

DEVELOPMENT OF SOLID-SELF MICRO EMULSIFYING FORMULATION TO IMPROVE ORAL BIOAVAILABILITY

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ABSTRACT

Nearly 40% of new drug candidates exhibit low solubility in water, which leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality. Various approaches should use to improve the dissolution rate of the drug. Among them, Self micro emulsifying drug delivery systems (SMEDDS) have shown great promise for enhancing bioavailability of low solubility compounds. Conventional SMEDDS are normally prepared in a liquid dosage form that can be administered in soft gelatin capsules, which have some disadvantages especially in the manufacturing process. Solid-SMEDDS prepared by solidification of liquid/semi-solid self emulsifying ingredients into powders in order to create solid dosage forms.

The main objective of the study was to develop and evaluate an optimal S-SMEDDS formulation containing Telmisartan by spray drying technique. In present study solubility of Telmisartan was determined in various oil, surfactant and co-surfactant. Pseudoternary phase diagrams were used to evaluate the microemulsification existence area. Three component SMEDDS formulation were established which contain Polyoxyl 35 castor oil, Tween 80 and Carbitol as oil, surfactant and co-surfactant respectively. Selected combinations were exposed to spray drying using water soluble maltodextrin as solid carrier. S-SMEDDS formulations were tested for microemulsifying properties and for solid state characterization. The *in-vitro* dissolution studies of S-SMEDDS of Telmisartan filled into hard gelatin capsule and marketed formulation NEWTEL 20[®] was carried out.

Results showed that the mean droplet size of all reconstituted S-SMEDDS were very low and all were found to be in the nanometric range (<100 nm). Drug releases from S-SMEDDS formulations were found to be significantly higher as compared with that of pure drug. Thus study concluded with S-SMEDDS provides useful solid dosage form to improve solubility and dissolution rate of Telmisartan and concomitantly bioavailability.

Keywords: Solid self micro emulsifying drug delivery system, spray drying, oral bioavailability

INTRODUCTION

The improvement of bio-availability of drugs presents one of the greatest challenges in drug formulations. One of the most popular and commercially viable formulation approaches for this challenge is self-micro emulsifying drug delivery systems (SMEDDS).¹ SMEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) microemulsion upon mild agitation followed by dilution in aqueous media, such as GI fluids.² Liquid SEDDS and SMEDDS are inconvenient to use and incompatibility problems with the shells of the soft gelatin are frequent. Solid SMEDDS have recently been described and they overcome the disadvantages of liquid SMEDDS as well as exhibited more commercial potential and patient acceptability.^{3,4}

Telmisartan is Angiotensin II Receptor Antagonist, which 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. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The solubility of Telmisartan in aqueous medium was very low i.e. 0.078 mg/ml in water. Absolute bioavailability of the Telmisartan was 42-58% and biological half-life is only 24 hours that results into poor bioavailability after oral administration. Poor solubility of Telmisartan leads to poor dissolution and hence variation in bioavailability. Thus increasing aqueous solubility and dissolution of Telmisartan is of therapeutic importance.^{5,6}

Hence main objective of the study was to develop and evaluate an optimal S-SMEDDS

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formulation containing Telmisartan by spray drying technique.

MATERIALS AND METHODS

MATERIALS

Telmisartan was obtained as a gift sample from Glochem Industries Ltd. Vishakhapatnam, AP, Different samples of oil, surfactants and co-surfactants were obtained from Abitec Corp. USA, Gattefosse Pvt. Ltd., Mumbai, Libraw pharma, New Delhi and BASF, Mumbai Maharashtra.

METHOD

Saturation solubility studies for screening of excipients:

In order to find out appropriate solvents with good solubilizing capacity of Telmisartan, the

bath. Oil, surfactant and co-surfactant were accurately weighed and mixed by gentle stirring. Based on solubility, 20 mg of Telmisartan was dispersed into the mixture of oil and surfactants. Then, the components were mixed by gentle stirring and vortex mixing at 37 °C until Telmisartan was completely dissolved. Then the mixture was sealed in glass vial and stored at room temperature until used.⁹

Preparation of Solid-SMEDDS:

Maltodextrin was dissolved in distilled water by magnetic stirring and sonicated for 5 min to completely dissolve. This solution is filtered through whatman filter paper to remove any undissolved particles. The liquid SMEDDS was then added with constant stirring, and the solution was kept at 50°C to obtain good O/W microemulsion.

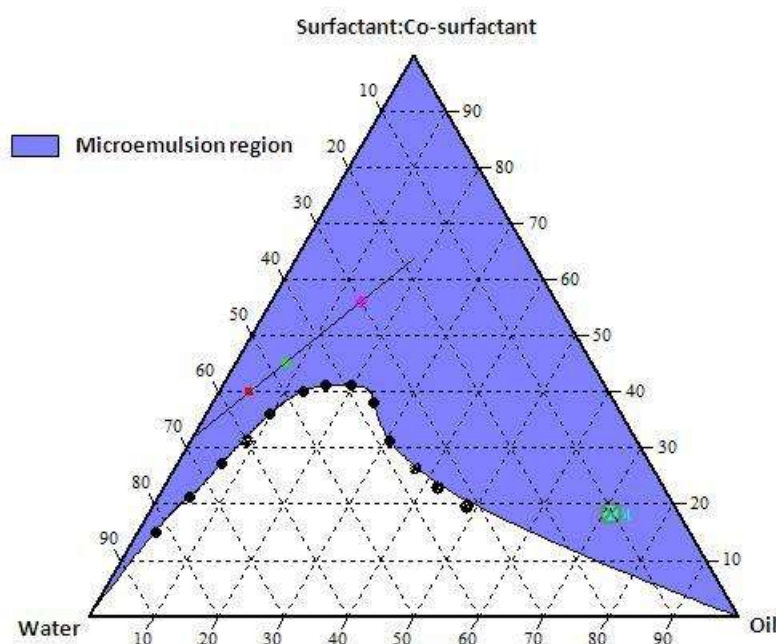


Figure 1: Pseudo ternary phase diagram using Oil, Surfactant: Co-surfactant and Water

saturation solubility of Telmisartan was investigated in some oils and surfactants by shake flask method.⁷

Construction of pseudo ternary phase diagram:

The pseudo-ternary phase diagrams were constructed by drop wise addition of double distilled water to homogenous liquid mixture of oil, surfactant and co-surfactant, at ambient temperature by water titration method.⁸

Preparation of Liquid SMEDDS:

Firstly liquid SMEDDS is prepared by taking 20 mg of Telmisartan in oil and melted it on water

The microemulsion was spray dried with lab scale spray dryer (JISL) optimized condition.⁹

Characterization of S-SMEDDS:

Dilution study by visual observation

Dilution study was done to study the effect of dilution on solid SMEDDS, because dilution may better mimic the condition of stomach after oral administration. In this method, solid SMEDDS were introduced into 100 ml of double distilled water in a glass beaker that was maintained at 37°C, and the contents mixed gently using a magnetic stirrer. The tendency to emulsify spontaneously and progress of emulsion droplets were observed with

respect to time. The emulsification ability of SMEDDS was judged qualitatively “good” when clear microemulsion formed and “bad” when there was turbid or milky white emulsion formed after stopping of stirring.¹⁰

Globule size and zeta potential determination

Solid-SMEDDS formulations were diluted with distilled water in a beaker with constant stirring on a magnetic stirrer. The average droplet size and zeta potential of microemulsion droplets from solid SMEDDS were assessed by lesser light scattering technique using Malvern zetasizer at 25°C (Nano-ZS, Malvern Instruments, UK).

All S-SMEDDS formulations showed spontaneous microemulsification (< 1 min) as same as liquid SMEDDS and there was no sign of phase separation or phase inversion of microemulsion.

The mean droplet size of all reconstituted S-SMEDDS were very low and all were found to be in the nanometric range (<100 nm). The zeta potential values of all solid SMEDDS were found to be in between -18 to -22.

Drug releases from S-SMEDDS formulations were found to be significantly higher as compared with that of conventional Telmisartan tablet

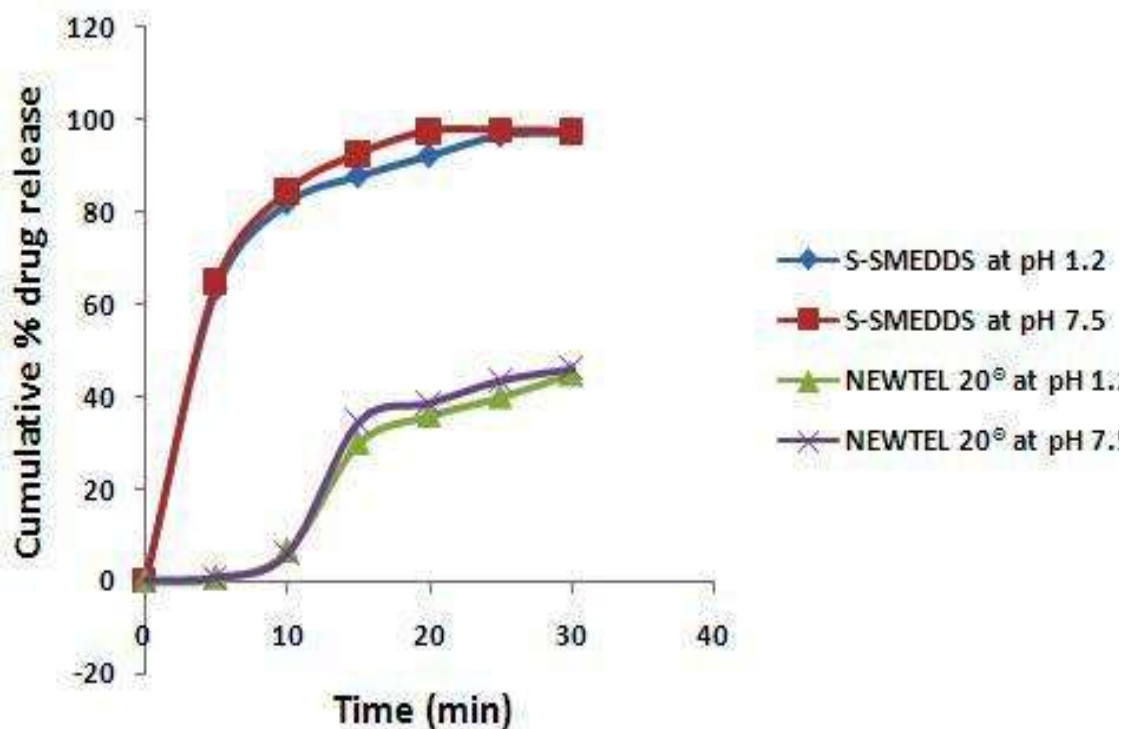


Figure 2: In-vitro drug release profile of S-SMEDDS and NEWTEL 20® at pH 1.2 and 7.5

In-vitro dissolution studies:

The in-vitro dissolution studies of prepared S-SMEDDS of Telmisartan were carried out using USP- type-II dissolution test apparatus in pH 1.2 and pH 7.5 buffer solutions and also compared the same with marketed formulation NEWTEL 20®.

RESULTS AND DISCUSSION

On the basis of solubility study and pseudo ternary phase diagram three component SMEDDS formulation were established which contain Acrysol EL 135, Tween 80 and Carbitol as oil, surfactant and co-surfactant respectively.

(NEWTEL 20®).

CONCLUSION

In this study Solid-SMEDDS of Telmisartan was prepared by spray drying, using water-soluble maltodextrin as solid carrier. The solid SMEDDS consisted of well-separated spherical particles and maintained the rapid self-emulsifying ability as that of liquid SMEDDS. This solid self-microemulsifying system enhance solubility and dissolution rate which may improve therapeutic performance. Hence study concluded that S-SMEDDS provide a useful solid dosage form for poorly water-soluble drug such as Telmisartan for enhanced bioavailability.

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