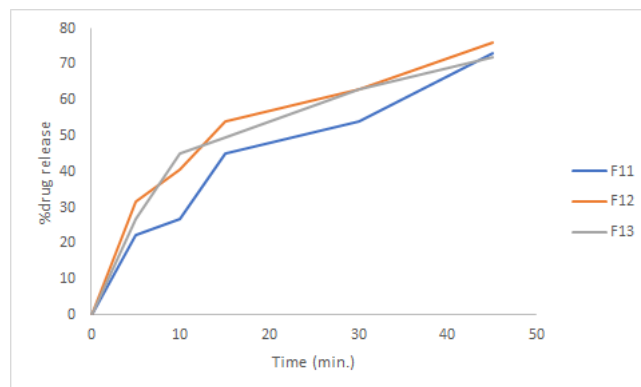
Formulation code	Disintegration time (mins)
FT11	4
FT12	4
FT13	6

The disintegration test for all formulation was performed. All the formulations passed disintegration test as per the pharmacopeia limits as shown in the Table 10.

**Dissolution study****Dissolution data of FT11 Telmisartan SNE tablet**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 900ml of 0.1N HCL buffer pH 1.2 at 50 rpm at a temperature of 37±0.5°C. Samples of 5ml were collected at

different time intervals up to 60 Min and has analyzed after appropriate dilution by using UV spectrophotometer. From the results, it was observed that, formulation F11 (76%) showed fastest drug release by the end of 45 min. Formulation F12 and F13 showed the release upto 72 and 58.5% respectively at the end of 45 min. % drug release of F11, F12 and F13 were showed in Figure 8 below.



**Figure 8: %drug release of F11, F12 & F13**

## Conclusion

Oral route is the most convenient route of administration but it faces the problem of low oral bioavailability. Self nano emulsifying therapeutic system (SNETS) can be used to overcome the problems faced while using low aqueous soluble drugs. These systems form emulsion *in situ* with have good stability. This study aimed at investigating the increase in the bioavailability by administering a BCS class II drug, in a SNEDDS form and was compared to the conventional telmisartan tablets. It can be concluded from the experimental study carried out that the formulation of a poorly water-soluble drug, telmisartan into Self Nanoemulsifying Drug Delivery System yields a formulation with nano size range & good zeta potential. The liquid was further made into tablet form for better stability. The prepared formulations were characterized for the size, zeta potential, self-emulsification time and drug content & compressed into tablets. The *in vitro* study of the best formulation FT12 SNE tablet showed 1.4-fold increase in the bioavailability when compared to the marketed formulation.

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