ABSTRACT
Telmisartan is a widely prescribed anti-hypertensive drug belongs to BCS class II and exhibit low aqueous solubility and poor oral bioavailability. It needs enhancement in solubility and dissolution rate in its formulation development to achieve maximum therapeutic effect.

The objective of the study is to enhance the solubility and dissolution rate of telmisartan by complexation with βCD and to develop Telmisartan- βCD tablets with fast dissolution rate comparable to the market branded products. The effect of βCD and its concentration on the aqueous solubility of telmisartan was evaluated by phase solubility studies. Telmisartan- βCD complexes in various ratios such as 1:1, 1:2 and 1:3 were prepared by kneading method. The dissolution rate of the Telmisartan- βCD complexes prepared was evaluated in comparison to pure drug. Telmisartan- βCD tablets were prepared by direct compression method and were evaluated in comparison to a market branded product.

The aqueous solubility of telmisartan was increased linearly as the concentration of βCD was increased. The phase solubility diagram of telmisartan –βCD (Fig.1) can be classified as type A_L. Telmisartan formed a 1:1 M complex in solution with βCD with a stability constant (K_c) of 700 M⁻¹. Telmisartan-βCD complexes prepared by kneading method gave much higher dissolution rates than telmisartan pure drug. A 6.95 fold increase in the dissolution rate (K₁) was observed with Telmisartan- βCD (1:3) complexes. Telmisartan- βCD tablets prepared disintegrated rapidly within 1min 30sec and gave very rapid dissolution of telmisartan, 86.85 % in 10 min. The dissolution rate of formulated Telmisartan- βCD tablets was higher than that of market branded product tested. Complexation with βCD could be used to enhance the
solubility and dissolution rate of telmisartan, a poorly soluble BCS class II drug and to formulate telmisartan tablets with fast dissolution rate characteristics.

KEYWORDS: Telmisartan tablets, β-cyclodextrin, Solubility, Dissolution rate, Formulation development, Cyclodextrin complexation.

INTRODUCTION
About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process. Telmisartan is a widely prescribed anti-hypertensive drug that belongs to BCS class II and exhibit low aqueous solubility and poor oral bioavailability. It needs enhancement in solubility and dissolution rate in its formulation development to achieve maximum therapeutic effect.

Several techniques\cite{1} such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches cyclodextrin complexation is a simple industrially useful approaches for enhancing the solubility and dissolution rate of poorly soluble drugs in their formulation development. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected.\cite{2-3} Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies.\cite{4-5}

The objective of the study is to enhance the solubility and dissolution rate of telmisartan by complexation with βCD and to develop Telmisartan- βCD tablets with fast dissolution rate comparable to the market branded products.
EXPERIMENTAL

Materials
Telmisartan was a gift sample from Dr. Reddy’s Laboratories. β- cyclodextrin was a gift sample from M/s. Natco Pharma Ltd., Hyderabad. Telmkind-40 tablets (uncoated tablets each containing 40 mg of telmisartan, M/s Sirmour Remedies (P) Limited, Village Kayarda, Sirmour (HP)-173025, Batch No: E4ALN103, Mfg. Date: 11/2014, Exp.Date: 10/2016) were procured from local retail pharmacies. All other materials used were of Pharmacopoeial grade.

Methods
Estimation of Telmisartan
An UV Spectrophotometric method based on the measurement of absorbance at 296 nm in phosphate buffer of pH 7.5 was used for the estimation of Telmisartan. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer’s law in the concentration range of 1 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.8% and 1.20% respectively. No interference by the excipients used in the study was observed.

Phase Solubility Study
The effect of βCD and its concentration on the aqueous solubility of telmisartan was evaluated by phase solubility studies.

Phase solubility studies were performed according to the method reported by Higuchi and Connors. Excess drug (25 mg) was added to 8 ml of each of aqueous solutions containing different concentrations of β CD (0, 1, 3, 6, 9, and 12 Mm) taken in a series of 15 ml stoppered test tubes and the mixtures were shaken thoroughly for 24 h at room temperature (28 °C). After 24 h of shaking to achieve equilibrium, the mixtures were filtered using 0.45 μ nylon disc filters. The filtered samples were diluted suitably with phosphate buffer of pH 7.5 and assayed at 296 nm. The solubility experiments were replicated three times each (n=3).

Preparation of Telmisartan - βCD Complexes
Solid inclusion complexes of Telmisartan – βCD were prepared by kneading method using different ratios of drug: βCD. Telmisartan and βCD were triturated in a mortar with a small volume of solvent consisting of a blend of water: ethanol (1:1). The thick slurry formed was
kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.

**Preparation of Telmisartan- βCD Tablets**
Telmisartan (40 mg) tablets were prepared by direct compression method as per the formula given in Table 2. The required quantities of Telmisartan, βCD, Cross carmellose sodium, and lactose-starch DCV as per the formula were blended thoroughly in a closed polyethene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. The blend of ingredients was then compressed directly into tablets using an 8-station RIMEK tablet punching machine employing 9mm round and flat punches.

**Evaluation of Tablets**
All the Telmisartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows.

**Hardness**
The hardness of the prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm².

**Friability**
The friability of the tablets was measured in a Roche friabilator using the formula:
Friability (%) = \[\frac{\text{(Initial weight - Final weight)}}{\text{(Initial weight)}}\] x 100

**Drug Content**
Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of telmisartan was taken into 25 ml volumetric flask, methanol was added to dissolve the drug and the solution was made upto 25 ml with methanol. The solution was suitably diluted with phosphate buffer of pH 7.5 and assayed for Telmisartan at 296 nm.

**Disintegration time**
Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.
Dissolution Rate Study

Dissolution rate of Telmisartan from the βCD inclusion complexes and Telmisartan- βCD tablets prepared was studied employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. Water (900 ml) and phosphate buffer of pH 7.5 (900 ml) were used as dissolution fluids for βCD inclusion complexes and Telmisartan- βCD tablets respectively. Inclusion complex equivalent to 40 mg of telmisartan or one tablet containing 40 mg of telmisartan was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for Telmisartan at 296 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data

The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan.[7]

RESULTS AND DISCUSSION

The objective of the study is to enhance the solubility and dissolution rate of telmisartan by complexation with βCD and to develop Telmisartan- βCD tablets with fast dissolution rate comparable to the market branded products. The effect of βCD and its concentration on the aqueous solubility of telmisartan was evaluated by phase solubility studies.

The aqueous solubility of telmisartan was increased linearly as the concentration of βCD was increased. The phase solubility diagram of telmisartan – βCD (Fig.1) can be classified as type A_L according to Higuchi and Connors. Because the straight line had a slope <1, the increase in solubility was due to the formation of a 1:1 M complex in solution with βCD. The apparent stability constant (K_c) was calculated from the slope of the linear plot of the phase solubility diagram according to the equation, K_c = Slope/S_o (1-Slope), where S_o is the solubility of the drug in the absence of β CD. The estimated K_c value was 700 M^{-1}. The value of K_c indicated that the complexes formed between telmisartan and β CD are quite stable.

Telmisartan- βCD complexes in various ratios such as 1:1, 1:2 and 1:3 were prepared by kneading method. The dissolution rate of the Telmisartan- βCD complexes prepared was
evaluated in comparison to pure drug. The dissolution profiles of the βCD complexes prepared are shown in Fig.2 and the dissolution parameters are summarized in Table 1.

Telmisartan-βCD complexes prepared exhibited much higher dissolution rates when compared to that of telmisartan pure drug. The dissolution rate was increased as the ratio of βCD in complex was increased. A 6.95 fold increase in the dissolution rate (K₁) was observed with Telmisartan- βCD (1:3) complexes. The dissolution efficiency (DE₃₀) was increased from 6.1 % for pure drug to 35.4 % for telmisartan- βCD (1:3) complex.

Telmisartan- βCD tablets were prepared by direct compression method as per the formula given in Table 2 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate. The physical parameters of the tablets prepared are given in Table 3. The hardness of the tablets prepared was in the range 4-5 Kg/ sq.cm. Percent weight loss in the friability test was 0.95 %. Drug content was within 100 ± 1 % of labeled content.

Telmisartan- βCD tablets prepared disintegrated rapidly within 1min 30sec and gave very rapid dissolution of telmisartan. For comparison, Telmikind-40 tablets, a market product was also evaluated. The dissolution profiles of the formulated and market tablets are shown in Fig.3 and dissolution parameter are given in Table 4. The dissolution rate of formulated Telmisartan- βCD tablets was higher than that of market branded product tested. The dissolution rate (K₁) was 0.194 and 0.124 min⁻¹ respectively for formulated and market products. The DE₂₀ was 76.47 and 52.37 % respectively for formulated and market products. However both the formulated and market products fulfilled the official (IP 2014) dissolution rate test specification of NLT 75% in 30 min prescribed for telmisartan tablets.

Thus complexation with βCD could be used to enhance the solubility and dissolution rate of telmisartan and to formulate telmisartan tablets with rapid dissolution rate, 86.85 % in 10 min.

Table 1: Dissolution Parameters of Telmisartan - βCD Inclusion Complexes

<table>
<thead>
<tr>
<th>Product</th>
<th>PD₁₀ (%)</th>
<th>K₁×10⁻³ (min⁻¹)</th>
<th>Increase in K₁ (No. of folds)</th>
<th>DE₃₀×10⁻² (%)</th>
<th>Increase in DE₃₀ (No. of folds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telmisartan</td>
<td>0.41</td>
<td>0.23</td>
<td>--------</td>
<td>6.1</td>
<td>--------</td>
</tr>
<tr>
<td>Tel-βCD (1:1) Complex</td>
<td>1.11</td>
<td>0.46</td>
<td>2</td>
<td>12.1</td>
<td>1.98</td>
</tr>
<tr>
<td>Tel-βCD (1:2) Complex</td>
<td>2.34</td>
<td>1.3</td>
<td>5.65</td>
<td>32.9</td>
<td>5.39</td>
</tr>
<tr>
<td>Tel-βCD (1:3) Complex</td>
<td>2.38</td>
<td>1.6</td>
<td>6.95</td>
<td>35.4</td>
<td>5.8</td>
</tr>
</tbody>
</table>
Table 2: Formula of Telmisartan-βCD Tablets Prepared

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/ tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telmisartan</td>
<td>40</td>
</tr>
<tr>
<td>β CD</td>
<td>120</td>
</tr>
<tr>
<td>Crosscarmellose</td>
<td>32</td>
</tr>
<tr>
<td>Lactose-starch DCV</td>
<td>48</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>250</td>
</tr>
</tbody>
</table>

Table 3: Physical Parameters of Telmisartan-βCD Tablets and Market Product

<table>
<thead>
<tr>
<th>Product</th>
<th>Hardness (Kg/sq-cm)</th>
<th>Friability (% loss)</th>
<th>Disintegration Time(min-sec)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tel-βCD Tablets</td>
<td>4.0-5.0</td>
<td>0.95</td>
<td>1-30</td>
<td>99.5</td>
</tr>
<tr>
<td>Telmikind Tablets</td>
<td>4.0-4.5</td>
<td>0.80</td>
<td>2-15</td>
<td>99.2</td>
</tr>
</tbody>
</table>

Table 4: Dissolution Parameters of Telmisartan-βCD Tablets Prepared and Market Product

<table>
<thead>
<tr>
<th>Dissolution Parameter</th>
<th>Tel-βCD Tablets</th>
<th>Market Product (Telmikind Tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD_{10} (%)</td>
<td>86.85</td>
<td>41.06</td>
</tr>
<tr>
<td>K_{1} (min^{-1})</td>
<td>0.194</td>
<td>0.124</td>
</tr>
<tr>
<td>DE 20(%)</td>
<td>76.47</td>
<td>52.37</td>
</tr>
</tbody>
</table>

Fig.1: Phase Solubility Diagram of Telmisartan - β CD Complexation

\[ y = 2.3655x + 6.3368 \]
\[ R^2 = 0.9752 \]
CONCLUSIONS

1. The aqueous solubility of telmisartan was increased linearly as the concentration of βCD was increased. The phase solubility diagram of telmisartan–βCD (Fig.1) can be classified as type A₁.

2. Telmisartan formed a 1:1 M complex in solution with βCD with a stability constant (K_c) of 700 M⁻¹.

3. Telmisartan-βCD complexes prepared by kneading method gave much higher dissolution rates than telmisartan pure drug.

4. A 6.95 fold increase in the dissolution rate (K₁) was observed with Telmisartan-βCD (1:3) complexes.

5. Telmisartan-βCD tablets prepared disintegrated rapidly within 1min 30sec and gave very rapid dissolution of telmisartan, 86.85 % in 10 min.
6. The dissolution rate of formulated Telmisartan- βCD tablets was higher than that of market branded product tested.

7. Complexation with βCD could be used to enhance the solubility and dissolution rate of telmisartan, a poorly soluble BCS class II drug and to formulate telmisartan tablets with fast dissolution rate characteristics.

REFERENCES