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Research Article

Self Nanoemulsifying Tablets of Telmisartan-Development, Characterization, Effect on Dissolution

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Abstract
The aim of the present study is to develop and characterize selfnano emulsifying tablets of telmisatran, its effect on dissolution. 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.
Keywords: telmisatran, drug delivery, in-vitro, nano emulsifying.

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CONTENTS

1. Introduction

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. Upon mild agitation followed by dilution with aqueous media, SEDDS can form fine oil-in-water emulsions spontaneously. 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 meta stable dispersed forms, SEDDS possess improved physical and/ or chemical stability profile uponlong-termstorage, and also easy manufacture property[1-3]. Thus, for the lipophilic drugs that exhibit poor water solubility and rate–limited dissolution, SEDDS may offer Improvement in the rate and extent of absorption and result in more reproducible blood–time profile

Types of SEDDS

SEDDS include both self-micro emulsifying drug delivery systems (SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS). SMEDDS indicate the formulations producing transparent microemulsions with droplets size range between 100 and 250 nm while SNEDDS form emulsions with the globule size range lower than 100 nm. The term 'droplet' is used to describe micelles, mixed micelles which exist in the emulsions. In details, the microemulsion is a thermodynamically stable colloidal dispersion consisting of small spheroid particles (comprised of oil, surfactant, and possibly co-surfactant) dispersed within an aqueous medium and thus in equilibrium. In contrast, the nanoemulsion is non-equilibrium colloidal dispersion system that over time spontaneously will exhibit coalescence of the dispersed droplets[3].

2. Methodology

Materials: Telmisartan, Cinnamon oil, Polyethylene glycol 400, Pluronic F127, Microcrystalline cellulose, Lactose.LR, Magnesium stearate.LR, Talc.LR, Dicalcium Phosphate were used for the study.

Preformulation Studies

Melting Point: A capillary tube was sealed with a Bunsen burner and it was filled with the drug telmisartan through the open end. The drug–filled capillary tube was placed in the melting point apparatus and temperature at which the drug started to melt was noted.

Solubility Studies

1g of the drug was dissolved in1ml, 10ml, 30ml and100ml of various solvents depending upon its solubility. The resulting solubility was compared with the solubility limits specified in the Indian pharmacopeia.

Determination of Lambda Max

10mg of drug was dissolved in 10ml of methanol to prepare stock solution–A of concentration 1mg/ml. 1ml of stock-A was further diluted to 100ml to get stock-B of concentration 20mcg/ml. This solution was scanned from200-400nm in a UV spectrophotometer to determine the lambda max.

Standard Curve

10mg of drug was dissolved in 100ml of methanol to get a stock solution –A of concentration 100mcg/ml.0.1ml of stock–A was diluted to10 ml to give a stock– B. A serial dilution of the stock-B were done to get solutions of concentrations 1, 2, 3, 4, 5, 6, 7,8mcg/ml. These solutions were analyzed in the UV-spectrophotometer at the 296nm. A calibration curve was plotted with concentration on x-axis and the absorbance on the y-axis, the correlation coefficient was also calculated (5-6).

Screening of components Solubility studies

The solubility of Telmisartan in various oils, surfactants and co-surfactants was done by the vial shake method. An excess of drug was added to the vial containing 5ml of the oil/surfactant and was sealed with an aluminum foil. The sealed vial was heated at 40°C and then centrifuged at 15,000 rpm for 10 mins. The insoluble drug was removed by filtering it and the resulting solution was analyzed in the UV spectrophotometer.

Emulsification study Surfactant

300mg of the surfactant was mixed with 300 mg of the selected oil, heated to 50°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 analyzed in the UV spectrophotometer for their percentage transparence at 650 nm using distilled water as blank. They were also observed visually for any signs of phase separation or turbidity (7).

Co-surfactant: 100 mg of co-surfactant, 200 mg of surfactant and 300 mg of the selected oil were taken and heated to 50°C and 300 mg of this mixture was diluted to 50 ml. This was assessed for the ease of emulsification by the above procedure.

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.

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 (8).

Evaluation of Solid – Snedds

Micrometrics properties of s-SNEDDS of telmisartan Characterization of telmisartan loaded S-SNEDDS Angle of repose (θ). 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 (9)

$\tan \theta = h/r$

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 = Weight of powder / Bulk Volume

TD=Weight of powder/Tapped Volume

Compressibility Index:

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

Carr's Compressibility Index (%) = [(TD-BD)/TD] X 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

Hausner ratio=TD/BD

Evaluation of telmisartan SNE tablet:

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.

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/cm2

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 (11-12).

In-Vitro dissolution Studies

Instrument : USPXXIV dissolution rate test apparatus
Type : paddle type
Medium : 0.1N HCL buffer pH1.2– 900ml
Temperature : 37± 0.5°C
Testing time : 60 mins
Sample withdrawal volume: 5ml at specified intervals
Sample : telmisartan S-SNE tablet

USP 24 paddle instrument (ELECTROLABTDT–06P):

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, analyzed spectrophotometrically. The experiments were performed in triplicate and the mean values are reported (13-16).

3. Results and Discussion

Preformulation

Melting point: The melting point was found to be 272˚C which confirms the identification of the drug. Solubility studies Solubility of Telmisartanin different solvents are Water – insoluble
Ethanol–slightly soluble; Methanol – soluble
Dissolves in 1M sodium hydroxide

Lambda max

The diluted stock which was scanned for maximum wavelength the peak at 296nm. This was selected and was used for further studies

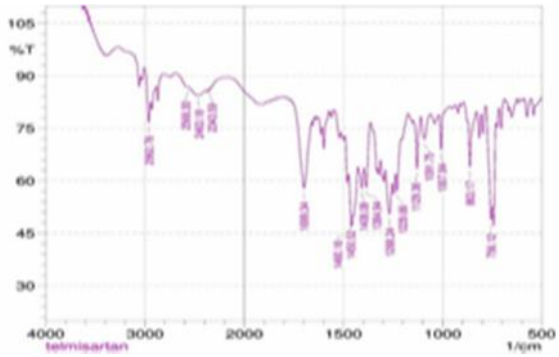

Figure 1: FT-IR data of Telmisartan

Table 1: FT-IR data of Telmisartan

S.No	Wave number cm-1	Assignment of group
1	1460	Methyl C-H asymmetric bond
2	1408	Carboxylic acid
3	1384	Aliphatic nitro compounds

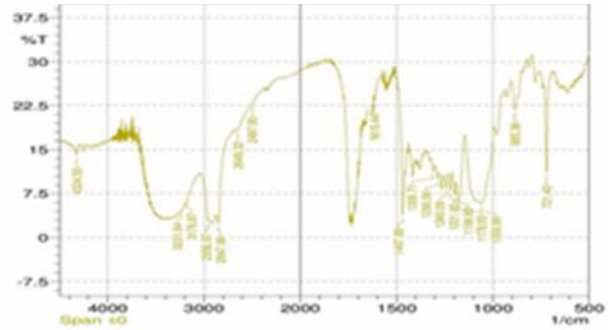

Figure 2: FT-IR data of Span 60

Table 2: FT-IR data of span 60

S.No	Wave number cm-1	Assignment of group
1	721	Aromatic C-H out plane bend
2	1058	Alkyl substituted C-O stretch

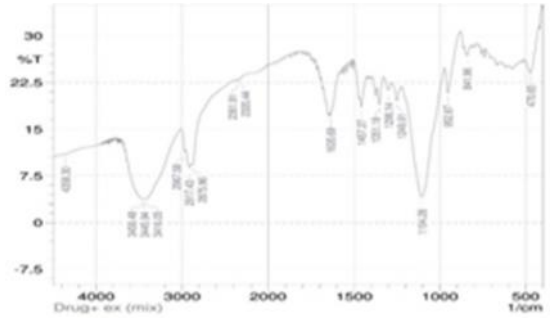

Figure 3: FT-IR data of Drug & Excipients

Table 3: FT-IR data of Drug & Excipients

S.No	Wave number cm-1	Assignment of group
1	3164	Normal polymeric OH Stretch
2	1460	Methyl C-H asymmetric Bond
3	3458	O-H stretch
4	1640	Aromatic combination bands

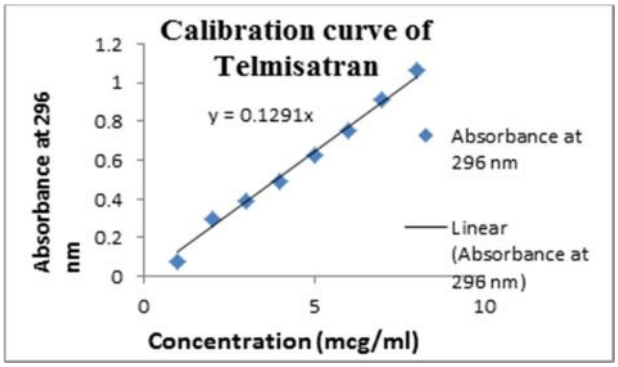

Figure 4: Calibration curve of Telmisartan

Table 4: Calibration curve of Telmisartan

Concentration (mcg/ml)	Absorbance at 296nm
1	0.076
2	0.296
3	0.386
4	0.493
5	0.626
6	0.748
7	0.915
8	1.064

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±1.43 mg ml. The various solubilities are depicted in the figure 5.

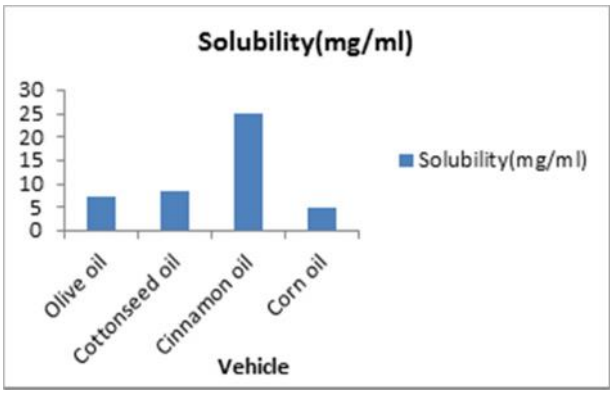

Figure 5: Solubility studies in oil

Table 5: Solubility studies in oil

S.No	Wave number cm-1	Assignment of group
1	Olive oil	7.21
2	Cottonseed oil	8.36
3	Cinnamon oil	25
4	Corn oil	4.89

Evaluation

Visual assessment and self-emulsification time

Formulations FT-11, FT-12, 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.

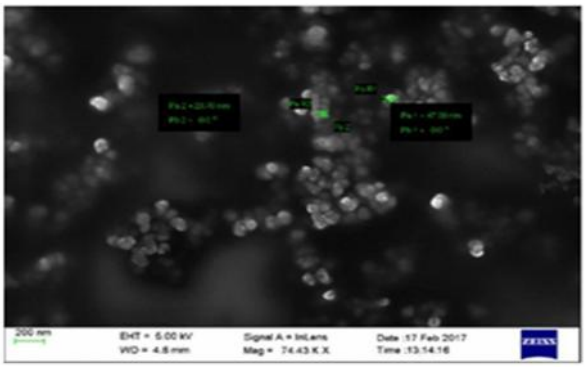

Figure 6: SEM image of FT11

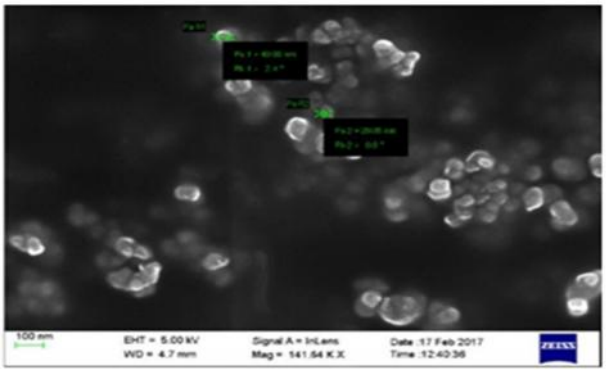

Figure 7: SEM image of FT12

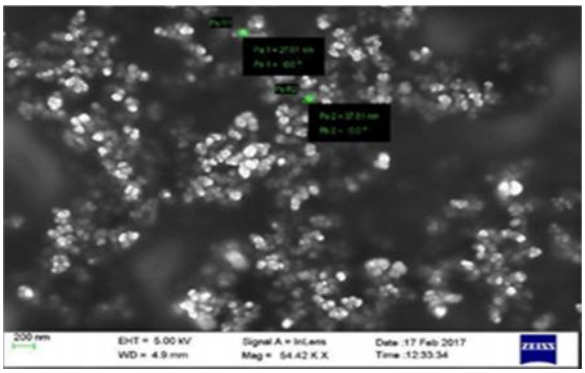

Figure 8: SEM image of FT13

4. 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 increases in the bioavailability when compared to the marketed formulation.

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