Design and Evaluation of Telmisartan SMEDDS for Enhancing Solubility and Dissolution Rate

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ABSTRACT

Telmisartan belongs to a BCS class II drug i.e. low solubility and high permeability. It is an angiotensin II type-I receptor blocker essentially used for the treatment and curing of hypertension. The critical problem facing with telmisartan as it shows low solubility in biological fluids which results into less bioavailability after oral administration. The aim of the present work is to enhance the solubility, dissolution rate of telmisartan by formulating an optimal SMEDDS formulation. SMEDDS were prepared by admixing method using Peceol and Captex 200 as oil phases. Labrafil M2125 as surfactant and Transcutol and Plurol Oleique as co-surfactants. Later they obtained liquid SMEDDS were converted in to free flowing powder using adsorbent like Aerosil 200. All the SMEDDS formulations were found to be stable and they were further evaluated for physical parameters such as phase separation, particle size and drug content. The formulation CT1 with oil to co-surfactant ratio 1:1 respectively showed highest rate of dissolution than the other ratios. The drug, excipients and optimized formulation were subjected to characterization studies such as FTIR and DSC studies shown that there were no interactions between drug and excipients used.

KEYWORDS: Telmisartan; Self-micro-emulsifying drug delivery system; Peceol; Captex 200; Labrafil M 2125; Transcutol HP; Plurol Oleique; Aerosil 200.

Introduction

Oral route has always been most chosen and has crossed over other routes of administration due to their easy convenience, non-invasiveness, and cost effectiveness thus it become necessary that drug should show some aqueous and lipid solubility for better absorption of drugs through this route (Singh et al., 2012). However, passage of 50% of the drug compounds through oral route is hampered because of the poor aqueous solubility of the drug. Moreover, majority of new chemical entities having poor aqueous solubility and due to that the oral delivery of drugs show low bioavailability, high intra and inter subject variability, and lack of dose proportionality. After oral delivery of poorly soluble drug over one-half of the drug compounds are diminished in the gastrointestinal (GI) tract. BCS class-II drugs are major challenge to pharmaceutical industries and to modern drug delivery system, because of their poor water solubility and there by poor dissolution which leads to low bioavailability (Pandya, 2015).

Self-micro emulsifying 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 (Charman et al., 1992). 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 (Spernath and Aserin, 2006; Chowdhary and Madhav, 2005). Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption (Kim et al., 2000).

Telmisartan is an angiotensin receptor blocker (ARBs), which antagonize angiotensin II type 1 (AT1) receptors. It 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. 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. Poor solubility of telmisartan leads to poor dissolution and hence variation in bioavailability. The solubility of telmisartan in aqueous medium was very low, i.e., 0.078 mg/mL in water. Absolute bioavailability of the telmisartan is 42-58% and biological half-life is only 24 hours that results into poor bioavailability after oral administration (Reynolds, 1996; Wienen et al., 2000; Kausalya et al., 2011).
Based on the above physicochemical and biopharmaceutical properties, telmisartan was selected as a drug candidate for developing self-micro emulsifying drug delivery system (SMEDDS) formulation for improving its solubility and dissolution rate. Ingredients such as oil, surfactant and co-surfactant were added. The components were mixed by gentle stirring and vortex mixed until telmisartan was completely dissolved and a transparent monophasic solution was formed (Robinson, 1996; Reddy and Murthy, 2002).

**Materials and Methods**

**Materials**

Telmisartan was obtained as a gift sample from Mylan Laboratories, Hyderabad. Pecol A 200 was obtained as a gift sample from Aurobindo Laboratories, Hyderabad. Captex, Transcutol HP Labrafil M2125, Plurrol Oleique were obtained as gift samples from Mylan Laboratories, Hyderabad. Aerosil 200 was obtained as a gift sample from Aurobindo Laboratories, Hyderabad. Methanol was procured from High- Pure Fine chem., Chennai.

**Saturated Solubility Studies**

The saturation solubility studies of telmisartan were performed in various oils, surfactants and co-surfactants. In this study, an excess amount of telmisartan was added to 2 mL of each vehicle in volumetric flasks. Mixing of the contents done at 100 rpm on a shaking incubator for 24 hours at ambient temperature. The solution was centrifuged at 3,000 rpm for 10 minutes to remove the undissolved drug. The supernatant was collected and filtered using a membrane filter (0.45 μm, 13nm, whatmann). The resulting solutions were suitably diluted with 0.1N HCl and the absorbance of the solutions was observed spectrophotometrically at 298 nm. The solubility of telmisartan in various oils, surfactants and co-surfactants were given in table 1.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Oil / Co surfactant</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Captex</td>
<td>1.79</td>
</tr>
<tr>
<td>2</td>
<td>Pecool</td>
<td>2.35</td>
</tr>
<tr>
<td>3</td>
<td>Labrafil M1944</td>
<td>3.07</td>
</tr>
<tr>
<td>4</td>
<td>Labrafil M2125</td>
<td>3.60</td>
</tr>
<tr>
<td>5</td>
<td>Plurrol Oleique</td>
<td>2.90</td>
</tr>
<tr>
<td>6</td>
<td>Transcutol HP</td>
<td>4.87</td>
</tr>
</tbody>
</table>

**Preparation of Telmisartan Liquid Self-Micro Emulsifying Drug Delivery Systems**

Self-emulsifying drug delivery systems were prepared by employing simple admixing method. Telmisartan SMEDDS were composed of Captex 200 and Pecol as oil phases, Labrafil M2125 as surfactant and Transcutol HP and Plurrol Oleique as co-surfactants. In all the formulations, the amount of telmisartan and surfactant were kept constant. The oils and co-surfactants were taken as a ratio of 1:0.5, 1:1, and 1:2 respectively. Accurately weighed telmisartan (40 mg) was placed in glass vials and oil, surfactant and co-surfactant were added. The components were mixed by gentle stirring and vortex mixed until telmisartan was completely dissolved and a transparent monophasic solution was formed. The compositions of various SMEDDS formulations were given in Table 2.

**Conversion to Solid Intermediates of Self-Micro Emulsifying Formulations**

The liquid self-emulsifying drug delivery systems prepared were then converted into free flowing powders by adsorption of liquid SMEDDS onto solid carries. The solid carrier used was Aerosil 200, which has high surface area, good adsorption and high disintegration characteristic. SMEDDS were adsorbed on 500 mg of Aerosil 200 uniformly till it formed free flowing powders for each dose of formulation. The resulting powder were stored at room temperature and evaluated for physical stability studies, drug content, droplet size, dissolution studies, stability and spectral analysis.

**Evaluation of Self-Micro Emulsifying Drug Delivery Systems**

**Physical evaluation:** The physical stability of a lipid-based formulation can be adversely affected by precipitation of drug in excipient matrix. Poor formulation physical stability can lead to phase separation of excipient and affect formulation performance. So, the following evaluation studies were performed on prepared SMEDDS.

**Phase separation studies:** Approximately 1mL of telmisartan SMEDDS was added to 5 mL of distilled water in a glass test tube at 25°C. The mixture was vortexed for 2 minutes and the stored for 2 hours and any phase separation was visually observed.
**Drug content:** Solid SMEDDS of telmisartan from a batch were taken at random and were transferred into a 100 mL volumetric flask and 70 mL of methanol was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100 mL by adding methanol. About 10mL of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using the Whatmann filter paper. Then the filtrate was subsequently diluted with 0.1 N HCl and the absorbance were measured at 298nm. This test was repeated six times (N=6) for each batch of tablets.

**Droplet size and particle size determination:** SMEDDS formulations were diluted to 100 times with distilled water in beaker with constant stirring on a magnetic stirrer. The droplet size distributions of resultant microemulsion were determined after 1 hour by Zetasizer Version 7.03 (Malvern Instruments). Size analysis was performed at 25.0°C by placing in an electrophoretic cell with an angle of detection of 90° for measurement. The droplet/particle sizes of the pure drug and optimized formulations were shown in figure 1 and given in table 3.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Particle size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telmisartan</td>
<td>4533</td>
</tr>
<tr>
<td>CT1</td>
<td>2876</td>
</tr>
</tbody>
</table>

**In vitro Dissolution Studies**

The dissolution test for the solid self- microemulsifying drug delivery systems were carried out in USP Apparatus Type II (paddle) [USPNF, 2007] with 900mL of 0.1N HCl as the dissolution medium. The samples were drawn at 5, 10, 15, 20, 30, 45, 60, 90 minutes. Fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by ELICO SL-210 double beam spectrophotometer at 298 nm and subsequently analyzed for the cumulative percentage of drug released.

**Fig. 1.** Particle Size Analysis of (a) Telmisartan (b) CT1.
Characterization and Evaluation of SMEDDS

Based on the dissolution studies performed on all the formulations, the optimized formulations were selected for further investigation by FT-IR (BRUKER), DSC (200F3 Shimadzu) studies to study drug excipient interactions and nature of drug in the formulation. The pure drug and optimized formulations were shown in figure 3 and 4.

Fig. 2. Drug Release Profiles of Telmisartan Self-Micro Emulsifying Drug Delivery Systems.
Fig. 3. IR Interpretations of (a) Telmisartan and (b) CT1 SMEDDS Formulation.

Fig. 4. Differential Scanning Calorimetry Curves for (a) Telmisartan Pure and (b) CT1 SMEDDS Formulation.
### Results and Discussion

In the present work mainly focused to improve the solubility and dissolution rate and to enhance the bioavailability of telmisartan by formulating it as SMEDDS. Saturated solubility studies were conducted for telmisartan using different oils and co-surfactants. The solubility of telmisartan in oils was found to be maximum in Peceol, Captex 200 and in co-surfactants the highest solubility was found in Transcutol HP. The solubility of telmisartan in various oils and co-surfactants are summarized in Table 1. All the formulations were then subjected for physical evaluation. The results were found to be stable. SMEDDS were prepared by admixing method using Captex 200, and paceol as oil phases, surfactant and co-surfactant at different ratios were found to be stable and suitable for increasing the dissolution rate of telmisartan.

The composition of various telmisartan SMEDDS are shown in Table 2. All the SMEDDS formulations were further evaluated for physical parameters such as phase separation, droplet/particle size and drug content. The studies of physical evaluation revealed that all the SMEDDS were found to be stable. The drug content of prepared SMEDDS was found to be in the range of 39.5–40.2 mg. Droplet size analysis of the formulation CT1 showed a particle size of 2876 nm in water.

The particle size values were given in table 3 and shown in the Fig. 1. The formulation CT1 with oil to co-surfactant ratio 1:1 respectively showed highest rates of dissolution than the other ratios studied. The dissolution test for the SMEDDS was carried out with 900 mL of 0.1N HCl as the dissolution medium. Drug release from the SMEDDS using Captex 200, and paceol as oil phase, and Labrafil M 2125 as surfactant and Transcutol HP and Plurol Oleique as co-surfactants was significantly higher as compared to pure drug.

The various in vitro dissolution parameters were given in table 4. Based on the dissolution studies CT1 was optimized and selected for characterization studies such as FTIR and DSC studies. The IR spectra of pure drug telmisartan showed the presence of principal peaks responsible for different functional groups. The wave number 3058.14 cm⁻¹ is due to stretching vibration of O-H 2956.21 cm⁻¹ due to C-H stretching vibrations, 1599.29 cm⁻¹ due to C=O stretching vibrations, 1695.85 cm⁻¹ due to C=N stretching, 1460.50 due to C=H stretching. The presence of all these peaks gives confirmation about purity of the drug. The FTIR spectra of optimized formulations were having similar fundamental peaks and pattern. This indicated that there were no drug-excipient interactions in the formulations. The IR Spectra of pure drug and optimized formulation were shown in the figure 3. DSC analysis was performed for the pure drug, Captex 200, and paceol Transcutol HP, aerosol 200, CLT1. The results revealed that there has been no major interaction between the drug and excipients. Sharp endothermic peak for telmisartan was observed at 271.32°C. A Sharp endothermic peak for telmisartan in CLT1 and SMEDDS were observed at 269.36°C respectively. DSC Thermograms for pure drug and optimized formulations were shown in figure 4.

### Conclusions

It can be shown that telmisartan solid-SMEDDS offer more predictable and more extensive drug release/absorption than the corresponding pure drug. The results from the study showed the utility of solid-SMEDDS to improve the solubility and dissolution rate and to enhance the bioavailability of telmisartan.
enhance solubility and bioavailability of sparingly soluble compounds like telmisartan. The present work successfully enumerates the potential utility of solid-SMEDDS for the delivery of poorly water-soluble compounds to increase the dissolution rate of poorly soluble drugs.

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References

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