



## Research Article

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# Development and Characterization of Telmisartan Self-microemulsifying drug delivery system for Bioavailability Enhancement

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## Abstract

Telmisartan is a potent, long-lasting, nonpeptide antagonist of the angiotensin II type-1 (AT1) receptor that is indicated for the treatment of essential hypertension. It belongs to a class II drug in BCS classification i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids which results into poor bioavailability after oral administration. The objective of present work was to develop a self microemulsifying drug delivery system (SMEDDS) to enhance the oral bioavailability of poorly water soluble Telmisartan. SMEDDS is a mixture of oil, surfactant, and cosurfactant, which are emulsified in aqueous medium under gentle digestive motility in the gastrointestinal tract. Pseudoternary phase diagrams were constructed to identify the efficient self-emulsifying region. A SMEDDS were further evaluated for its percentage transmittance, emulsification time, drug content, phase separation, globule size, zeta potential, pH, refractive index, X-ray diffraction, Differential scanning calorimetry and in vitro dissolution studies. Optimized formulation was also compared with marketed product (Telma 20) in male sprague dawley rats. The pharmacokinetic study exhibited 1.54 fold increase in the oral bioavailability of Telmisartan SMEDDS compared with the Marketed product.

**Keywords:** SMEDDS, Telmisartan, Bioavailability, Globule size, *In-vitro* release studies.

## Introduction

Telmisartan is Angiotensin receptor blockers (ARBs), which antagonize angiotensin II type1 (AT1) receptors. It is used in the prevention and treatment of Hypertension. Telmisartan belongs to class II drug in BCS classification i.e. low solubility and high permeability. The solubility of Telmisartan in aqueous solutions is strongly pH dependent, with maximum solubility observed at high and low pH. In the range of pH 3–9 it is only poorly soluble. Poor solubility of Telmisartan leads to poor dissolution and hence variation in bioavailability. The solubility of Telmisartan in aqueous medium was very low i.e. 0.078 mg/ml in water. Absolute bioavailability of the Telmisartan is 42–58% and biological half-life is only 24 hours that results into poor bioavailability after oral administration<sup>[1-3]</sup>.

The oral route has been traditionally preferred for prolonged use. However, Oral delivery of poorly soluble drugs creates critical problems during their formulation. Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra and inter subject variability and a lack of dose proportionality<sup>[4,5]</sup>. Several recent techniques have been used for their solubilization including micronization, complexation, solid dispersion, cyclodextrins, nanoparticles and co-precipitation. Recently, much attention has been paid to lipidbased formulations with particular emphasis on self-emulsifying drug delivery systems (SEEDS) to improve the oral bioavailability of lipophilic drugs<sup>[6-8]</sup>.

self-emulsifying drug delivery systems (SEEDS) is the mixture of oil and surfactants, ideally isotropic containing co-solvents, which emulsify spontaneously to produce fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation followed by dilution in aqueous media such as gastrointestinal (GI) fluids<sup>[9-11]</sup>. SEDDS are generally encapsulated either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell<sup>[12]</sup>.

The main objective of this study was to formulate an o/w microemulsion system of Telmisartan for oral administration. Telmisartan is available in various doses (20mg, 40mg, 80mg); for our study we selected 20 mg as working dose to limit the total formulation volume. According to a solubility study and Pseudoternary phase diagrams, the formulation composed of various vehicles in different ratios were

investigated and Globule size, stability after dilution, pH, Percentage Transmittance, X-ray diffraction, Drug content, Differential scanning calorimetry and in vitro dissolution studies were performed for the optimized formulation. In addition, different formulations were compared by the evaluation of the pharmacokinetics.

## Materials and Methods

### Materials

Telmisartan was a generous gift from Cadila Healthcare Ltd. (Ahmedabad, India). PEG 400 (polyethylene glycol 400), Tween 80 (polyoxyethylenesorbitanmonooleate), Tween 20 (polyoxyethylenesorbitanmonolaurate), Span 80 (sorbitanmonooleate), Propylene Glycol (PG), Glycerol were obtained from Merck Chemicals (Mumbai, India). Castor oil, Olive oil and Cottonseed oil were obtained from S. D. fine chem (Mumbai, India). Solutol HS 15 (macrogol 15 hydroxystearate) and Kolliphore RH 40 (polyoxyl 40 hydrogenated castor oil) were also donated from BASF (Mumbai, India). Capmul MCM (glycerol mono-dicaprylate) and Capmul PG 8 (propylene glycol monocaprylate) were gifted from Abitec Corporation (USA). Transcutol was received as a gift sample from Gattefosse (Mumbai, India). Acrysol EL 135 (polyoxyl 35 castor oil) was obtained from Corel Pharma (Gujarat, India). Acetonitrile and methanol used in the present study were of high performance liquid chromatography (HPLC) grade. Double distilled water was used throughout the study. All other chemicals were reagent grade. Empty hard gelatin capsule shells were generously donated by Associated capsules Pvt. Ltd, (Mumbai, India)

### Animals

Male Sprague Dawley rats (weighing approximately 250±30g) were used for the pharmacokinetic study. The animals were maintained at temperature (25±2°C), humidity (60±5%) and were supplied food, water and libitum. The animal requirement was approved by the Institute Animal Ethics committee (IAEC) and all experiments were conducted as per the norms of the committee for the purpose of supervision of experiments on Animals, India

### Methods

#### Solubility Study

The solubility of Telmisartan in various oils, surfactant, and cosurfactants were determined by super saturation method. An excess amount of Telmisartan was added into each vial containing 2 mL of selected vehicle. After sealing the mixture was vortexed using a cyclomixer for 10 min in order to facilitate proper mixing of drug with vehicle. Then, the formed suspensions were shaken for 24 h in a mechanical shaker (Remi, India) maintained at 37±1°C. After reaching equilibrium, the mixtures were centrifuged at 5000 rpm for 5 min to remove undissolved Telmisartan, followed by filtration through a 0.45-µm millipore membrane filter paper. The concentration of Telmisartan was quantified by UV spectrophotometrically (UV-1601, Shimadzu Corporation, Japan)<sup>[13]</sup>.

#### Construction of Psuedoternary phase diagram

Psuedoternary phase diagrams of oil, surfactant/Cosurfactant (Smix) and water were developed using the water titration method. On basis of the solubility studies oil, surfactants and cosurfactants were grouped in different combinations for phase studies. Distilled water was used as an aqueous phase for the preparation of Microemulsions. For each phase diagram at a specific ratio (1:1, 1:2, 2:1) of Surfactant and

cosurfactant(Smix) were mixed, a transparent and homogenous mixture of oil and Smix was formed by vortexing for 5 min. The resultant mixture titrated with distilled water dropwise and observed for transparency and flowability. The concentration of water at which gel formation, turbidity to transparency and transparency to turbidity transitions occurred was noted. Phase diagrams were plotted using Chemix 3.5 software<sup>[14]</sup>.

### Preparation of Liquid SMEDDS

The phase diagrams were constructed at different Km values and the Km value at which high micro emulsion region obtained was selected for formulation of Liquid SMEDDS. Formulation was prepared using Capmul MCM as oil, Tween 80 as surfactant and Propylene Glycol as cosurfactant. In all the formulations, the level of Telmisartan was kept constant (i.e.20mg) briefly, oil, surfactant and cosurfactant were accurately weighed into glass vials according to their ratios. The amount of SMEDDS should be such that it should solubilizes the drug (single dose) completely. Then the components were mixed by gentle stirring and vortex mixing, and heated at 60°C in water bath till Telmisartan dissolved completely. Then the mixture was sealed in glass vial and stored at room temperature until used.

### Evaluation of Liquid SMEDDS

#### Thermodynamic Stability Studies

Thermodynamic stability study of prepared SMEDDS was determined by carrying Emulsification time, Robustness to Dilution, centrifugation test and freeze thaw cycle.

#### Emulsification time

Self-emulsifying formulations can be graded for self-emulsification time, dispersibility and appearance (Table 1.) 1 mL of Preconcentrate of SMEDDS was added in to 250 mL of distilled water & contents were stirred using magnetic stirrer at approx 100 rpm & the time required for the formation of emulsion, appearance & dispersibility is noted<sup>[15]</sup>.

**Table 1:** Visual assessment criteria for self emulsification

Grade	Time for self-emulsification	Appearance	Dispersibility
I	within 1 min	Clear or slightly bluish	Rapid emulsification
II	within 2 min	Slightly less clear, bluish white	Rapid emulsification
III	within 3 min	Bright white, similar in appearance to milk	Rapid emulsification
IV	Longer than 3 min	Dull, grayish white emulsion, slightly oily appearance	Slow to emulsify
V	Longer than 3 min	Large oil droplets present on the surface	Poor or minimal emulsification

#### Robustness to Dilution

Robustness to dilution was studied by diluting the SMEDDS up to 250 times with various dissolution media viz. Distilled water, 0.1N HCl and phosphate buffer (pH 6.8). The diluted SMEDDS were stored for 24 h and observed for any signs of phase separation or drug precipitation.

### Centrifugation test & Freeze thaw cycle

Passed SMEDDS was centrifuged at 3500 rpm for 30 min using digital centrifuge (Remi motors Ltd.). If SMEDDS did not show any phase separation was taken for freeze thaw stress test.

The emulsions were subjected to freeze thawing cycles which include freezing at 4°C & 45°C for 24 h up to 7 days. The formulations were observed for phase separation or precipitation of drug. The formulations which were stable at these temperatures, selected for further study.

### % Transmittance

Liquid SMEDDS was diluted to 250 mL distilled water and observed for any turbidity and % transmittance was measured at 650 nm using UV-vis spectrophotometer (Shimadzu-1800, Japan) against distilled water as a blank.

### Electroconductance

Type of emulsion (o/w or w/o) can be determined by measure of conductance. For the conductivity measurements, Liquid SMEDDS was diluted to 250 mL with a 0.01 N aqueous solution of sodium chloride instead of distilled water. Electroconductance was measured using Conductivity meter, (CM 200, welltronix India)

### Globule size, PDI and Zeta potential

Liquid SMEDDS was diluted to 100 times with distilled water and globule size, PDI and zeta potential were determined using Dynamic Light Scattering (also known as PCS- Photon Correlation Spectroscopy) with a Zetasizer Nano ZS 90 (Malvern Instruments, U.K.)

### Determination of drug content

Drug content was estimated by extracting Telmisartan from SMEDDS. In brief SMEDDS was dissolved in sufficient quantity of methanol. Solution was sonicated for 10-15 min for extraction of the Telmisartan in methanol and filtered. The sample was analysed at 298 nm on high performance liquid chromatography (HPLC -Agilent, 1200 series)

### Stability Studies

Optimized formulation were put into empty hard gelatin capsules (size 0) and subjected to stability studies in to accelerated condition  $40 \pm 2^\circ\text{C}$  and  $75 \pm 5\%$  RH up to 6 months. They were withdrawn at specified intervals for analysis over at period of 3 & 6 months for accelerated conditions. Drug content of the capsules was analyzed using a previously developed and validated stability-indicating HPLC method. Globule size & dissolution parameter were also studied.

### In vitro Dissolution Study

In vitro dissolution study of SMEDDS filled in empty hard gelatin capsules (size 0), Plain Telmisartan drug and marketed product (Telma 20) were carried out using USP-Type-II dissolution test apparatus in 0.1 N HCl and pH 7.5 phosphate buffer solutions at  $37 \pm 0.5^\circ\text{C}$  with 75 rpm speed. Sample of 5 mL were withdrawn at regular time interval of 5, 10, 15, 30 and 60 mins and filtered using 0.45  $\mu\text{m}$  filter. An equal volume of respective dissolution medium was added to maintain the volume constant. Drug content from sample was analysed using UV-spectrophotometer at 296nm. All measurements were done in triplicate from three independent samples.

### Formulation of S-SMEDDS

S-SMEDDS were prepared by mixing liquid SMEDDS containing Telmisartan with PEG 6000 in 1:1 proportion. In brief Liquid SMEDDS was added dropwise over PEG 6000 contained in glass beaker. After each addition, mixture was homogenized using glass rod to ensure uniform distribution of formulation. Prepared S-SMEDDS were evaluated for FTIR, DSC and XRD studies.

### FTIR Study

FTIR spectrum was recorded for Telmisartan and Prepared S-SMEDDS using Shimadzu FTIR 8300 spectrophotometer in the region of 4000 to 400  $\text{cm}^{-1}$ . Samples were mixed with Potassium bromide (200-400 mg) and compressed in to discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The compressed discs were placed in the light path and spectrum was obtained. After running the spectra, significant peaks relating to major functional groups were identified; spectra of subsequent sample of the same compound were compared with the original.

### Differential scanning calorimetry

DSC is very useful in investigation of thermal properties of S-SMEDDS providing both qualitative & quantitative information about the physicochemical state of drug inside S-SMEDDS. Differential Scanning Calorimetry instrument equipped with an intracooler (TA Instruments, SDT-2960, USA). Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powder samples was hermetically kept in the aluminium pan and heated at constant rate  $10^\circ\text{C}/\text{min}$ , over a temperature range of  $50^\circ\text{C}$  to  $300^\circ\text{C}$ . Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 mL/min.

### Powder X-Ray Diffraction studies

XRD patterns of pure Telmisartan and Telmisartan S-SMEDDS were obtained using a powder X-ray diffractometer (X'pert, MPD, Philips, Holland). The samples were studied by placing a thin layer of powder in conventional cavity mounts. The scanning rate was  $5^\circ\text{C}/\text{min}$  and diffraction angle ( $2\theta$ ) was 0 to  $40^\circ\text{C}$ .

### Pharmacokinetic Study

The rats were deprived of food but had free access to water 24 h before the day of the experiment. Comparative of pharmacokinetic parameters of Telmisartan following oral administration of Telmisartan containing SMEDDS (Test formulation) and Marketed product (Telma 20) (reference product) were studied in male Sprague Dawley rats. Two group (n=6) were administered required amount of Test and Reference formulation were filled in the empty mini hard gelatin capsules (Size 9el) with help of funnel provided with Torpac<sup>®</sup> kit one day prior dosing. Each rat from respective group was administered with single test and reference capsule at the dose 1.75 mg API per rat using oral gavage needle which contains capsule holding cup.

Approximately 0.20 mL of blood was collected at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24 and 48 h post dose from each rat via retro orbital plexus under light isoflurane anesthesia. Blood samples were placed on ice before collection of plasma. All samples were centrifuged at 5000 rpm for 5 min at  $4 \pm 2^\circ\text{C}$  within 60 min of scheduled time to obtain plasma. The plasma samples were stored below  $-20^\circ\text{C}$  until bioanalysis. Telmisartan in rat plasma samples was analysed using fit for purpose RP-HPLC method.

## Pharmacokinetic parameter

Pharmacokinetic parameters for Telmisartan were calculated using the non-compartmental analysis tool of the Phoenix WinNonlin software (Version 6.3). The area under the plasma concentration-time curve ( $AUC_{last}$ ) was calculated by the linear trapezoidal rule from time zero to the time of last quantifiable concentration. The  $AUC_{inf}$  were obtained by adding  $AUC_{last}$  and the extrapolated area determined by  $C_{last}/K_{el}$ , provided there is a well-defined elimination phase. Peak plasma concentration ( $C_{max}$ ) and time for the peak plasma concentration ( $T_{max}$ ) were the observed values. The elimination rate constant ( $K_{el}$ ) were calculated by log-linear regression of concentration data during the elimination phase with a correlation coefficient of  $>0.8$  and the terminal half-life ( $t_{1/2}$ ) were calculated as  $0.693/K_{el}$  and were reported if found appropriate. The relative bioavailability of test formulation with respect to reference formulation were calculated and reported. The test to reference exposure ratio was calculated and reported.

## Result and Discussion

### Solubility Study

One important consideration when formulating a self-emulsifying formulation is avoiding precipitation of the drug. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results from solubility studies are reported. (Fig.1 and Fig.2)

As seen from the Fig.1 Capmul MCM showed the highest solubilization capacity for Telmisartan. Thus, for our study we selected Capmul MCM as oils and Tween 80 and Propylene Glycol as surfactant and cosurfactant, respectively.

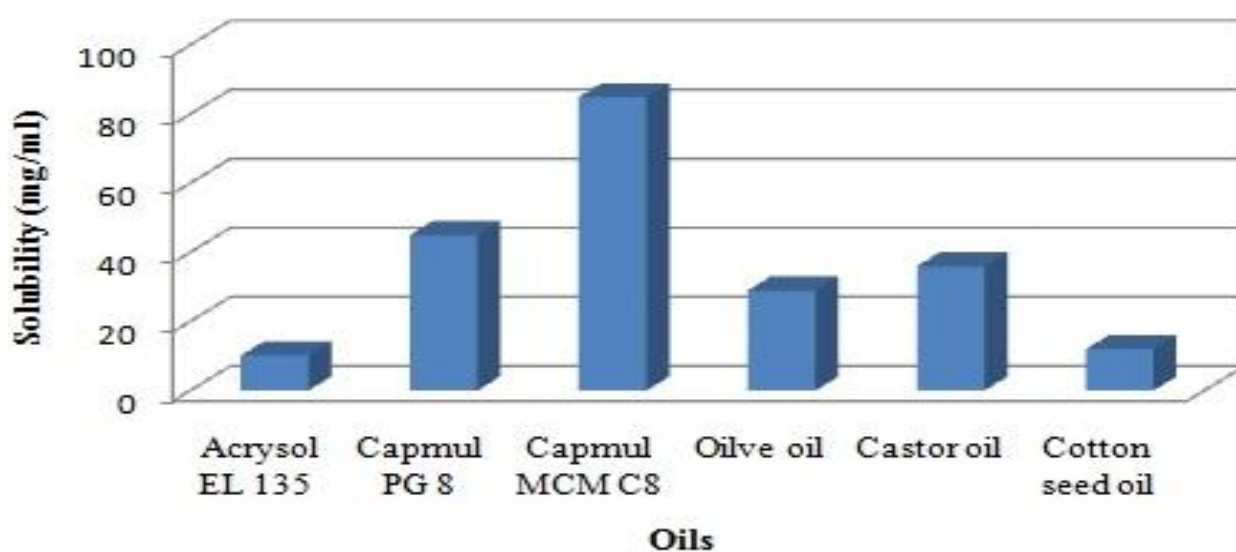


Fig 1: Solubility in Oils

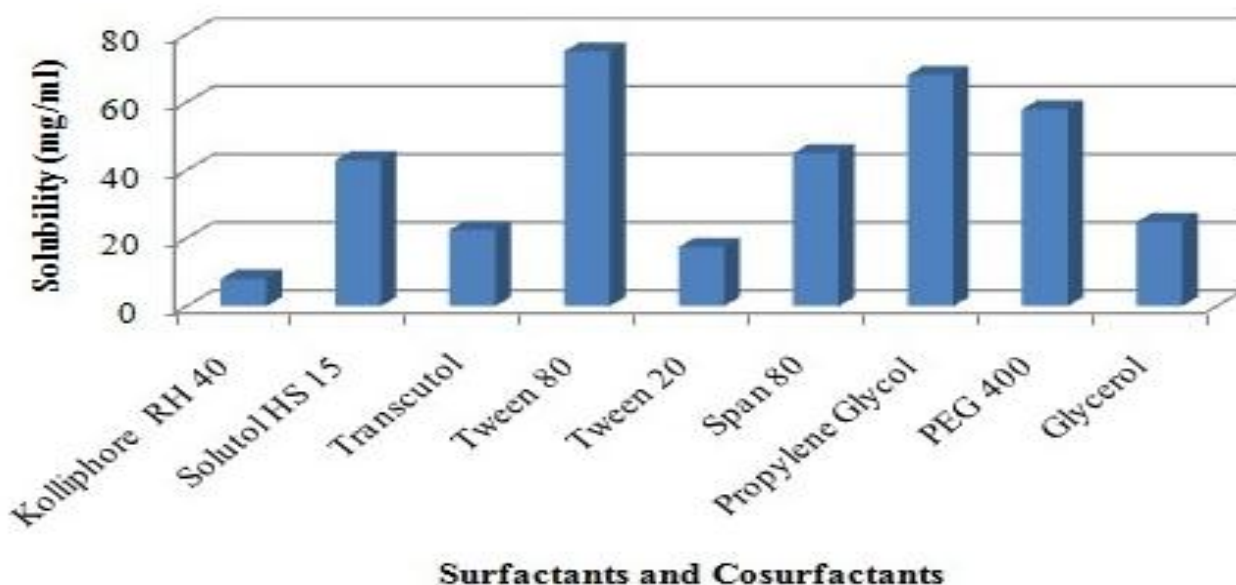


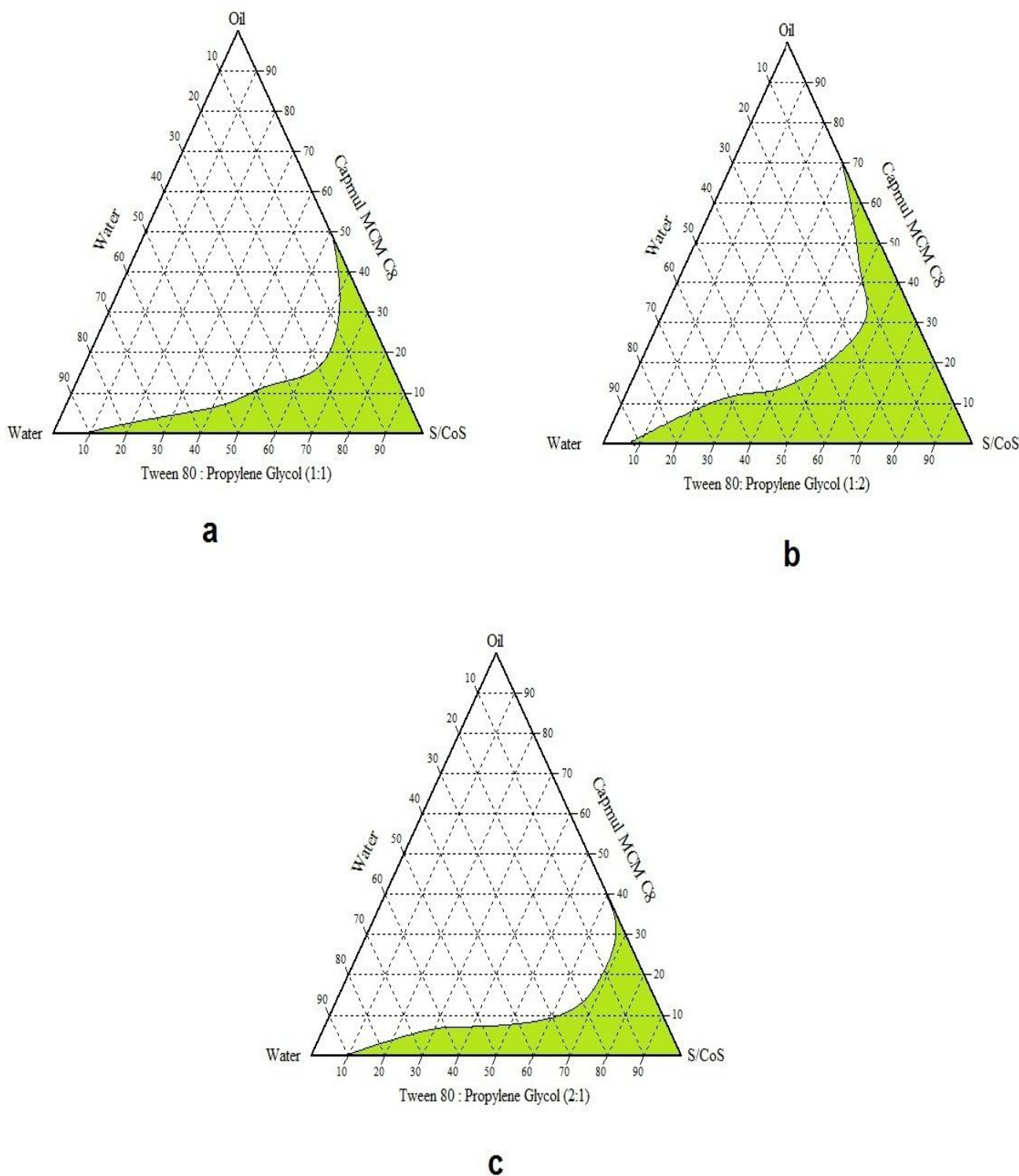
Fig 2: Solubility in Surfactants and Cosurfactants

## Construction of Pseudo ternary phase diagram

A series of SMEDDS were prepared and their self emulsifying properties were observed visually. Pseudoternary phase diagrams were

constructed in the absence of Telmisartan to identify the self emulsifying regions and to optimize the concentration of oil, surfactants and cosurfactant in the SMEDDS formulation. In the present study Capmul MCM was tested for phase behavior studies with Tween 80 and

Propylene Glycol as the Smix ratio of 1:1, 1:2, 2:1(% w/w). As shown in ternary plot (Fig. 3) the maximum self emulsifying region found at Smix ratio of 1:2 (% w/w).



**Fig 3:**Phase diagram prepared with the following components: oil—Capmul MCM C8, surfactant—Tween 80, and cosurfactant—Propylene glycol. Smix ratio of a is 1:1, b is 2:1, and c is 2:1

Based on above results, a three component SMEDDS formulation was established containing 14.40% w/w Capmul MCM as an oil (on the basis of the solubility study), required target amount of Telmisartan (20mg), 27.20% w/w Tween 80 as surfactant, and 54.40% w/w propylene glycol as cosurfactant (on the basis of Phase diagrams).

#### Evaluation of Liquid SMEDDS

#### Thermodynamic Stability Studies

Physical stability of SMEDDS was essential to its performance, which can be affected by precipitation of the drug. In addition, the formulation having poor physical stability can affect the formulation performance and it also leads to phase separation or cracking. Hence thermodynamic

stability studies were performed by performing robustness to dilution, emulsification time, centrifugation test and freeze thaw cycle.

#### Emulsification time

In SMEDDS, the primary means of self-emulsification assessment is visual estimation. The in-vitro performance of SMEDDS was visually assessed using the grading system and it was found that, SMEDDS rapidly formed microemulsion within 1 min which was clear and slightly bluish in appearance as per grade A.

#### Robustness to dilution

After diluting Liquid SMEDDS up to 250 times with various dissolution media viz. Distilled water, 0.1N HCl and phosphate buffer (pH 6.8) and storing for 24 h, it was observed that there were no signs of phase separation or drug precipitation.

#### Centrifugation test & Freeze thaw cycle

It was observed that, SMEDDS was passed the robustness to dilution test hence, further exposed to centrifugation test. SMEDDS did not show any phase separation or cracking after centrifugation test formulation was taken for freeze thaw stress test. There is no cracking, phase separation, or precipitation after freeze thaw stress test which showed SMEDDS of good stability.

#### % Transmittance

% Transmittance of reconstituted liquid SMEDDS was found to be  $98.40 \pm 1.20$  % (mean  $\pm$  SD, n=3). These results indicate the high clarity of microemulsion. This may be due to smaller globule size and zeta potential of formulation. Higher globule size may reduce the transparency of microemulsion and thereby decrease the value of %Transmittance

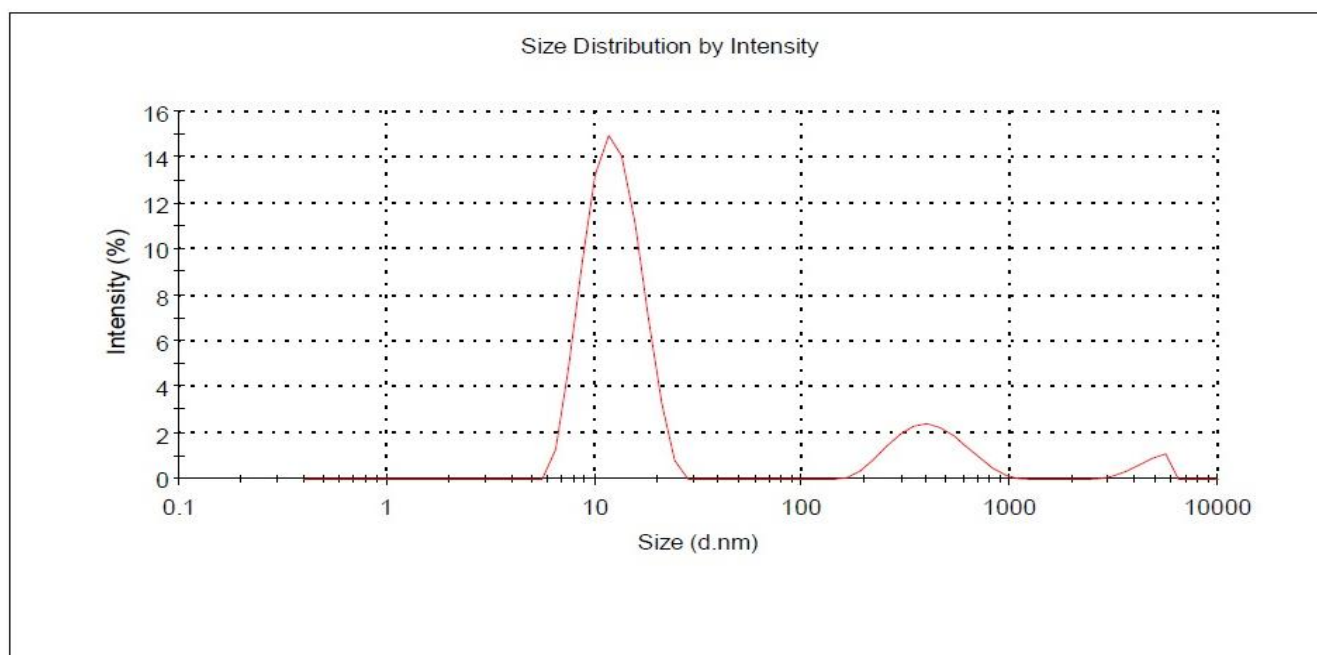
#### Electroconductance

The type of emulsion was confirmed by using electroconductivity test. Electroconductance of reconstituted liquid SMEDDS was found to be  $98.20 \pm 1.06$   $\mu$ s/cm (mean  $\pm$  SD, n=3), which indicate that the continuous phase was water, which signified the formation of o/w microemulsion.

#### Globule size, PDI and Zeta potential

The globule size of microemulsion is a crucial factor in self emulsification performance because it determines the rate and extent of drug release as well as absorption. The charge of oil globules of SMEDDS is another property that should be assessed for increased absorption. An ideal SMEDDS should be widely distributed with globule size less than 200 nm. Results of Globule size with PDI and Zeta potential are shown on Fig.4 and Fig.5 respectively.

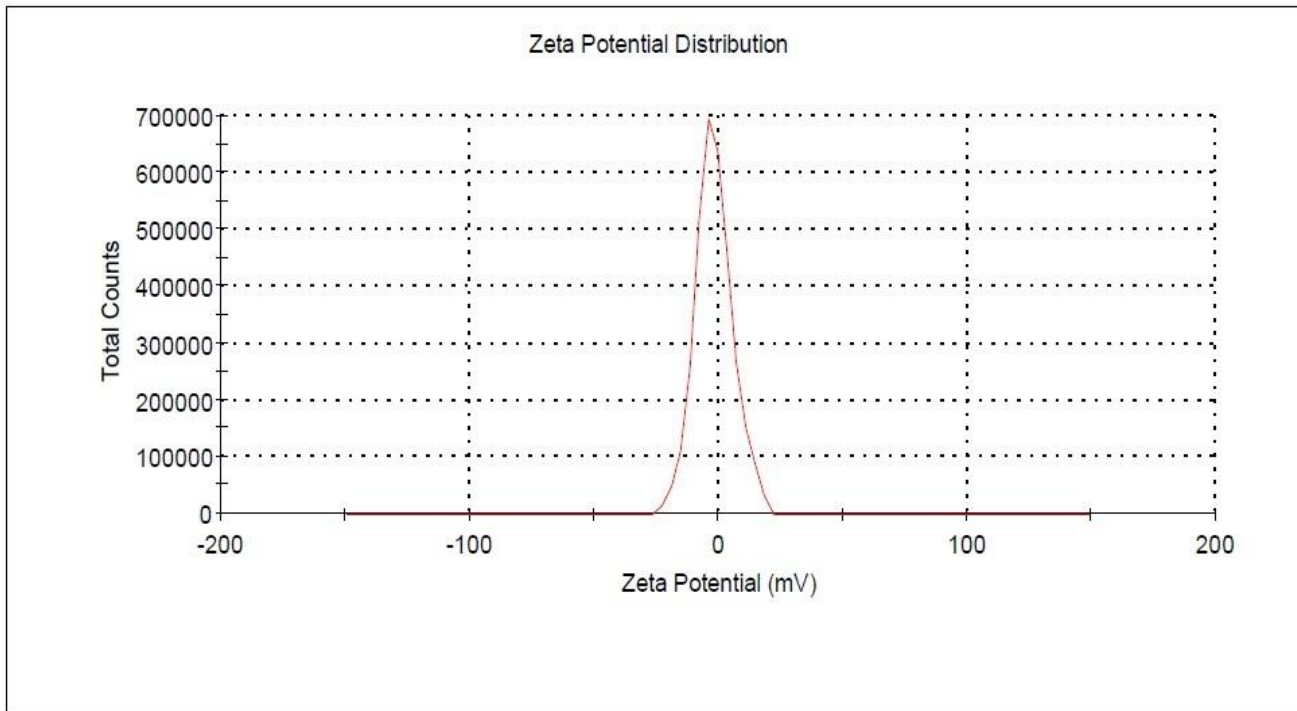
	Size (d.nm):	% Intensity	Width (d.n...
<b>Z-Average (d.nm):</b> 14.98	<b>Peak 1:</b> 12.71	80.2	3.700
<b>Pdl:</b> 0.381	<b>Peak 2:</b> 429.2	16.7	163.2
<b>Intercept:</b> 0.764	<b>Peak 3:</b> 4716	3.1	775.7
<b>Result quality :</b> <b>Good</b>			



**Fig 4:** Globule size and PDI of reconstituted Telmisartan SMEDDS

	Mean (mV)	Area (%)	Width (mV)
<b>Zeta Potential (mV): -1.70</b>	<b>Peak 1: -1.70</b>	100.0	7.52
<b>Zeta Deviation (mV): 7.52</b>	<b>Peak 2: 0.00</b>	0.0	0.00
<b>Conductivity (mS/cm): 0.0246</b>	<b>Peak 3: 0.00</b>	0.0	0.00

**Result quality : Good**



**Fig 5:**Zeta potential of reconstituted Telmisartan SMEDDS

An optimized SMEDDS formulation gave smallest globule size Globule size was found to be 14.98 nm with polydispersity index 0.381. The charge in SMEDDS was negative due to free fatty acids; zeta potential of Optimized formulation was found to be  $-1.70 \pm 7.52$  mV. In general, zeta potential value of  $\pm 30$  mV is sufficient for the stability of microemulsion.

**Determination of drug content**

The drug content of optimized formulation was found to be  $98.63 \pm 0.46$  % (mean  $\pm$  SD, n=3).

**Stability Studies**

The developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. The formulation was found to be stable for accelerated condition  $40 \pm 2^\circ\text{C}$  and  $75 \pm 5\%$  RH up to 6 months (Table 2). There was no significant change in the drug content, dissolution or globule size of the resultant emulsion. It was also

seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. Furthermore, the formulation was found to show no phase separation, drug precipitation. Thus, these studies confirmed the stability of the developed formulation and its compatibility with hard gelatin capsules.

**Table 2:**Stability study data at accelerated condition  $40 \pm 2^\circ\text{C}$  and  $75 \pm 5\%$  RH

Parameter	Initial	3 months	6 months
Assay (%)	$98.63 \pm 1.26$	$98.40 \pm 1.22$	$98.40 \pm 2.14$
Dissolution(% drug release)	$97.40 \pm 3.52$	$99.40 \pm 2.28$	$98.60 \pm 1.82$
Globule Size (nm)	$14.98 \pm 2.15$	$18.4 \pm 1.49$	$16.4 \pm 1.26$

*The values are expressed as mean  $\pm$  SD (n=3)*

**In vitro Dissolution Study**

Fig.6 and Fig.7 shows cumulative percent drug release of Telmisartan SMEDDS and Plain Telmisartan and marketed product (Telma 20) in 0.1 N HCl and pH 7.5 Phosphate buffer media respectively.

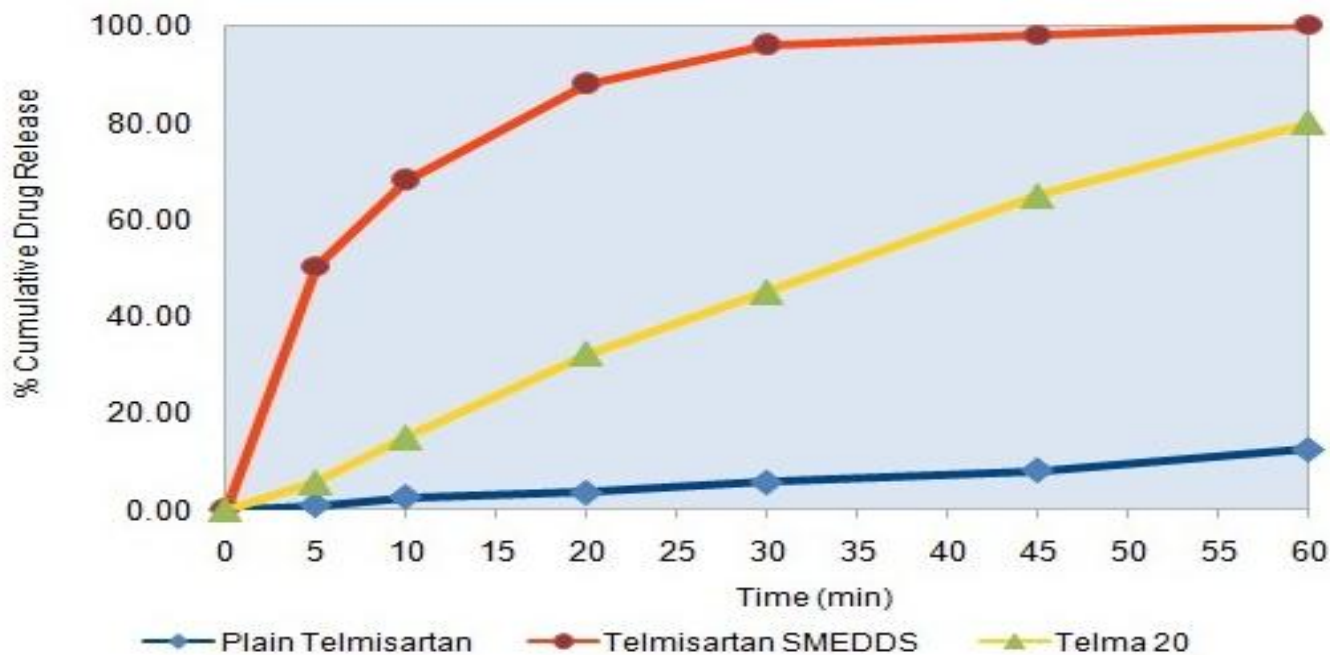


Fig 6: % Cumulative drug release of Telmisartan SMEDDS, Plain Telmisartan and marketed product in 0.1 N HCl

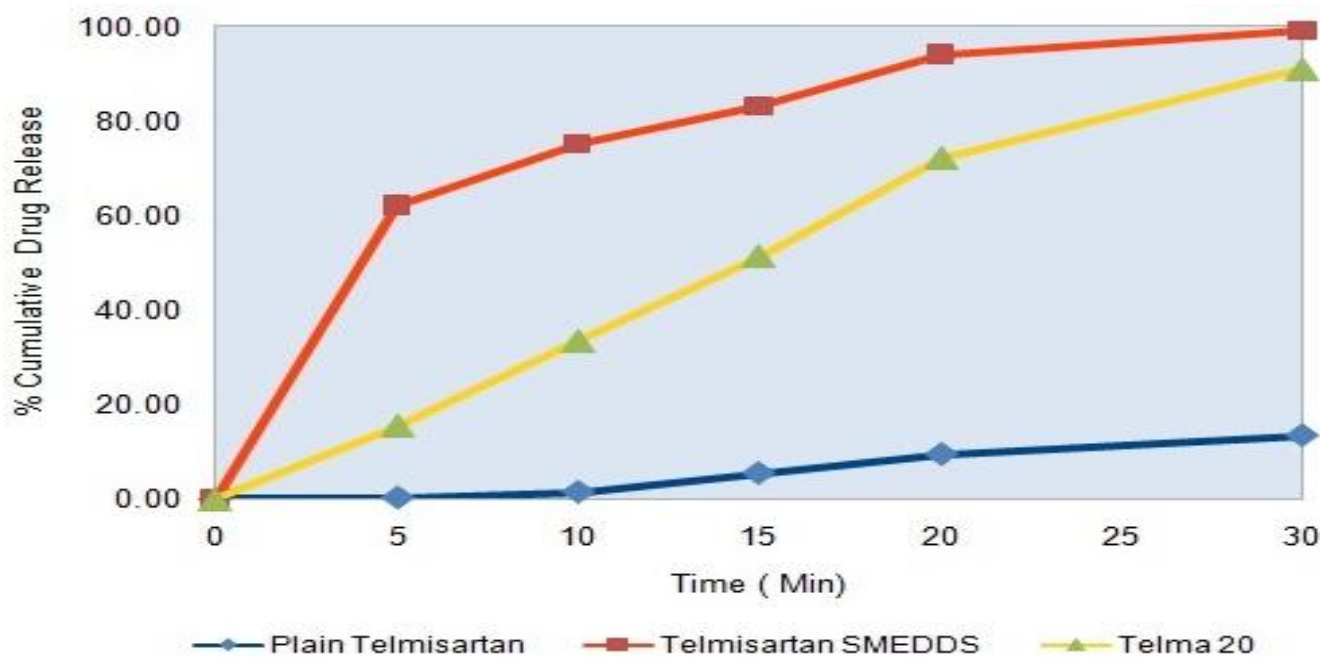


Fig 7: % Cumulative drug release of Telmisartan SMEDDS, Plain Telmisartan and marketed product in pH 7.5 Phosphate buffer

As shown (Table 3) drug releases from SMEDDS was found to be significantly higher as compared to plain Telmisartan drug and marketed preparation (Telma 20).

Table 3 In vitro dissolution data

Product	% Cumulative drug release	
	0.1 N HCl	pH 7.5 Phosphate buffer
Telmisartan SMEDDS	99.60 ± 1.25	98.46 ± 2.34
Plain Drug	12.40 ± 2.16	13.40 ± 1.39
Marketed Product (Telma 20)	79.59 ± 2.64	88.12 ± 2.48

The values are expressed as mean ± SD (n=3)

#### FTIR Study

Fig. 8 shows FTIR spectrum of Telmisartan and Telmisartan S-SMEDDS. FT IR spectrum of Telmisartan exhibits characteristic peaks at 3446  $\text{cm}^{-1}$  (N-H stretch), 3063  $\text{cm}^{-1}$  (aromatic C-H stretch), 2957  $\text{cm}^{-1}$  (aliphatic C-H stretch), 1697  $\text{cm}^{-1}$  (carbonyl group), and 1599  $\text{cm}^{-1}$  (aromatic C=C bend and stretch) and the peak at 1458  $\text{cm}^{-1}$  indicates the presence of C=C aromatic group. Appearance of all these peaks and absence of any new peaks in the SMEDDS formulation indicate no chemical interaction between the drug and excipients.



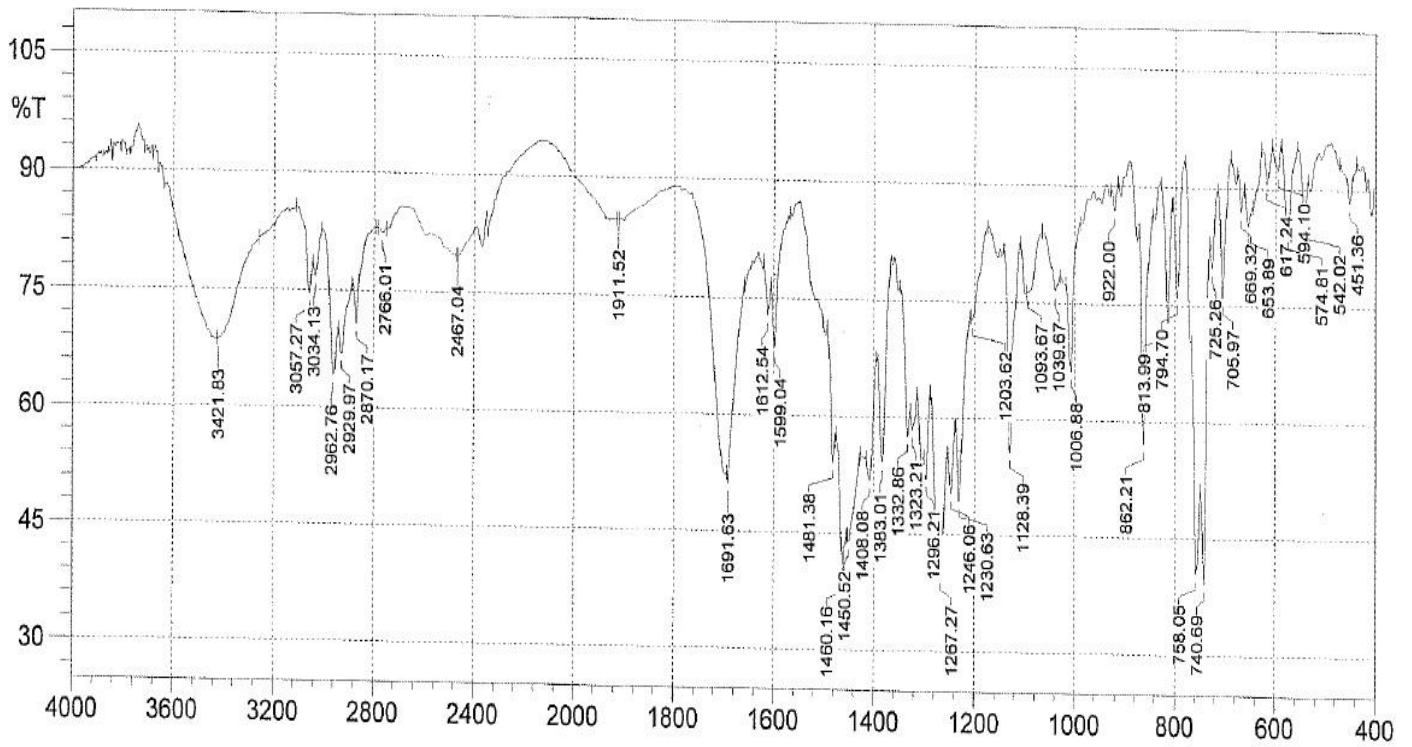


Fig 8:FTIR spectra of Pure Telmisartan

**Differential scanning calorimetry**

DSC was used to assess the thermal behavior of the Pure drug (Telmisartan) and its SMEDDS prepared. DSC thermogram of Telmisartan (Fig.9) shows a single sharp characteristic endothermic peak (T<sub>peak</sub> = 264.93°C) corresponding to its melting, indicating its

crystalline nature and a single peak indicates that the drug sample is free from impurities. However, the characteristic endothermic peak corresponding to drug melting was broadened and shifted toward lower temperature with reduced intensity in the SMEDDS formulation (Fig.10). This could be attributed to change of crystalline nature of drug in the SMEDDS (solubilization of Telmisartan in SMEDDS).

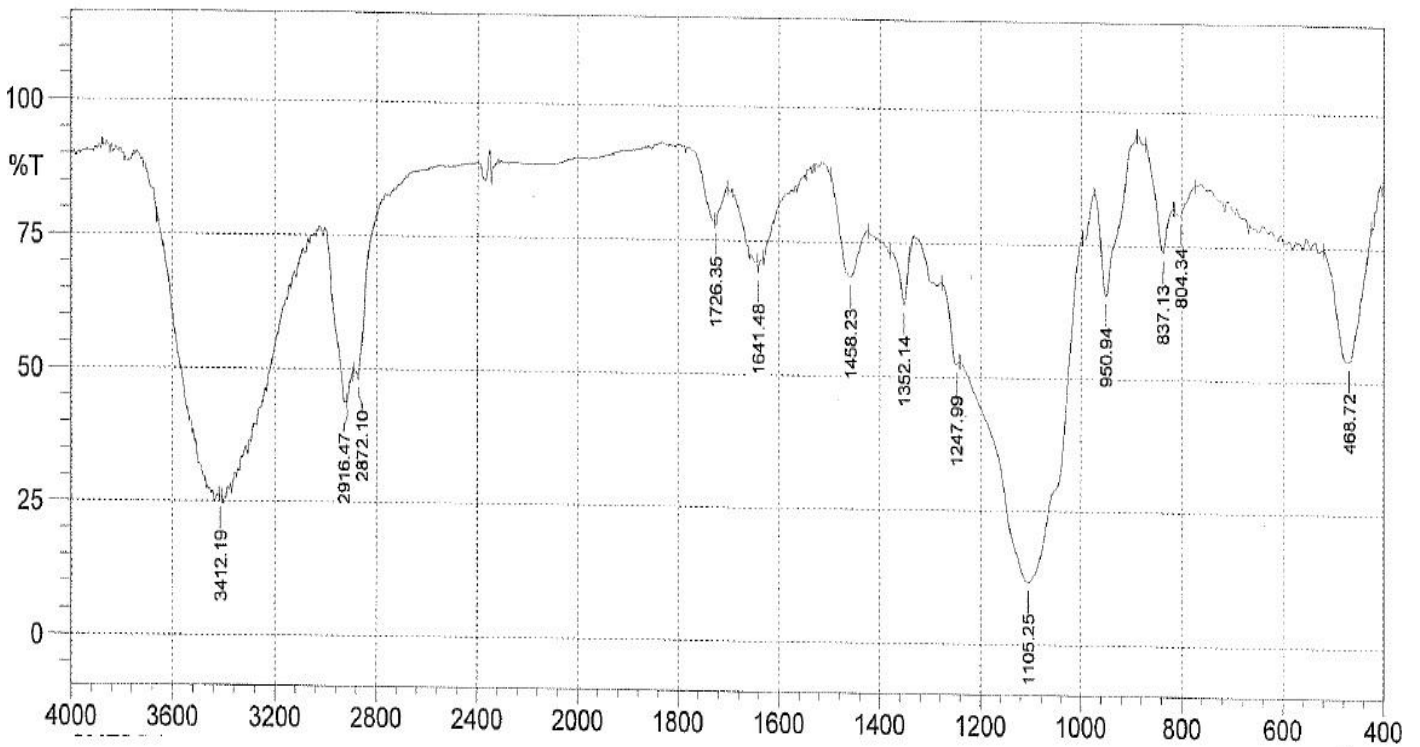
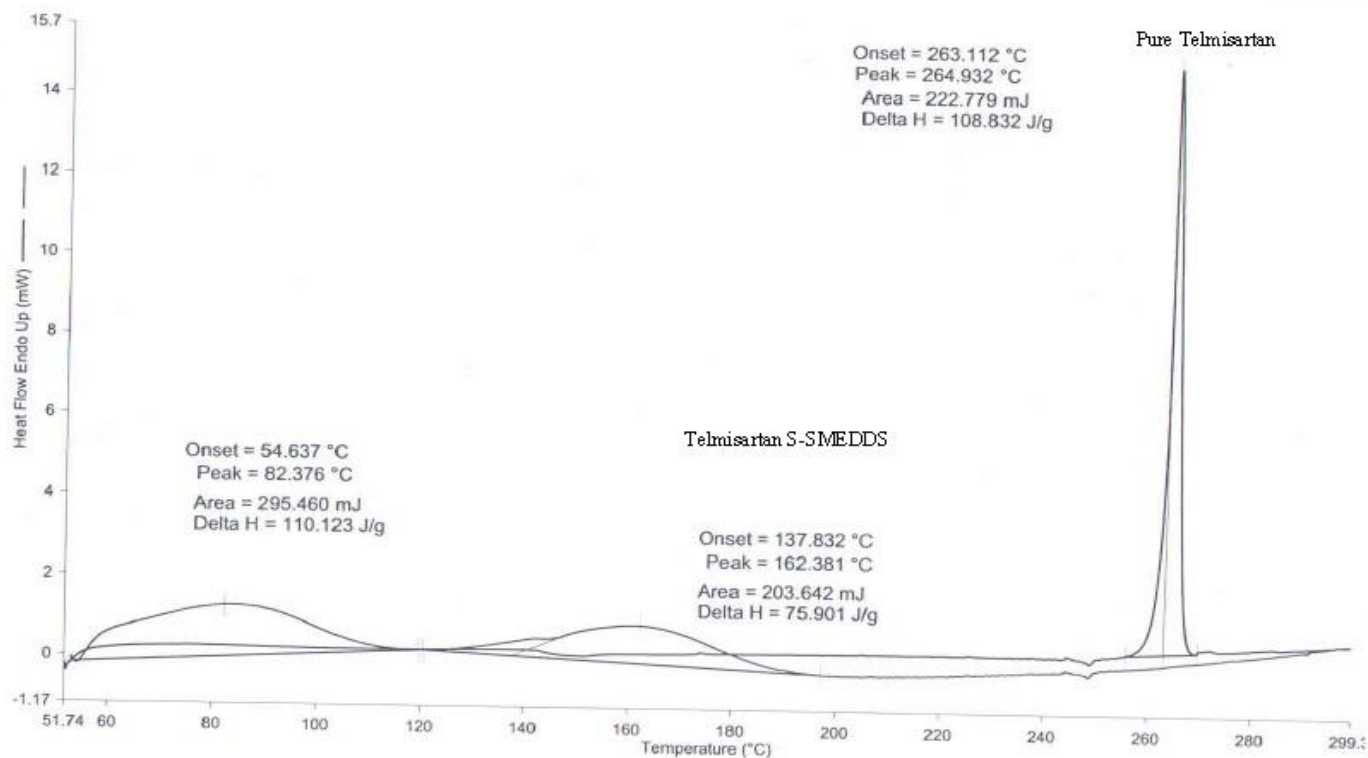


Fig 9:FTIR Spectra of Telmisartan S-SMEDDS

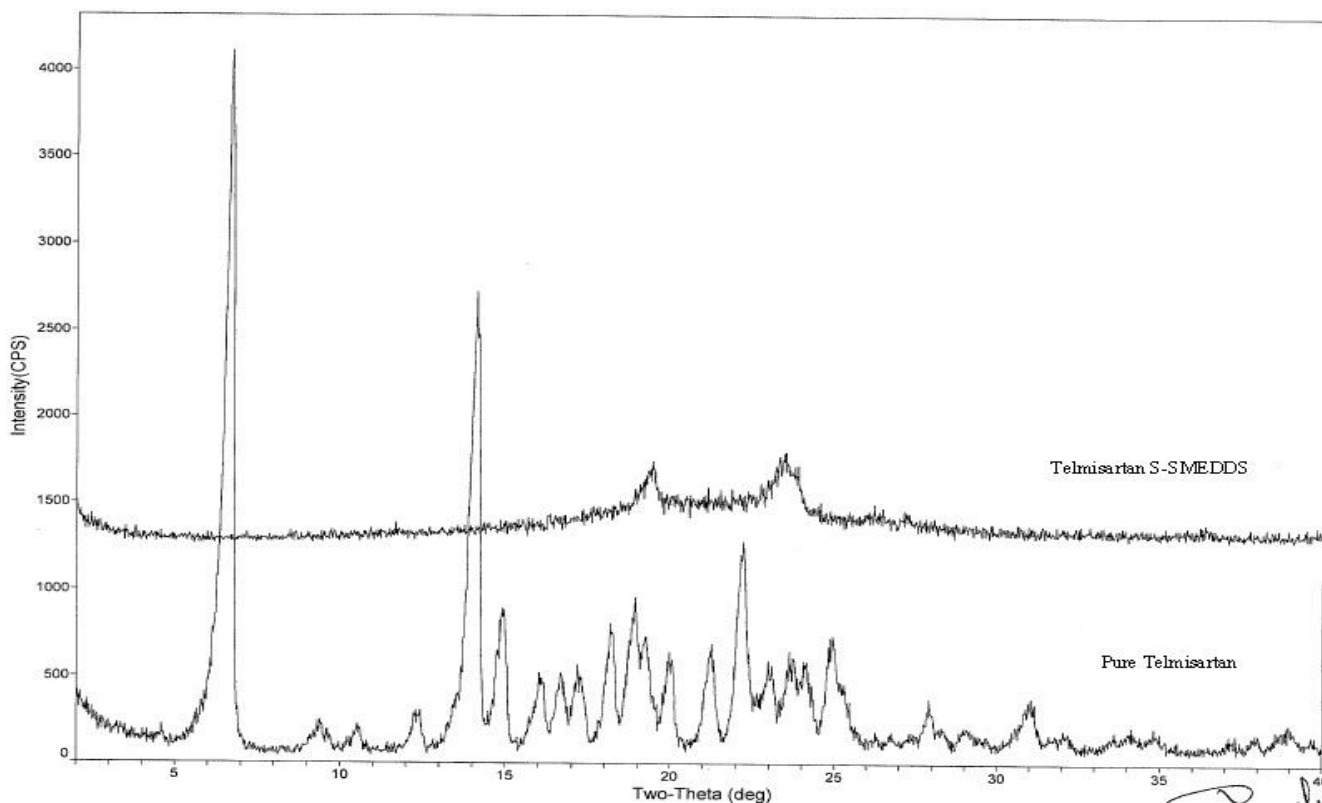


**Fig 10:**DSC Thermogram of Pure Telmisartan and Telmisartan S-SMEDDS

**Powder X-Ray Diffraction studies**

XRD patterns of pure Telmisartan and Telmisartan S-SMEDDS is shown (Fig.11). The diffraction pattern of Telmisartan revealed several sharp high intensity peaks at diffraction angles ( $2\theta$ ) of 6.8°, 9.7°, 14.23°, 14.2°, 15.1°, 16.2°, 18.3°, 20.7°, 22.3°, and 25.1° suggesting that the drug existed as crystalline material. The XRD pattern of

Telmisartan S-SMEDDS showed considerable reduction in the peak intensity compared with characteristic peaks of pure Telmisartan. This diminished peak suggests conversion of drug mostly into amorphous form. This marked reduction in peak intensities provides an explanation for the significant increase in the dissolution rates and hence bioavailability by SMEDDS formulation.



**Fig 11:**XRD Spectra of Pure Telmisartan and Telmisartan S-SMEDDS

## Pharmacokinetic Study

The comparative plasma concentrations versus time profiles (Fig. 12) for both test (Telmisartan SMEDDS) and reference formulations

(Telma20) were obtained. The mean (Mean  $\pm$  SD; n=6) pharmacokinetic parameters of Telmisartan following oral administration of test and reference formulation in Sprague Dawley rats are given in Table.4

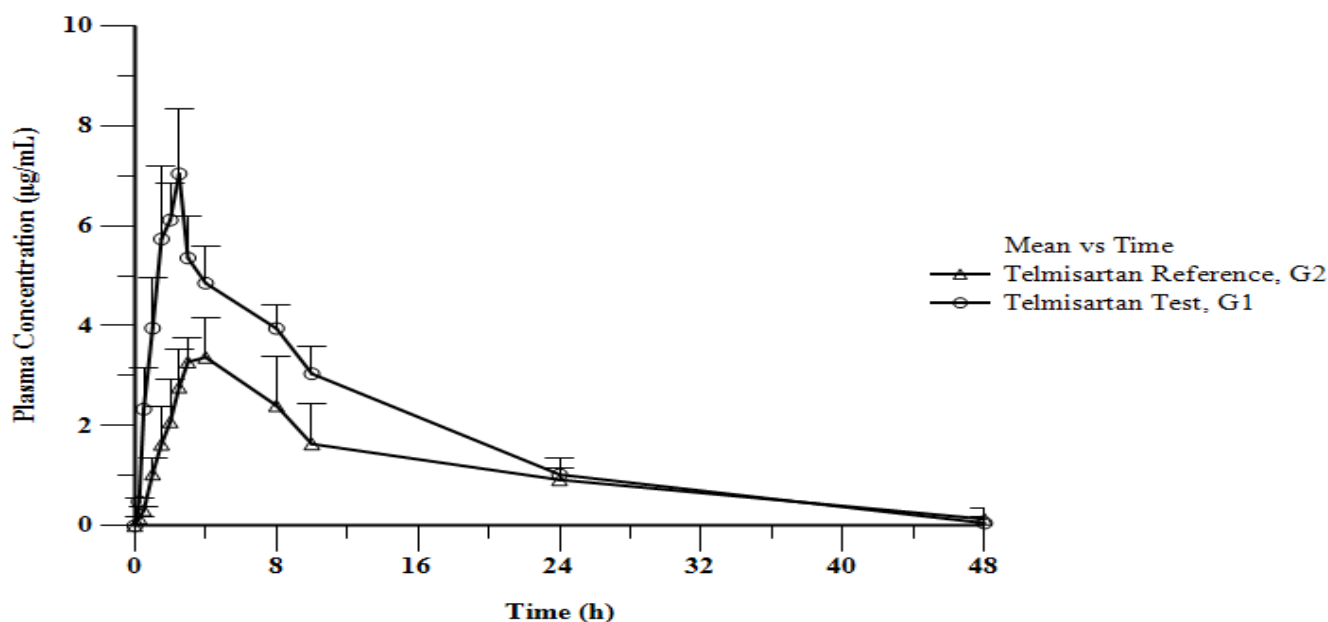


Fig 12: Mean plasma concentration–time profiles in male Sprague Dawley rats

Table 4: pharmacokinetic parameters of Telmisartan in Sprague Dawley rats

Treatment/Group (Dose)	T <sub>max</sub> (h)	C <sub>max</sub> (µg/mL)	AUC <sub>last</sub> (µg*h/mL)	T/R ratio	F <sup>a</sup>
Test Formulation(SMEDDS)	2.08 $\pm$ 0.492	7.68 $\pm$ 0.54	74.7 $\pm$ 12.7	1.54	154
ReferenceFormulation(Telma 20)	3.83 $\pm$ 0.408	3.60 $\pm$ 0.49	48.5 $\pm$ 24.6	NA	NA

<sup>a</sup>Nominal doses and AUC<sub>last</sub> of test and reference were used to calculate relative bioavailability(F); T/R: Test to reference ratio was calculated by AUC<sub>last</sub> of test/AUC<sub>last</sub>Of reference;

NA: not applicable

Following oral administration of test formulation (SMEDDS) filled capsules in male Sprague Dawley rats, the mean time to reach maximum plasma concentration (T<sub>max</sub>) was found to be 2.08 h. The plasma exposures (C<sub>max</sub> and AUC<sub>last</sub>) were found to be 7.68 µg/mL and 74.7 µg\*h/mL, respectively. Following oral administration of reference formulation the mean time to reach maximum plasma concentration (T<sub>max</sub>) was found to be 3.83 h. The plasma exposures (C<sub>max</sub> and AUC<sub>last</sub>) were found to be 3.60 µg/mL and 48.5 µg\*h/mL, respectively. The test to reference (T/R) ratio was found to be 1.54, suggesting higher exposure of test compared to reference formulation.

## Conclusion

In this study, SMEDDS of Telmisartan were prepared and evaluated for their in vitro and in vivo behavior. Prepared liquid SMEDDS was thermodynamically stable with good self emulsification efficiency and having globule size in nanometric range which may be physiologically stable. The optimized formulation consisting of Telmisartan (20mg), Capmul MCM (14.40% w/w), Tween 80 (27.20% w/w) and Propylene glycol (54.40% w/w) exhibited faster release profiles with a rapid rate of emulsification. The optimized SMEDDS formulation of Telmisartan showed a significant increase in oral absorption compared to the marketed product. The exposure (C<sub>max</sub> and AUC<sub>last</sub>) of developed SMEDDS was found to be comparatively higher (1.54 fold) than reference marketed product indicating better rate and extent of absorption than reference formulation. Thus, SMEDDS can be regarded

as a novel and commercially feasible alternative to current Telmisartan formulations. However, further studies in the higher animals and human beings need to be performed before this formulation can be commercially exploited.

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