

## FORMULATION AND CHARACTERIZATION OF TELMISARTAN SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

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Received: 30 July 2013, Revised and Accepted 9 Oct 2013

### ABSTRACT

The objective of the present study was to develop a novel self micro emulsifying drug delivery system of a poorly water soluble drug, Telmisartan. Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with implications of low bio availability, high intra and inters subject variability and lack of dose proportionality. Hydrophobic drugs can often be dissolved in micro emulsion allowing them to be encapsulated in the form of fine globules, so that drug remains undissolved in the gut avoiding the dissolution step, which frequently limit the rate of absorption of hydrophobic drugs.

Phase solubility studies were conducted for the maximum solubility of Telmisartan. Ternary phase diagrams were constructed to evaluate micro emulsion regions. FTIR analysis was done for investigating the drug-excipient interactions, Globule size, zeta potential and TEM analysis was done to investigate the particle size of micro emulsions.

Highest solubility was found in tween 20 (surfactant), carbitol (co surfactant) and miglyol (oil). The mean globule size of SMEDDS was observed to be below 200nm for the optimized formulations and the zeta potential was negative. The dissolution of emulsion formulations was compared with commercial tablets; the results indicated that the rate of dissolution of developed formulations containing Telmisartan was 2 to 3 folds increased compared with that of commercial tablets.

Thus, SMEDDS can be regarded as novel and commercially feasible alternative to the current Telmisartan formulations.

**Keywords:** Tween20, Carbitol, Miglyol, Ternary phase diagrams, Zeta potential.

### INTRODUCTION

Selection of an appropriate salt form or for liquid dosage forms and adjustment of pH of the solution is the basic fundamental step involved in the solubilisation of the drug products. Majority of newer solubilisation techniques like nanosuspensions and micro emulsions utilize co-solvents when applied to polar compound which becomes an important selection [1]. Particle size reduction via comminution, spray drying, addition of surfactants, inclusion in cyclodextrin-drug complexes and the use of more novel mechanisms such as self-emulsifying systems, micronisation via nanoparticles, pH adjustment and salting in processes are the solubility enhancement of both traditional methods which are included by these technologies [2,3].

The reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract is the thought of solubilising and absorption promoting effect of potential solubility enhancing technologies which is emerged by micro emulsions and self-micro emulsifying system. To incorporate drugs into self-emulsifying systems, long and medium chain triglycerides (LCT's and MCT's, respectively) have been employed with surfactants, traditionally [4, 5]. To ensure immediate formation of oil-in-water (O/W) droplets during production, non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hydrophile-lipophile balances (HLB) are often used. Drug solubilisation in higher degrees and precipitation of the drug may be prevented out of micro emulsion in-vivo is allowed by amphiphilic, non-ionic surfactants. To increase the amount of drug capacity of being dissolved into the lipid base, frequently co-surfactants are employed, this is because the concentration of surfactant should be excess of 30% W/W in most of self emulsifying systems. Co-surfactants (such as ethanol, propylene glycol and poly ethylene glycol) used should be suitable for oral administration, hence co-surfactants are often organic solvents. Alike to the effect of introducing these organic solvents in manufacturing of drug product, complexity is processed during improving the potential drug load of the emulsion as the use of co-solvents increased [6].

Due to the liquid nature of the product, most of these self-emulsifying systems are limited to administered in lipid-filled soft or

hard-shelled gelatin capsules. To prevent the hydroscopic contents from dehydrating or migrating into the capsule shell, the interaction between the capsule shell and the emulsion should be considered. Telmisartan is an oral anti-hypertensive agent drugs used by the patients to avoid heart failure, kidney failure and acute stroke induced by hypertension and delay the development of atherosclerosis by controlling blood pressure. Hence formulation of the drug as a SMEDDS formulation can improve the absorption and bioavailability.

### MATERIALS AND METHODS

#### Materials

Telmisartan was procured from Yarrow chemicals, Mumbai. Cremophor RH40, sun flower oil, miglyol, Span 20, span 80, PEG 400, brij 30, carbitol, olive oil, cotton seed oil were purchased from Sd-Fine chemicals limited, Mumbai; Tween 20, tween 60, tween 80, oleic acid, castor oil were purchased from Merck specialities pvt limited, Mumbai.

#### Methods

##### Solubility study of Telmisartan in various excipients

The solubility of Telmisartan in various oil, surfactant, co-surfactant was determined. Solubility studies were conducted by placing an excess amount of drug in each vehicle in a 2ml Micro tube (Axygen MCT 200) containing 1.5ml of the vehicle. Then the mixture was vortexed and kept for 48hrs at 25°C in a Orbital shaking incubator (Remi electrotechnik ltd.) to facilitate the solubilization. The samples were centrifuged at 3000rpm for 15min to remove the undissolved drug. The supernatant was taken and the concentration of drug in each vehicle was quantified by U.V-spectrophotometer.

##### Construction of Pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams of oil, surfactant: co-surfactant and water were developed using surfactant titration method: The mixtures of oil and water at certain weight ratios were titrated with surfactant: co-surfactant mix in a drop wise manner. Three types of surfactant phases were prepared: Tween 20+ carbitol (1:1, 2:1, 3:1).

For each phase diagram at a specific ratio of surfactant/co-surfactant transparent and homogenous mixture of oil and water was formed under the mixing by cyclomixer. Then, visually observed for phase clarity and flow ability. After the identification of micro emulsion region in the phase diagrams, the micro emulsion formulations were selected at desired component ratios, in order to form the micro emulsion.

#### Formulation design of SMEDDS containing Telmisartan

Table 1: Formulation table of Telmisartan SMEDDS

| F             | F1   | F2   | F3 | F4 | F5   | F6   | F7 | F8   | F9   | F10 | F11 | F12  | F13  | F14  | F15 | F16 | F17  | F18  | F19 | F20  |
|---------------|------|------|----|----|------|------|----|------|------|-----|-----|------|------|------|-----|-----|------|------|-----|------|
| % Tween 20    | 47.5 | 63.3 | 4  | 6  | 42.5 | 56.6 | 4  | 53.3 | 37.5 | 50  | 35  | 46.6 | 32.5 | 43.3 | 30  | 40  | 27.5 | 36.6 | 25  | 33.3 |
| % of carbitol | 47.5 | 31.6 | 4  | 3  | 42.5 | 28.3 | 4  | 26.6 | 37.5 | 25  | 35  | 46.6 | 32.5 | 21.6 | 30  | 20  | 27.5 | 18.3 | 25  | 16.6 |
| % of meglyol  | 5    | 5    | 1  | 1  | 15   | 20   | 2  | 25   | 25   | 25  | 30  | 30   | 35   | 35   | 40  | 40  | 45   | 45   | 50  | 50   |

#### Evaluation of SMEDDS of telmisartan

**Drug excipient compatibility studies:** FTIR spectrums of telmisartan and drug-micro emulsion formulation were obtained by means of a FTIR spectrophotometer (bruker-alpha T). The samples were prepared by the potassium bromide disk method and measurements were attempted with the accumulations of 20 scans and a resolution of 4 cm<sup>-1</sup> over the range of 400-4000 cm<sup>-1</sup>. After running the spectra, significant peaks relating to major functional groups were identified; spectra of the subsequent samples of the same compound were compared with the original [7]

#### Cloud point Measurement, droplet size analysis and zeta potential study

**Cloud point Measurement:** Dilute the formulation with 50ml of water in beaker and placed on a water bath with gradually increasing the temperature until the diluted formulation turned to cloudy. It gives the information about the stability of the microemulsion at body temperature.

**Droplet size measurement:** The mean droplet size of emulsion globules was determined by using photon correlation spectroscopy (which analysis the fluctuations in light scattering due to Brownian motion of the particles) using nano zeta sizer able to measure sizes between 10-3000nm. Light scattering was monitored at 25°C at a 90° angle. The dispersed formulations were measured after dilution (1:100) to produce the required count rate (50-200) to enable the accurate measurement [ 8, 9, 10].

**Zeta potential:** The zeta potential of microemulsion was determined using nano zeta sizer. Charge on emulsion droplets and their mean zeta potential value (± SD) were obtained from the instruments [8, 10].

**Drug content:** A measured quantity of microemulsion was added to 100ml of pH 1.2 buffers. The resulting mixture was kept at 24hrs at a dark place. Then the solution was filtered through membrane filter of 0.45µm pore size and 1ml of this solution was diluted to 10ml using 1.2 pH buffer. After further dilutions with mobile phase, the samples were analysed by UV spectrophotometer for drug content at 297nm. The drug content was determined using the relationship [11]

$$\frac{\text{experimental drug content}}{\text{theoretical drug content}} \times 100 = \text{Drug content}$$

**Transmission electron microscopic studies:** Examining the surface of a polymeric drug delivery system can provide vital information on the porosity and microstructure of this system. The distribution and morphology of the surface and the encapsulated matrix can also be directly observed. The most common technique used for characterizing the surface morphology of drug delivery

The formulations were prepared by initially dissolving the formulation amount of telmisartan in co-surfactant at 45°C in an isothermal water bath. Oil was then added and mixture was cooled to ambient temperature, then surfactant was added and the final mixture was sonicated until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48hrs and examined for signs of turbidity (or) phase separation. In all the formulations the amount of Telmisartan was constant at 20mg/ml.

systems is transmission electron microscopy (TEM). The sample sizes, which can be analysed using this method, range from nanometers to micrometers to centimeters.

**In vitro dissolution studies:** The release of telmisartan from the microemulsion formulations was determined according to USP dissolution apparatus type II. To permit the quantitative drug release from microemulsion formulation, 900ml of pH 1.2 buffer was placed in the dissolution vessel and then the microemulsion formulation filled ion hard gelatin capsule was placed in the dissolution medium and was agitated at 500rpm at 37°C. At pre-determined time intervals of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes, 5ml of the samples were withdrawn and the drug concentration was determined by UV spectrophotometer at wavelength 296nm. The volume withdrawn was replaced each time with fresh dissolution medium. Cumulated released amounts were plotted as a function of time [12].

**Determination of self emulsification time:** the primary means of self micro emulsification assessment is visual evaluation. The efficiency of self micro emulsification could be estimated by using magnetic stirrer with 100 rpm, water and 0.1N Hcl solution as medium. Temperature was maintained at 37±0.5°C. Fill the beaker with 100ml of medium and pour the SMEDDS formulation into the medium and the contents being mixed gently at 100 rpm and determining the time required to form micro emulsion upon dilution of SMEDDS with water.[13,14]

**Visual observation, phase separation and stability study of emulsion:** Each formulation of SMEDDS containing Telmisartan was taken in a small beaker and was diluted with 200ml of distilled water at 37°C, check visual appearance and the diluted preparation was vortexed for 1min, and then the mixtures was stored for a period of 24 hrs, and observe phase separation and precipitation visually. Mixtures exhibiting a negligible phase separation during the 2 hr period were used for subsequent studies. It gives the information about stability and viability of the formed microemulsion. [15, 16]

#### Dispersibility and Appearances of SMEDDS

| Grade | Dispersibility and appearances                               |
|-------|--|
| I     | Clear or slightly bluish in appearance                       |
| II    | Bluish white appearance                                      |
| III   | Bright white emulsion (similar to milk)                      |
| IV    | Dull, grayish white emulsion with a slightly oily appearance |
| V     | Turbid appearance  |

#### RESULTS AND DISCUSSION

**Solubility study of Telmisartan in various excipients:** Selection of right component is important prerequisite for formulation of stable SMEDDS. The drug should have good solubility in components of micro emulsion so as the

precipitation of drug during shelf life of formulation and after dilution in GI lumen can be avoided. The solubility of Telmisartan in various vehicles is presented in table 2 & fig 1. Tween20 and carbitol provided higher solubility than other

vehicles and miglyol as oil was selected for the optimal novel emulsion formulation resulting in improved drug loading capabilities. 20mg dose of Telmisartan was selected to prepare formulations.

Table 2: Solubility studies of telmisartan in various vehicles.

| Vehicle            | Span 20 | Span 40 | Span 80 | Tween 20 | Tween 60 | Tween 80 | Cremophor RH40 | PEG 400 | Brij 30 | Carbitol | Olive oil | Sunflower oil | Meglyol | Cottonseed oil | Oleic acid | Iso propyl myristate | Castor oil |
|--------------------|---------|---------|---------|----------|----------|----------|----------------|---------|---------|----------|-----------|---------------|---------|----------------|------------|----------------------|------------|
| Solubility (mg/ml) | 62.68   | 55.21   | 67.55   | 108.01   | 99.21    | 107.63   | 5.96           | 82.76   | 12.69   | 118.69   | 6.61      | 9.62          | 38.13   | 12.15          | 8.02       | 2.16                 | 4.19       |

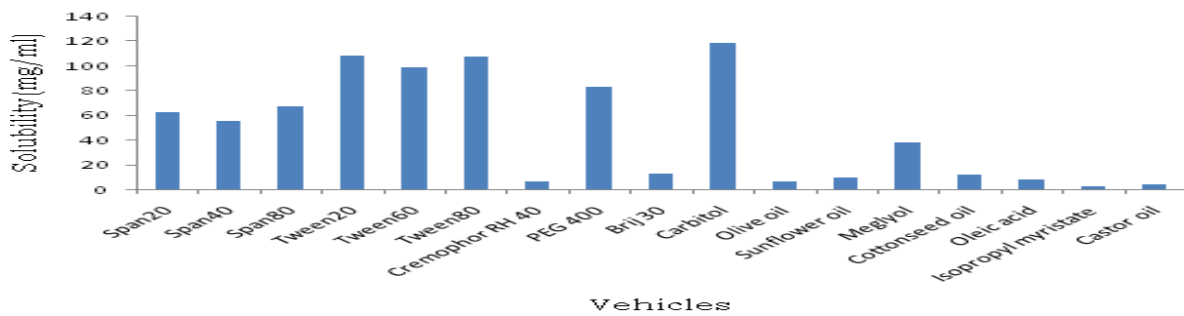


Fig. 1: Graph showing solubility of Telmisartan in various oils and surfactants, the solubility of Telmisartan was determined in various vehicles by UV spectroscopic method. The solubility of Telmisartan was found to be high in Tween20 (surfactant) and Carbitol (cosurfactant), miglyol (oil).

**Ternary phase diagrams**

Phase diagrams were constructed in the presence of Telmisartan to obtain the optimum concentrations of oil, surfactants and co-surfactants and to identify the self emulsifying regions. A pseudo ternary phase diagram of investigated quaternary system

Water/Meglyol/Tween20/Carbitol is presented in fig2 (a). Formation of microemulsion was found at room temperature. The phase study revealed that the maximum proportion of oil was incorporated in microemulsion system when the surfactant/co-surfactant ratio was 2:1 as shown in fig2 (b).

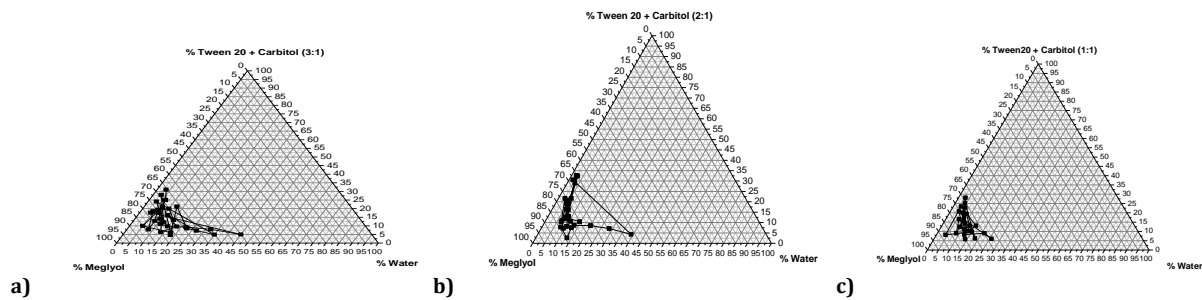


Fig. 2: Pseudo ternary phase diagrams indicating the efficient microemulsion region containing ( Tween20 / Carbitol) = (a) 3:1 (w/w) (b) 2:1 (w/w) (c) 1:1 (w/w). The shaded area represents O/W microemulsion existence range.

**FTIR studies**

FTIR spectrums of formulations were obtained by means of a FTIR spectrophotometer (Bruker-AlphaT). The FTIR spectrum of pure Telmisartan has three characteristic peaks at 3442cm<sup>-1</sup>, 2958cm<sup>-1</sup>, 1268cm<sup>-1</sup> for O-H stretching vibration, C-H vibration and Carboxylic acid functional group respectively as shown in fig3 and the FTIR spectrum of Telmisartan SMEDDS formulation has two characteristic peaks at 3451cm<sup>-1</sup>, 1249cm<sup>-1</sup> as shown in fig 3 and fig 4. It is indicated that there was no interaction between Telmisartan and excipients used in the formulation as the functional groups obtained for three spectrums are almost similar.

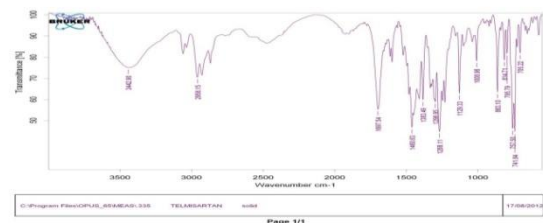


Fig. 3: FTIR spectra of Telmisartan

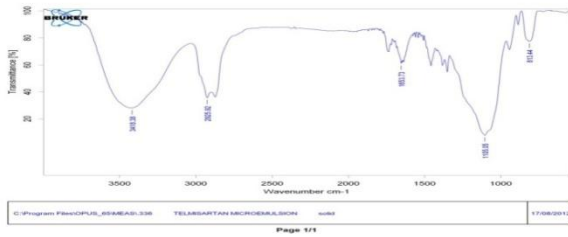


Fig. 4: FTIR spectra of Telmisartan SMEDDS

**Cloud point Measurement, droplet size analysis and zeta potential study**

Cloud point is the temperature above which the formulation clarity turns into cloudiness. The cloud point of the formulation should be over 37°C. The cloud point is affected by the factors such as drug hydrophobicity, kind, combination, mixing ratio and amount of each of the oils, surfactants/cosurfactants used. In this study, cloud points of all formulations were very high about 80°C as reported in table 3 & fig 5.

**Table 3: cloud point, droplet size and zeta potential values of SMEDDS**

| Formulation code   | F1      | F2      | F4      | F6     |
|--------------------|---------|---------|---------|--------|
| Cloud point        | 74±6.52 | 73±5.15 | 80±4.64 | 76±5.8 |
| Droplet size(nm)   | 251     | 242     | 122     | 178    |
| Zeta potential(mv) | -8.6    | -12.1   | -15.2   | -10.8  |

**Drug content**

Percentage drug content was quantified by dissolving SMEDDS formulations equivalent to 20mg in methanol and made concentration equivalent to 100µg/ml with pH 1.2 buffer and analyzed by UV method. Percent drug was calculated using the formula given in methodology and results are shown in table 4.

**Table 4: Drug content values of SMEDDS**

| Formulation code | F1    | F2    | F4    | F6    |
|------------------|-------|-------|-------|-------|
| % of drug        | 99.52 | 98.42 | 99.67 | 99.33 |

**TEM studies**

Physical analysis of globules was studies using transmission electron microscopy for SMEDDS formulations. Droplet size of micro emulsion is very important characteristic. The surface morphology,

roundness, smoothness and formation of aggregates and the size distribution of microemulsion is clearly seen in fig 6 as round particles as studied by transmission electron microscopy (TEM).

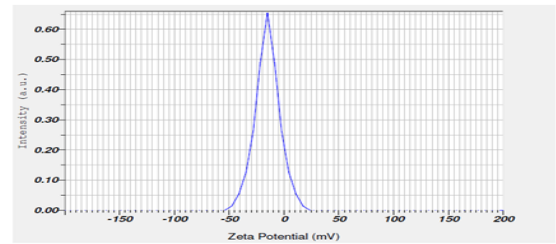


Fig. 5: Zeta potential of SMEDDS

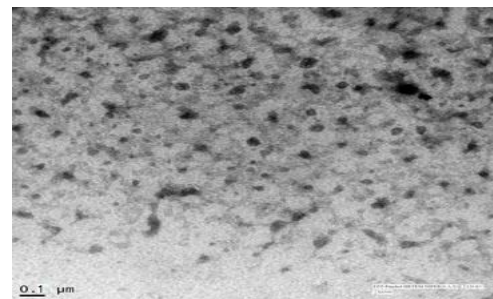


Fig. 6: TEM micrograph of Telmisartan SMEDDS

**In vitro dissolution studies**

The results of dissolution studies are shown in fig 10, at the end of one hour, the dissolution of F4 SMEDDS formulation was significantly greater (99.65%) than that of other formulations as seen in fig 7. It suggests that Telmisartan dissolved perfectly in SMEDDS formulation, and could be released due to its small droplet size which permits a faster rate of drug release into the aqueous phase.

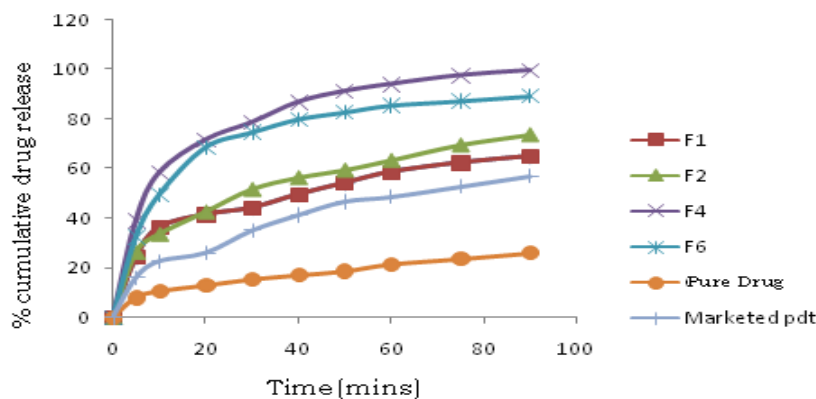


Fig. 7: % cumulative drug release from various formulations.

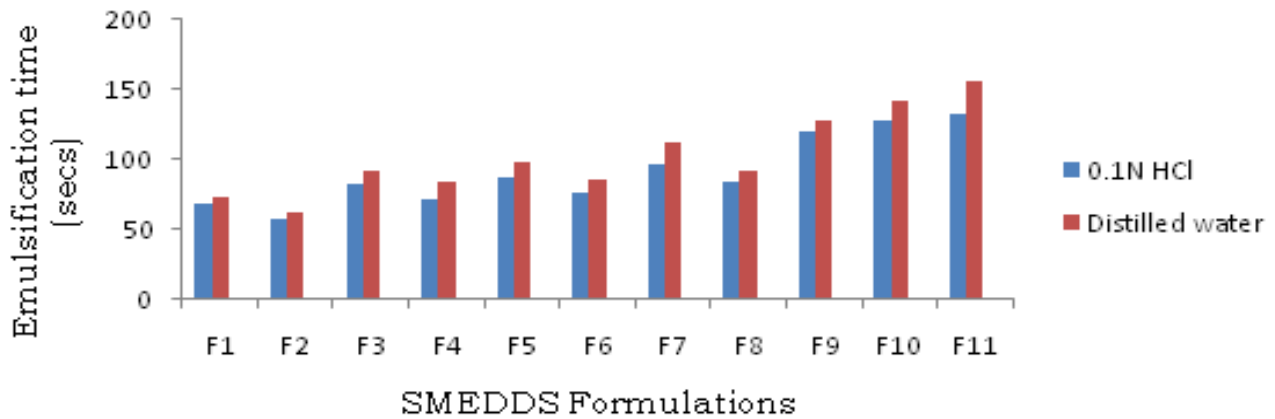
### Emulsification time

To evaluate the emulsification time for the formulations prepared were conducted both in acidic medium (0.1N HCl) and water to stimulate the range of conditions encountered in GIT. In study of formulations(F1-F10) shown a good spontaneity of emulsification and good stability without any signs of drug or excipient precipitation and self

emulsification time of various formulations were shown in table 5 & fig 8. With increase in oil proportion, emulsification time and interfacial tension between larger volume of oil and aqueous phase is increased and rate of emulsification and concentration of surfactant system is decreased. Emulsification time decreased in 0.1N HCl medium than the aqueous medium which suggests that pH has considerable influence on the self micro emulsification region.

**Table 5: Emulsification times of SMEDDS in various media**

| Formulation code |                             | F1   | F2   | F3   | F4   | F5   | F6   | F7   | F8   | F9   | F10  | F11  |
|------------------|-----------------------------|------|------|------|------|------|------|------|------|------|------|------|
| 0.1N HCl         | Emulsification time(secs)   | 67   | 56   | 82   | 71   | 87   | 76   | 96   | 83   | 119  | 128  | 132  |
|                  | Tendency for emulsification | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good | Good |
| Distilled water  | Emulsification time(secs)   | 73   | 61   | 92   | 84   | 98   | 85   | 112  | 91   | 127  | 142  | 156  |
|                  | Tendency for emulsification | Good | Good | Good | Good | Good | Good | Good | Bad  | Good | Bad  | Bad  |



**Fig. 8: Emulsification times of various formulations in 0.1N HCl and Distilled water.**

**Table 6: Phase separation and visibility grade of SMEDDS**

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9  | F10 | F11 | F12 | F13 | F14 | F15 | F16 | F17 | F18 | F19 | F20 |
|------------------|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Visibility grade | II | I  | II | I  | II | II | II | II | III | IV  | III | IV  | V   | V   | V   | V   | V   | V   | V   | V   |
| Phase separation | x  | x  | x  | x  | x  | x  | x  | x  | x   | x   | x   | +   | +   | +   | +   | +   | +   | +   | +   | +   |
| Precipitation    | xx | xx | xx | xx | xx | xx | xx | xx | xx  | xx  | xx  | xx  | ++  | ++  | ++  | ++  | ++  | ++  | ++  | ++  |

x- no phase separation, xx- no precipitation, +- phase separation, ++- precipitation.

### Phase separation and Visibility grade

All formulations after dilution in the ratio of 1:100 with distilled water were shown to form emulsions, micro emulsions and nano emulsions which form milky, bluish and slightly bluish color respectively. Formulations F1 to F10 showed no crystal growth or no precipitation and formed micro emulsion upon dilution with aqueous media and remained physically stable for more than 24hrs. Remaining formulations showed phase separation and precipitation. These results indicates as the concentration of oil increases the stability of formulation decreased and it is deduced that increase in surfactant content increased the clarity of produced micro emulsions, detailed results are shown in table 6.

### CONCLUSION

Telmisartan SMEDDS were prepared as a novel technique to improve the solubility of poorly soluble drug. The preformulation studies done clearly indicate good compatibility of the drug with the various excipients used. The reduction of particle size was clearly depicted in the droplet size measurements where the size is reduced to nanometer range, which has led to increase in dissolution rates as shown in the dissolution studies and graph.. Thus it can be concluded that micro emulsion formulation can be

used as a successful tool to enhance the bioavailability of the drug, and there formulations can be further tested in vivo by using animal models.

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