



Available Online at www.pharmacia.ipsgwalior.org
ISSN. No. 2229-4309 (Online), Vol. 3, Issue 1, July 2016
Pharmacia: An International Journal of Pharmaceutical Sciences

RESEARCH ARTICLE

PREPARATION AND CHARACTERIZATION OF SELF EMULSIFYING DRUG
DELIVERY SYSTEM OF TELMISARTAN

Manoj Goyal*¹, Vikas Rathore², Ashutosh Dubey³

^{1,2,3} IPS college of Pharmacy, Gwalior, India

ABSTRACT

Improvement of bio-availability of poorly water soluble drugs presents one of the further most challenges in drug formulations. One of the most admired and commercially viable formulation approaches for this challenge is self emulsifying drug delivery system (SEDDS). There are many techniques to convert liquid SEDDS to solid, but an adsorption technique is simple and economic. Hence aim of present study was to develop SEDDS of poorly water soluble drug Telmisartan (TEL) using Aerosil 200 as solid carrier. Liquid SEDDS was prepared using Acrysol EL 135, Tween 80 and PEG 400 as oil, surfactant and co-surfactant and was converted to SEDDS by adsorbing it on Aerosil 200. Prepared SEDDS was evaluated for flow properties, drug content, reconstitution properties, DSC, SEM, in-vitro drug release and ex-vivo intestinal permeability study. Results showed that prepared SEDDS have good flow property with $99.45 \pm 0.02\%$ drug content. Dilution study by visual observation showed that there was spontaneous micro emulsification and no sign of phase separation. Droplet size was found to be $0.34 \mu\text{m}$ with polydispersity index of 0.25. DSC thermogram showed that crystallization of TEL was inhibited. SEM photograph showed smooth surface of SEDDS with less aggregation. Drug releases from SEDDS were found to be significantly higher as compared with that of plain TEL. Ex-vivo intestinal permeability study revealed that diffusion of drug was significantly higher from SEDDS than that of suspension of plain TEL. Study concluded that SEDDS can effectively formulated by adsorption technique with enhanced dissolution rate and concomitantly bioavailability.

Keywords: Telmisartan, SEDDS, solubility enhancement, ternary phase diagram, bioavailability.

Corresponding Address

Dr. Manoj Goyal
Associate Professor
IPS college of Pharmacy, Gwalior, (India)



INTRODUCTION

Oral route has been the major route of drug delivery for the chronic treatment of many diseases. However, oral delivery of 50% of the drug compounds is hampered because of the high lipophilicity of the drug itself. 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. Thus, for such compounds, the absorption rate from the gastrointestinal (GI) lumen is controlled by dissolution. Modification of the physicochemical properties, such as salt formation and particle size reduction of the compound may be one approach to improve the dissolution rate of the drug. However, these methods have their own limitations. For instance, salt formation of neutral compounds is not feasible and the synthesis of weak acid and weak base salts may not always be practical. Moreover, the salts that are formed may convert back to their original acid or base forms and lead to aggregation in the gastrointestinal tract. Particle size reduction may not be desirable in situations where handling difficulties and poor wettability are experienced for very fine powders. In recent years, much attention has focused

on lipid-based formulations to improve the oral bioavailability of poorly water soluble drug compounds. In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations.¹

Self-microemulsifying drug delivery system formulations are isotropic mixtures of an oil, a surfactant, a co-surfactant (or solubilizer) and a drug. The basic principle of this system is its ability to form fine oil in water (o/w) microemulsions under gentle agitation following dilution by aqueous phases that is, the digestive motility of the stomach and intestine provide the agitation required for self-emulsification in vivo in the lumen of the gut. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption.²

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

selectively and insurmountably inhibits stimulation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. It is a white crystalline powder with a molecular weight of 514.6 and a melting point of 261 to 263°C. 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.^{3,4}

Telmisartan with its low daily oral dose (10-80 mg) and high log P (octanol/water) of 6.6 providing strong justification to develop SMEDDS and solid-SMEDDS of telmisartan.¹⁰ SMEDDS can be converted into solid-SMEDDS by using methods such as wet granulation, spray-drying, adsorption etc. Furthermore, solid-SMEDDS have better prospects for the development of solid dosage forms such as tablets, capsules, dry emulsion, pellets etc. Solid-SMEDDS also combines the advantages of both SMEDDS and solid dosage form. Further, solid-SMEDDS are more superior in terms of stability when compared to SMEDDS. The aim of the present study was to develop a solid-SMEDDS of telmisartan to increase its

aqueous solubility as well as its bioavailability.⁵

MATERIAL AND METHODS

Telmisartan was obtained as a gift from Skymap Pharmaceuticals, Roorkee, India. All other excipients/chemicals were of analytical grade and were used as procured.

Solubility study of telmisartan

The solubility of Telmisartan in various oil, surfactant, and co-surfactant was determined. Solubility studies were performed 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 an 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.⁶

Construction of Pseudo-ternary phase diagram

From solubility study olive oil, Tween 80 and PEG 400 were selected as oil,

surfactant and co-surfactant respectively and for preparation of stable SEDDS; micro emulsion region was identified by constructing pseudo ternary phase diagram containing different proportion of surfactant: co-surfactant (Km value 1:1, 2:1 and 3:1), oil and water. In brief S_{mix} (surfactant: co-surfactant) and oil were mixed at ratio of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 in different test tubes. To the resultant mixtures, double distilled water was added drop wise till the first sign of turbidity in order to identify the end point and after equilibrium; if the system became clear then the water addition was continued.⁶

Formulation of SEDDS containing Telmisartan

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. In brief TEL (20 mg/10gm) was placed in glass vial. To this Oleic acid (10 % w/w) added and warmed on water bath. To this oily mixture Tween 80 and PEG 400 in the proportion of 3:1 (40 % w/w) was added. Then the components were mixed by gentle stirring and vortex mixing at 37 °C until TEL was completely dissolved. Then the mixture

was sealed in glass vial and stored at room temperature until used.⁶

Evaluation of SEDDS

Drug excipient compatibility studies

FTIR spectrums of telmisartan and SEDDS formulation were obtained to assess the compatibility between the drug and the excipients.

Thermodynamic Stability Studies

Thermodynamic stability study of prepared SMEDDS was determined by performing the heating cooling cycle and centrifugation test.

Heating cooling cycle

Six cycles between refrigerator temperatures 4°C and 45°C with storage at each temperature for not less than 48 hours was studied. If SEDDS found stable at these temperatures, was subjected to centrifugation test.⁶

Centrifugation test

SEDDS was centrifuged at 3500 rpm for 30 min using centrifuge (Remi motors Ltd.) and was checked for the presence of phase separation.⁶

Cloud point measurement

SEDDS was diluted with distilled water in the ratio of 1:250, placed in a water bath and its temperature was increased gradually. Cloud point was measured as the temperature at which there was a sudden appearance of cloudiness visually.⁶

Assessment of self-emulsification efficiency

Self-emulsification efficiency (the time for a pre-concentrate to form a homogeneous mixture upon dilution) was monitored by visually observing the disappearance of SEDDS and the final appearance of the emulsion. Self-emulsification efficiency of the prepared SEDDS formulation was assessed by using USP type-II dissolution test apparatus (Veego VDA- 8DR). 1 mL of SEDDS was added drop wise to 200 ml of 0.1 N HCl at 37°C at 60 rpm.⁶

Robustness to dilution

Robustness to dilution was studied by diluting 1 ml of liquid SEDDS to 50, 100 and 1000 times with water, buffer pH 1.2 and buffer pH 7.5. All the diluted SEDDS samples were stored for 12 h and observed visually for any signs of phase separation or drug precipitation.⁶

% Transmittance

1 mL of Liquid SEDDS was diluted to 100 mL with distilled water and observed for any turbidity and % transmittance was measured at 650 nm by using UV-vis spectrophotometer (Shimadzu-1800, Japan) against distilled water as a blank.⁶

In-vitro dissolution study

In-vitro dissolution study of SEDDS formulation and plain telmisartan in an USP type II dissolution apparatus was performed to assess the drug release. HCl buffer (pH 1.2) and Phosphate buffer (pH 7.4) were used as the dissolution medium at 37±0.5 °C at 50 rpm. Samples (5 mL) were withdrawn at regular time intervals (5, 10, 15, 30, 45, 60, 90, and 120 min) and filtered using a 0.45 µm filter. An equal volume of the respective dissolution medium was added to maintain the volume constant. After appropriate dilution (if required), the samples were analyzed spectrophotometrically by UV-Vis spectrophotometer at 296 nm. All the measurements were performed in triplicate.⁶

RESULTS AND DISCUSSION

Solubility study of telmisartan

Solubility studies were performed to identify a suitable oily phase for the development of the SEDDS. Identifying the suitable oily phase, which can solubilize maximum amount of drug, is very important to achieve optimum drug loading. The solubility of telmisartan in various oily phases, surfactant and co-surfactant solutions is presented in Table 1. On the basis of results of solubility study Olive oil, tween 80 and PEG 400 were selected as the oily phase, surfactant and co-surfactant, respectively.

S.N.	MEDIUM	SOLUBILITY
1.	Water	Insoluble
2.	Hcl	Springly soluble
3.	Methanol	Soluble
4.	Oils	Soluble
5.	PEG400	Soluble
6.	Tween 80	Springly soluble
7.	Tween 20	Springly soluble
8.	Span 80	Springly soluble

Table 1: solubility of telmisartan in different medium.

Thermodynamic Stability Studies

The prepared SEDDS was subjected to the Thermodynamic Stability Studies to check its stability. The prepared SEDDS passed the heating-cooling cycle and hence, further subjected to the centrifugation test. The SEDDS did not show phase separation after centrifugation test. It can be concluded that the prepared SEDDS was stable without any phase separation, creaming or cracking.

Cloud point measurement and self-emulsification efficiency

Cloud point of prepared SEDDS was found to be 87.5 °C which suggest that the SEDDS will be stable at physiological temperature without any phase separation. 1 ml of liquid SEDDS was diluted to 50, 100 and 1000 times with water, buffer pH 1.2 and buffer pH 7.5 to asses its ability to resist phase separation after dilution. After a period of 12 hrs, there was no phase separation or drug precipitation detected.

% Transmittance, Droplet size and zeta potential determination

% Transmittance of the prepared SEDDS formulation was found to be 93.5. The droplet size of an emulsion is an important factor for self emulsification efficacy

because it affects the rate and extent of drug release as well as its absorption. The droplet size was found to be 35.1 nm. Zeta potential of liquid SEDDS was found to be -30.1 mV

In-vitro dissolution study

To get an idea about the drug release, the SEDDS formulation was subjected to dissolution study in buffer pH 1.2 and pH7.4 and the results were compared to

that of pure drug. Results are presented in Figure 1 and 2. Cumulative % drug release of TEL in pH 1.2 and 7.5 was found to be 95.56 ± 3.14 and 98.12 ± 3.24 respectively and that of plain TEL was found to be 29.48 ± 1.36 and 33.46 ± 2.06 respectively. This showed that drug releases from SEDDS was found to be significantly higher as compared to plain TEL and it was also found that, dissolution of TEL is pH independent.

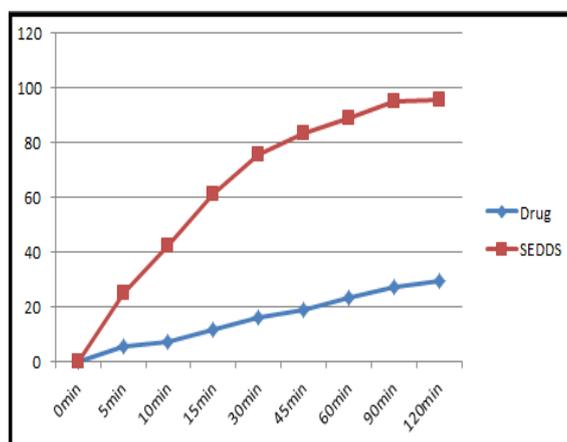


Figure 1: Cumulative % drug release of SEDDS and plain telmisartain at pH 1.2

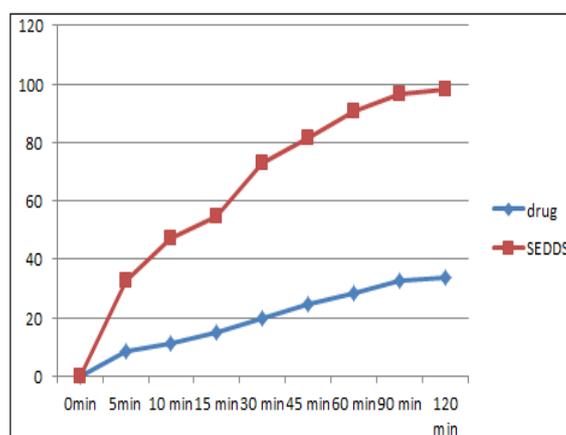


Figure 2: Cumulative % drug release of SEDDS and plain telmisartain at pH 7.4

CONCLUSION

From study it was concluded that, prepared liquid SMEDDS was thermodynamically stable with good selfemulsification efficiency. In-vitro drug release of S-SMEDDS was much higher than that of plain TEL. Hence it was concluded that SEDDS can be efficiently formulated to enhance dissolution rate of poorly soluble drug such as telmisartan.

REFERENCES

1. Kohli K, Chopra S, Dhar D, Arora S, Khar RK, Selfemulsifying drug delivery systems: an approach to enhance oral bioavailability, *Drug Discovery Today* 2010; 15 (21/22): 958-965.
2. Shah SP, Shah MD, Agrawal YK, Self-Micro Emulsifying Drug Delivery System: A Novel Approach for Enhancement of Oral Bioavailability of Poorly Soluable Drugs, *American Journal of PharmTech Research* 2012; 2(1): 193-215.
3. Kausalya J, Suresh K, Padmapriya S, Rupenagunta A, Senthilnathan B, Solubility and Dissolution Enhancement Profile of Telmisartan using various techniques, *Int.J. PharmTech Res.* 2011; 3(3): 1737-1749.
4. Agarwal V, Siddiqui A, Ali H, Nazzal S, Dissolution and powder flow characterization of solid selfemulsified drug delivery system (SEDDS).
5. Singh MK, Chandel V, Gupta V, Ramteke S, Formulation development and characterization of microemulsion for topical delivery of Glipizide 2010; *Der Pharmacia Lettre*, 2(3): 33-42.
6. Bhagwat Durgacharan A, D'Souza John I "Development of Solid Self Micro Emulsifying Drug Delivery System with Neusilin US2 for Enhanced Dissolution Rate of Telmisartan" *Int. J. Drug Dev. & Res.*, October-December 2012, 4(4):398-407.