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DESIGN AND EVALUATION OF SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) OF A BCS CLASS II ANTIHYPERTENSIVE DRUG

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ABSTRACT

Self-nanoemulsifying drug delivery system (SNEDDS) of Telmisartan was developed with an objective to overcome problem of its poor solubility, less bioavailability and high hepatic degradation. Solubility of Telmisartan in oily phase and surfactant was determined first to identify the components of SNEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify selected oily phase. Optimized SNEDDS formulation consists of Clove oil, Tween 80 and PEG 400. Optimized batch contains oil to Smix (surfactant-cosurfactant mixture) ratio 1:1 with surfactant to co-surfactant ratio of 2:1. The mean globule size of optimized Telmisartan SNEDDS was found to be 65nm with zeta potential value of +8.45Mv. Globule size and shape was confirmed by TEM analysis. Optimized Optimized SNEDDS formulation of Telmisartan showed more than 80% drug release in 20 minutes. Optimized SNEDDS showed significant improvement in rate of release in Telmisartan dissolution as compared to plain drug.

Keywords *– Telmisartan, Clove oil, SNEDDS*

1. INTRODUCTION

Oral route is preferred for drug administration, but more than 40% of new chemical entities exhibit poor aqueous solubility that lead to unsatisfactory oral drug delivery [1]. Lipid based drug delivery systems such as solutions, suspensions; solid dispersion and self-emulsifying drug delivery system (SEDDS) are used to improve oral bioavailability of poorly water-soluble drugs [2-5]. Self-emulsifying formulations comprises of mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactant and co-surfactants which spontaneously emulsify when exposed to the fluids of the gastrointestinal tract [6-11].

SEDDS produces milky emulsion upon dispersion in water with droplet size ranging from microns to few nanometers. Self-micro emulsifying drug delivery systems (SMEDDS) are clear transparent micro-emulsions with droplet size ranging from 100-250 nm [7,8]. Self-nanoemulsifying drug delivery systems (SNEDDS) form nanoemulsion upon dispersion in water with globule size range less than 100 nm [7, 12-14].

SNEDDS are anhydrous forms of nanoemulsion which when introduced into aqueous phase under conditions of gentle agitation; spontaneously form O/W nanoemulsion. SNEDDS are usually prepared in a liquid dosage form that can be administered in soft gelatin capsule and in the form of solid SNEDDS [7, 15-17].

SNEDDS contain co-emulsifier or co-surfactant and/or solubilizer in order to facilitate nanoemulsification or improve the drug incorporation in SNEDDS. They offers advantages like physical /chemical stability, palatability, better dissolution, reduction in inter and intra subject variability, quick onset of action, reduction in the drug dose, reduces first pass metabolism, enhances lymphatic transport of drugs, enhances solubility and oral bioavailability of drugs, ease of manufacture and scale up [9].

Key material used in SNEDDS includes oils (e.g. Fixed oils, Medium chain and Long chain Triglycerides, Herbal oils etc.), surfactants (e.g. Labrasol, Cremophor EL, Cremophore RH 40,Tweens, Spans etc.) and co- surfactants (e.g. Transcutol P, PEG 400, ethanol etc.) [7, 15, 16].

Telmisartan is Angiotensin II receptor antagonist, which is used in the prevention and treatment of Hypertension. It belongs to class II drug in BCS classification. It has poor solubility, high hepatic degradation and poor bioavailability after oral administration. Solubility of telmisartan is 0.0035mg/ml in water, bioavailability is 42% and biological half-life is 24 hrs. This results in poor bioavailability after oral administration. In the present research work, self-nanoemulsifying drug delivery system (SNEDDS) of Telmisartan was developed with an objective to overcome its problem of poor solubility, less bioavailability and high hepatic degradation.

2. MATERIALS AND METHODS

2.1 Materials

Telmisartan was a generous gift from Watson Pharma Pvt. Ltd., Maharashtra, India. Other used material includes Captex 200, Capmul MCM C8 EP, (Abitech Corporation, USA) Lauroglycol 90, Labrafil M 1944 CS (LM 1944), Labrafil M 2125 CS (LM 2125), Labrasol, Transcutol P, Lauroglycol 90, (Gattefosse, Mumbai, India), Cremophore RH 40 (Cr-RH 40) and Cremophore EL(BASF, Mumbai, India). Oleic acid pure, coconut oil, soyabean oil, clove oil, ground nut oil, PEG 200, Tween 20, Tween 80, Span 80 and Span 20 were purchased from SD fine chem., Mumbai. Hard gelatin capsules were obtained as gift sample from Associated Capsules, Mumbai, India. Freshly prepared double distilled water was used in all formulations and experiments.

2.2 Methods

2.2.1 Solubility studies

The solubility of Telmisartan in various oils and surfactant solutions was determined by using shake flask method [7,10,18]. Briefly, an excess amount of drug was added to each vial containing 1g of selected vehicle either oil or surfactant solution. After sealing, the mixture was vortexed using a cyclomixer for 10 minutes in order to facilitate proper mixing of drug with the vehicles.

The solubility of Telmisartan in various natural and modified oils, co-surfactants and surfactants was determined at two stages. In first stage, the approximate solubility of Telmisartan in various vehicles was checked by visual observations to select the promising vehicles from the pool which can solubilize higher amount of Telmisartan. In the second stage, the solubility of Telmisartan in selected vehicles was measured using routine shake flask method. Briefly, in each vial containing 1g of the selected vehicles, an excess amount of Telmisartan (based on approximate solubility data) was added. These mixtures were heated at 50-60°C on water bath. Mixing of the systems was performed using a vortex mixer. Mixtures were then shaken for 48 h in a water bath shaker maintained at 37°C ± 2°C and then centrifuged at 3000 rpm for 5 min, followed by filtration through membrane filter. The concentration of Telmisartan was then quantified by UV-Visible spectrophotometer by measuring the absorbance at 296nm using appropriate blank [9].

2.2.2 Screening of surfactants

3. Emulsification ability of various surfactants was screened. Briefly, 300mg of surfactant was added to 300 mg of the selected oily phase. The mixture was gently heated at 40-60°C for homogenizing the components. The isotropic mixture (50 mg) was accurately weighed and diluted with double distilled water to 50 ml to yield fine emulsion. The ease of formation of emulsion was monitored by noting the number of volumetric flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2 hr and the transmittance was assessed at 638.2 nm by UV spectrophotometer (Shimadzu, Japan) using double distilled water as blank [7,15,19].

2.2.3 Screening of co-surfactants

Various co-surfactants were screened to improve the nanoemulsification ability of surfactants and to select the best co-surfactant by using turbidimetric method. A 200 mg of surfactant was mixed with 100mg of co-surfactant. A 300 mg of oil was added to this mixture and the mixture was homogenized with the help of gentle heat (45-60°C). The isotropic mixture (50 mg) was accurately weighed and diluted to 50 ml with double distilled water to yield fine emulsion. The formation of emulsion was determined by noting the number of flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2 hr and their transmittance was measured at 638.2 nm by UV spectrophotometer (Shimadzu, Japan) using double distilled water as blank [15,16,20].

2.2.4 Formulation Development of SNEDDS of Telmisartan

A series of six different formulation systems as given in Table **1** were developed by changing surfactant to co-surfactant ratio from 1:1 to 3:1. Two different ratios i.e. 1:1 and 1:1.5 of oil to surfactant mixture were used in the study. Level of Telmisartan (20 mg) and Clove oil (400 mg) were kept constant. Telmisartan was added in the vial containing the respective amount of oily phase. This oily mixture was heated at 40°C to 50°C in water bath followed by sonication in bath sonicator (5-10 min) to ensure the complete solubilization of drug. Respective quantity of Tween 80 and PEG 400 (Prewarmed in separate vial at 50°C-60°C) in molten state were added and homogenized on cyclomixer for 10-15 min to ensure homogeneity. The molten mixtures (equivalent to 20 mg of Telmisartan) were then manually filled in hard gelatin capsules with the help of micropipette. Capsules were stored at room temperature for not less than 24 h prior to *in vitro* dissolution study [12,21].

Table-1: Composition of Liquid SNEDDS of Telmisartan (LST)

Ingredients (mg)	LST_1	LST_2	LST_3	LST_4	LST_5	LST_6
Telmisartan	20	20	20	20	20	20
Clove oil	400	400	400	400	400	400
Tween 80	200	265	300	300	400	450
PEG 400	200	135	100	300	200	150
Total mass per capsule	820	820	820	1020	1020	1020
Oil : Smix	**1:1**	**1:1**	**1:1**	**1:1.5**	**1:1.5**	**1:1.5**
S : Co-s	**1:1**	**2:1**	**3:1**	**1:1**	**2:1**	**3:1**

2.2.5 Optimization of Telmisartan SNEDDS

2.2.5.1 Freeze-thaw cycles and Centrifugation study

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3 to 4 freeze-thaw cycles, which included freezing at 4°C for 48 hours followed by thawing at 40°C for 48 hours. Centrifugation was performed at 5000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.

2.2.5.2 Self emulsification and percent transmittance study

The formulation (50mg) was diluted to 50 ml with 0.1 N HCl (SGF) and Phosphate buffer pH 6.8 (SIF). Visual observations were made immediately after dilution for assessment of self nano-emulsification efficiency, appearance (transparency), phase separation and precipitation of drug. Percent transmittance of resultant nanoemulsion was measured at 638.2 by using UV Spectrophotometer (Shimadzu, Japan) [15].

2.2.5.3 Globule size, Zeta potential and Transmission electron microscopy (TEM)

The mean globule size and polydispersity index (P.I.) of resulting nanoemulsions were determined by PCS. Measurements were obtained at an angle of 90◦. Nanoemulsions were diluted with respective vehicles to ensure that the light scattering intensity was within the instruments sensitivity range. The resultant nano-emulsions were allowed to stand for 6 hr at room temperature to ensure dilution stability.

Morphology of globules present in microemulsion obtained by diluting optimized batch formulation in distilled water was evaluated by TEM analysis. Prior to the analysis, the optimized sample was diluted 1000 fold in distilled water to form microemulsion, stained with 2% (w/v) phosphotungstic acid for 30s and placed on 400-mesh copper grids with films for observation.

2.2.5.4 *In-vitro* dissolution study

Dissolution profile of plain Telmisartan powder and optimized Telmisartan SNEDDS filled in hard gelatin capsules were evaluated and compared. Study was carried out using USP II basket apparatus at 37 ± 1◦C with rotating speed of 50 rpm in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) separately as a dissolution medium. Aliquots of 5 ml were withdrawn at regular time intervals of 10, 20, 30, 40, 50, 60 minutes and filtered using 0.45 µm filters. An equal volume of respective dissolution medium was replaced to maintain volume constant. Drug content of the dissolution samples were determined using UV Spectrophotometer (Shimadzu, Japan) at 296 nm [15,22].

3. RESULTS AND DISCUSSION

3.1 Solubility studies

Solubility of Telmisartan was determined in ten different natural and synthetic oils. Eight surfactants and six co surfactants were screened. Telmisartan showed maximum solubility in clove oil. The results of solubility results are depicted in fig.1.

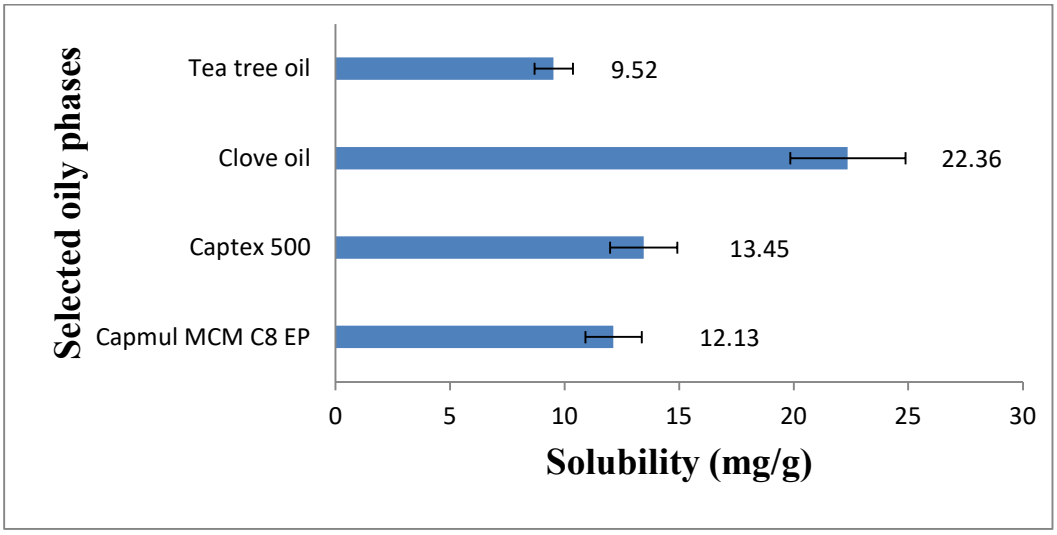

Fig.1: Quantitative solubility profile of Telmisartan in few selected oily phases, n=3

3.2 Screening of surfactants for emulsifying ability

The results of screening of surfactants for emulsifying ability are summarized in table-2. From the emulsification studies, tween 80 was selected as the surfactant as it gives maximum transmittance (% T) of 99.80% with minimum number of flask inversions (FI) value of 5.

Table-2: Results of screening of surfactant to emulsify oily phase; Clove oil

Surfactant	% T	FI
Tween 80	99.80	5
Span 80	85.69	6
Tween 60	70.05	7
Cremophor RH 40	65.78	8

3.3 Screening of co-surfactants

The results of screening of co-surfactants are summarized in table-2. From the emulsification studies, PEG 400 was selected as the surfactant as it gives maximum transmittance of 101.22% with minimum number of flask inversions value of 2.

Table-3: Screening of Co-surfactant to enhance spontaneity of Tween 80 to emulsify oily phase (Clove oil)

Co-surfactant	% T	FI
PEG 400	101.22	2
Ethanol	87.65	4
Transcutol P	79.39	4

3.4 Optimization

3.4.1 Self emulsification and % T study

LST_1, LST_3 and LST_6 fail to produce fine transparent nanoemulsion, while other 3 batches spontaneously produced clear, transparent or faint bluish nanoemulsion with %T value >98.

3.4.2 Freeze-thaw cycles and Centrifugation study

All selected batches i.e. LST_2, LST_4 and LST_5 were found to be stable at the end of three cycles followed by centrifugation. No drug separation and phase separation was observed. Batch LST_2 was considered as optimized batch because of its lowest volume which can be filled in hard gelatin capsule.

3.5 Globule size, Zeta potential and Transmission electron microscopy (TEM)

The globule size analysis of the optimized batch was carried out in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The results of the globule size analysis are given in table 4.

Table 4: Data representing globule size analysis of LST_2

Medium	Globule size (nm)*	Zeta potential (mV)
SGF	65.23 ± 3.54	+ 8.25
SIF	68.12 ± 4.42	+ 8.74

** Mean ±Standard deviation (n=2)*

Transmission electron microscopy was performed on the optimized batch LST_2 after 1000-fold dilution by distilled water. The image (Fig. 2) confirms the ability of formulation to produce spherical oil globules of nano size, the oil globules were equally distributed all over the film. This observations of TEM image are in good agreement with the results obtained from droplet size analysis.

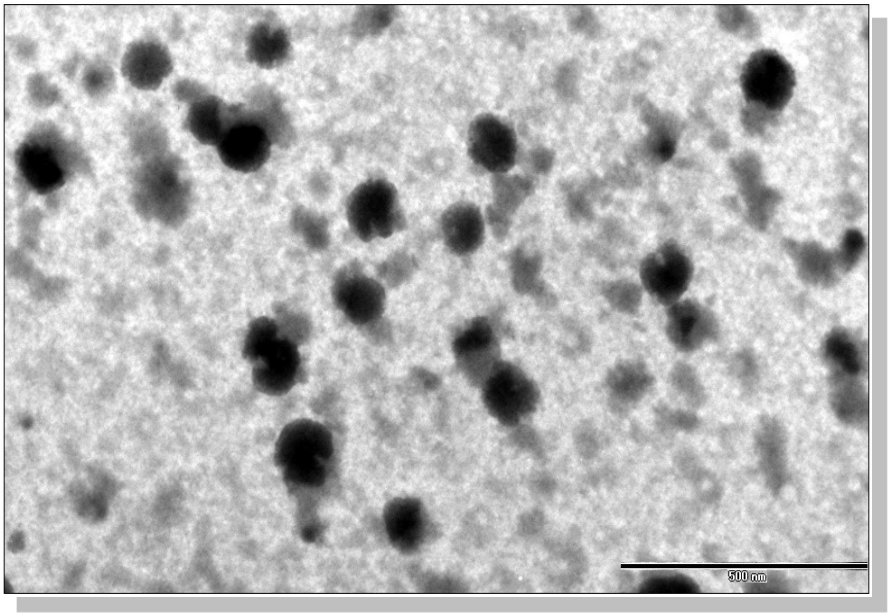

Fig. 2: TEM image obtained from 1000 fold dilution of optimized batch LST_2 in distilled water

3.6 *In vitro* dissolution study

The dissolution profile of optimized batch of Telmisartan SNEDDS showed more than 80% release in 20 minutes in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

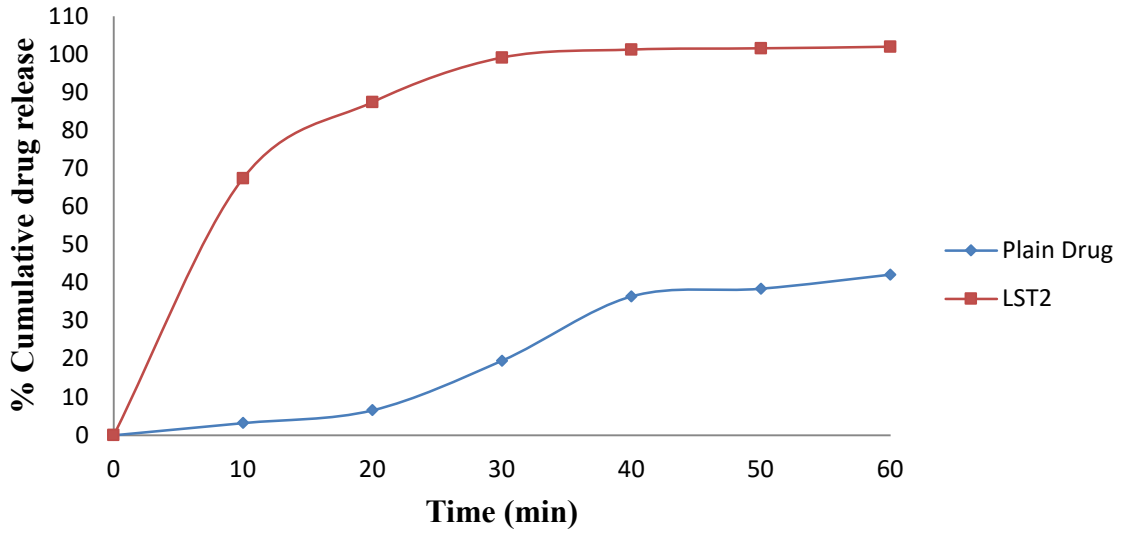

Fig. 2: *In vitro* dissolution profiles of Liquid SNEDDS of Telmisartan (LST_2) and plain Telmisartan in SGF.

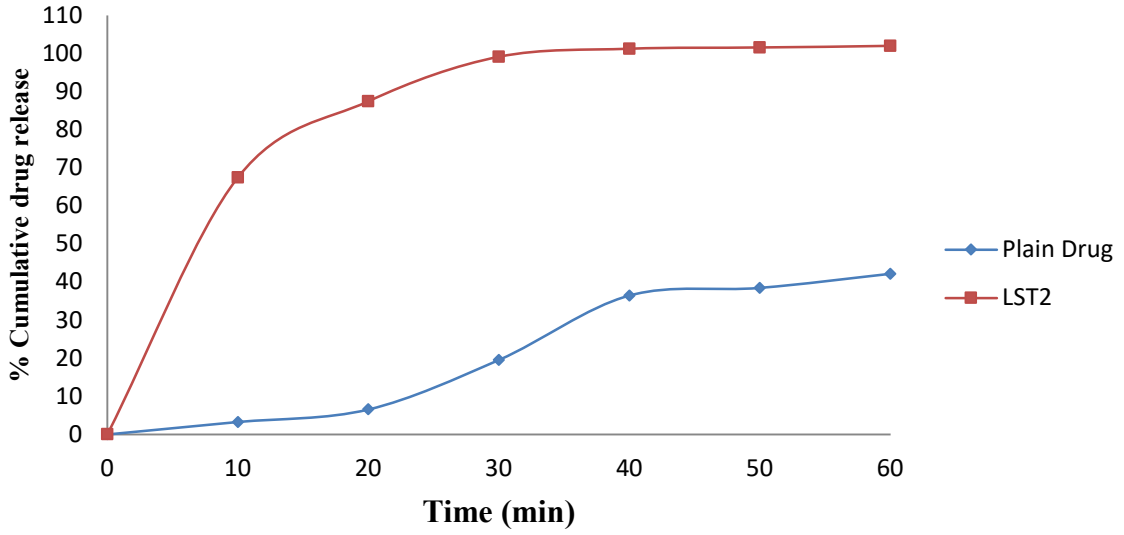

Fig. 3: *In vitro* dissolution profiles of Liquid SNEDDS of Telmisartan (LST_2) and plain Telmisartan in SIF

4. CONCLUSION

Thermodynamically stable and isotropic SNEDDS of poorly soluble drug Telmisartan was successfully developed. Optimized SNEDDS formulation consists of Clove oil, Tween 80 and PEG 400. The developed SNEDDS spontaneously self-emulsify and produces oil globules of size 65 nm with zeta potential value of +8.45Mv. Globule size and shape was confirmed by TEM analysis. Optimized SNEDDS showed significant improvement in rate of release in Telmisartan dissolution as compared to plain drug.

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