Preparation, physicochemical characterization, dissolution and formulation studies of telmisartan cyclodextrin inclusion complexes

Rajesh N Kane, Bhanudas S Kuchekar

Sinhgad Institute of Pharmaceutical Sciences, Lonavala, Pune 410 401, ‘MIT’s Maharashtra Institute of Pharmacy, Erandavane, Pune, Maharashtra, India

The objective of this research was to prepare, characterize, and to study dissolution properties of inclusion complexes of telmisartan (TLM), with β-cyclodextrin and hydroxypropyl-β-cyclodextrin and to study effect of complexation on aqueous solubility and rate of dissolution in dissolution media. The phase solubility curve was classified as an Ap type for both the CDs, which indicated formation of the inclusion complex of TLM in 1:2 stoichiometries with β-CD and HP-β-CD. The inclusion complexes in molar ratio of 1:2 were prepared by various methods. The molecular behavior of TLM in all samples were characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and powder X-ray diffraction studies. The result of studies showed inclusion of TLM molecule into cyclodextrin cavities. The highest improvement in in-vitro dissolution of TLM was observed in a complex prepared with HP-β-CD using the kneading method. Mean dissolution time (MDT) and similarity factor (f2) indicated a significant difference between the release profile of TLM from complexes, physical mixture, and pure TLM. The highest improvement in solubility and in-vitro drug release were observed in inclusion complex prepared with HP-β-CD by kneading method. Improvement in solubility and in-vitro drug release of telmisartan was more with HP-β-CD as compared to β-CD.

Key words: β-cyclodextrin, dissolution studies, hydroxypropyl-β-cyclodextrin, inclusion complexes, telmisartan

INTRODUCTION

Telmisartan (TLM): [4’-[1,4’-dimethyl-2’-propyl][2,6’-bi-1H-benzimidazo]-1’-ylmethyl]-[1,1’-biphenyl]-2-carboxylic acid [Figure 1] is an orally active direct-acting AT1 receptor antagonist and possess therapeutic potential in the pharmacotherapy of hypertension. Its molecular formula is C33H30N4O2, and molecular weight is 514.6. The results have established that TLM exerts potent and sustained antagonism of AII-mediated pressor responses in vivo and effectively lowers blood pressure in animal models of hypertension as well as in humans. The hypotensive effects are of long duration and have potential superiority over other similar type of drugs like losartan. TLM also acts as a selective modulator of insulin and glucose metabolism. It is believed that TLM’s dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).

TLM is practically insoluble in water; its aqueous solubility is strongly pH-dependent with maximum solubility observed at high and low pH. Due to its hydrophobic nature TLM shows low dissolution profile in gastrointestinal fluid resulting poor absorption, distribution and consequently poor target organ delivery. Improvement of aqueous solubility in such cases shall lead to improved therapeutic efficacy of the drug.

Cyclodextrins (CDs) with their cylinder-shaped cavities are capable to form inclusion complexes with a wide range of commonly used drugs by taking the whole molecule or part of it into the cavity and are known to improve the aqueous solubility of drugs. Many drugs such as valsartan, Lovastatin, Praziquantel etc have been complexed with CDs and formulated for enhancing solubility and therapeutic activity.

β-cyclodextrin and its more hydrophilic derivative hydroxypropyl-β-cyclodextrin (HP-β-CD) have been selected for the complexation study of TLM. In the
The present study inclusion complexes of TLM with β-CD and HP-β-CD were prepared by kneading, co-evaporation, and physical mixing, and characterized by FTIR spectroscopy, differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) with the aim of improving the aqueous solubility and dissolution profile of the TLM.

**MATERIALS AND METHODS**

**Materials**
HP-β-CD (Mole. Wt. 1500) and β-CD (Mole. Wt. 1135) were obtained from Gangwal Chemicals Pvt. Ltd Mumbai, India. TLM was received as a gift sample from Unichem Laboratories, Raigad Maharashtra. All chemicals and solvents used in this study were of A.R. grade. Freshly prepared double distilled water was used throughout the work.

**Phase solubility study**
Phase-solubility studies were performed in triplicate by the method of Higuchi and Connors. TLM, in constant amounts (5 mg) exceeding its solubility, was transferred to screw capped vials containing 15 ml of aqueous solution of β-CD or HP-β-CD at various molar concentrations (0, 3.0, 6.0, 9.0, 12.0, and 15.0 mM). The contents were stirred on rotary shaker (Remi, India) for 72 h at 37°C ± 0.1°C and 300 rpm. The time duration was fixed based on pilot experiment and found to be sufficient to achieve equilibrium of mixture.

After reaching equilibrium, samples were filtered through a 0.22 µm membrane filter, suitably diluted and analyzed spectrophotometrically for drug content at 297 nm (Jasco-V 530, UV/Visible spectrophotometer, Jasco Inc., Japan).

**Preparation of inclusion complexes**
TLM and CDs were sieved through 120 # prior to their use. Complexes of TLM with β-CD and HP-β-CD were prepared in the molar ratio of 1:2 by different methods mentioned below. For better identification, the samples are designated with different abbreviations [Table 1].

**Physical mixture**
Physical mixture (PM) of CDs and TLM were prepared by simply mixing powders with a spatula in 1:2 molar ratios for 15 min and then sieved through 120 #.

**Co-evaporation method**
For preparation of complexes by the co-evaporation method TLM and CDs were mixed in 1:2 molar ratio and 10 ml of methanolic solution of TLM was added slowly to 10 ml aqueous solution of CD followed by stirring at 1000 rpm using magnetic stirrer at 37°C for 24 h. The solvents were then evaporated at 45-50°C. The resultant solids were pulverized and then sieved through 120 #.

**Kneading method**
For preparation of complexes by the kneading method, the TLM and CDs were taken in 1:2 molar ratios. The CD was triturated in a mortar with small quantity of water to obtain a homogeneous paste, TLM was then added slowly while grinding; a small quantity of methanol was added to facilitate the dissolution of TLM. The mixtures were then grounded for 6 h. During this process, an appropriate quantity of water was added to the mixture to maintain a desired consistency. The pastes were dried in an oven at 45-50°C for 24 h. The dried complexes were pulverized and then sieved through 120 #.

**Determination of drug content in complexes**
The samples of complexes and physical mixtures were assayed for TLM content by dissolving a fixed amount of the complexes in methanol and analyzing for the TLM content spectrophotometrically at 297 nm.

**Characterization of complexes**

**Fourier transform infrared spectroscopic analysis**
FTIR spectra of moisture free powdered samples of TLM, CDs, its PM’s, and complexes with β-CD and HP-β-CD were taken using a FTIR spectrometer (Jasco FTIR 4100, Japan) by mixing with potassium bromide.

**Powder X-ray diffraction analysis**
Powder X-ray diffraction patterns of all samples were determined using Powder X-ray diffractometer (Bruker AXS Advance™ Germany), at a scan rate of 1° per min from 20 range from 5° to 50°.

**Differential scanning calorimetry analysis**
DSC scans of all powdered samples were recorded using
Shimadzu DSC 60. The samples (1 mg) were analyzed at a scanning rate of 10°C/min, over the temperature range of 30°C to 300°C.

**Dissolution studies**

Dissolution studies of TLM in powder form, its PM’s and complexes with β-CD and HP-β-CD were performed to evaluate drug release profile. Dissolution studies were performed on USP dissolution apparatus type II with 900 ml dissolution medium Phosphate buffer (pH 7.5) at 37°C ± 0.5°C at 75 rpm for 45 min. At fixed time intervals, 5 ml aliquots were withdrawn, filtered, suitably diluted, and assayed for TLM content by measuring the absorbance at 297 nm. (Pilot experimental data indicated no change in the λ_max of TLM due to the presence of CDs in the dissolution medium.) Equal volumes of fresh medium (pre-warmed to 37°C) were replaced into the dissolution medium to maintain constant volume throughout the test period. Dissolution studies were performed in six replicates, and calculated mean values of cumulative drug release were used while plotting the release curves.

**Formulation studies**

Tablets containing 40 mg of TLM were prepared by direct compression using different excipients like lactose monohydrate, colloidal silicon dioxide, and magnesium stearate. Tablets containing complexes (equivalent to 40 mg TLM) prepared by kneading and co-evaporation methods were also prepared similarly using less quantity of lactose. The blend was compressed on a six-station single rotary machine (Jaguar, India) using oval-shaped, punches to obtain tablets having length 16 mm, width 7 mm, thickness 4.5 mm, and hardness 3-5 kg/cm^2_. The tablets were studied in six replicates for a release profile of TLM using the same method described in dissolution studies.

**Statistical analysis**

A model-independent mathematical approach proposed by Moore and Flanner for calculating a similarity factor f_2 was used for comparison between dissolution profiles of different samples.[11] It also has been adopted by the US Food and Drug Administration’s Center for Drug Evaluation and Research,[12] and by the Human Medicines Evaluation Unit of the European Medicines Agency,[13] as a criterion for assessing the similarity of two dissolution profiles.[14,15] The similarity factor (f_j) is a measure of similarity in the percentage dissolution between two dissolution curves and is defined by using equation (1):

\[
f_j = 50 \times \log \left[ \left( 1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{-0.5} \times 100 \right]
\]  

(1)

where \( n \) is the number of withdrawal points, \( R_i \) and \( T_i \) is the percentage dissolved of reference and test respectively at the time point \( t \). A value of 100% for the similarity factor (f_j) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar whilst smaller values imply an increase in dissimilarity between release profiles. In order to understand extent of improvement in dissolution rate of TLM from its complexes and physical mixture, the obtained dissolution data of pure TLM, it’s PM, and complexes with CDs were fitted into equation (2):

\[
MDT_{in-vitro} = \frac{\sum_{i=1}^{n} t_{mid} \Delta M}{\sum_{i=1}^{n} \Delta M}
\]  

(2)

Here, \( i \) is dissolution sample number, \( n \) is number of dissolution times, \( t_{mid} \) is time at the midpoint between times \( t_i \) and \( t_{i+1} \), and \( \Delta M \) is the amount of TLM dissolved (µg) between times \( t_i \) and \( t_{i+1} \). MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate. It is accurate expression for drug release rate. A higher MDT value indicates greater drug retarding ability.[16,17]

**RESULTS AND DISCUSSION**

**Phase solubility**

Phase solubility analysis is among the preliminary requirements for optimization of the development into inclusion complexes of the drugs that can be used for evaluation of the affinity between CDs and drug molecule in water. Albeit CDs are known to generate aggregates (self-associates) in aqueous solvents,[18-20] the method is widely used for the determination of the molar ratios in drugs–CD complexes with CDs. The phase solubility curve of TLM showed a linear increase in solubility of TLM with an increase in concentrations of CDs in water [Figure 2]. Solubility of TLM is increased by 9.93-fold and 25.49-fold at 37°C at 15 mM concentrations of β-CD and HP-β-CD, respectively. The Gibbs free energy of transfer (ΔG°) of TLM

![Figure 2: Phase solubility curve of telmisartan in aqueous solution of β-CD and HPβ-CD at 37°C](image-url)
from pure water to aqueous solutions of CDs was calculated using the values from phase solubility curve [Figure 2] and applying equation (3), where,

\[ \frac{S_0}{S_{s}} = \text{the ratio of molar solubility of TLM in aqueous solution of CDs to that of the pure water.} \]

The obtained values of \( \Delta G_{tr}^{o} \) are shown in Table 2.

\[
\Delta G_{tr}^{o} = -2.303RT \log \left( \frac{S_0}{S_{s}} \right)
\]  

In the present experiment, \( \Delta G_{tr}^{o} \) values were all negative for CDs at various concentrations, suggesting the spontaneous nature of TLM solubilization. These values further indicate greater degree of solubility improvement with HP-\( \beta \)-CD as compared to \( \beta \)-CD. The phase solubility plot showed an A type solubility curve for both the CDs, which indicated formation of inclusion complex of TLM in 1:2 stoichiometric ratios with \( \beta \)-CD and HP-\( \beta \)-CD. The stability constants (\( K_s \)) for the complexes at 37°C, assuming a 1:2 stoichiometry, calculated from the slope of preliminary straight line portion of the phase solubility curve were 699.844 M\(^{-1}\) for TLM: \( \beta \)-CD and 2389.93 M\(^{-1}\) for TLM: HP-\( \beta \)-CD which indicated stable complex formation, since \( K_s \) in the range of 200-5000 M\(^{-1}\) indicates good complexation ability. This also suggests that there is an increase in the dissolution profile which would certainly increase bioavailability of TLM.

Drug content
The drug content of the PMB, PMH, COB, COH, KNB, and KNH were found to be 95.98% (±4.48), 95.44% (±5.03), 96.74% (±3.54), 97.16% (±3.15), 96.81% (±3.6), and 97.82% (±2.76), respectively.

Characterization of complexes
Fourier transform infrared spectroscopic analysis
The FT-IR spectra of PMB, KNB, COB, PMH, KNH, and COH were compared with spectra of \( \beta \)-CD, HP\( \beta \)-CD, and TLM [Figure 3]. The spectrum of pure TLM depicts the characteristic peaks at 3059 cm\(^{-1}\) (aromatic C-H stretch), 2957 cm\(^{-1}\) (aliphatic C–H stretch), 1697 cm\(^{-1}\) (–COOH acid), 1599 cm\(^{-1}\) (aromatic C=C Bend and Stretch), 1459 cm\(^{-1}\) (C-H bend), 1382 cm\(^{-1}\) (–OH bending and –C=O stretching of -COOH acid), 741 and 756 cm\(^{-1}\) (ring vibration due to 1,2-disubstituted benzene), respectively. The FT-IR spectra of \( \beta \)-CD and HP-\( \beta \)-CD are characterized by intense bands at 3300-3500 cm\(^{-1}\) due to O-H stretching vibrations. The vibration of the -CH and CH\(_2\) groups appears in the 2800-3000 cm\(^{-1}\) region. The presence or absence of characteristic peaks associated with specific structural groups of the drug molecule was noted. The chemical interaction has been reflected by changes in the characteristic peaks of TLM, depending on the degree of interaction. The FT-IR spectra of PMB, KNB, COB, PMH, KNH, and COH showed shift in peaks than those of CDs and TLM indicating chemical interaction between CDs and TLM during co-evaporation, kneading, and physical mixing. The FT-IR spectra showed the absence of the characteristic peak of TLM at 1697.05 cm\(^{-1}\) (–COOH acid), 2957.30 cm\(^{-1}\) (aliphatic C–H stretch), 1382.71 cm\(^{-1}\) (–OH bending and –C=O stretching of -COOH acid), 741 and 756 cm\(^{-1}\) (ring vibration due to 1,2-disubstituted benzene) in complexes, indicating inclusion of TLM in CDs cavity in them. Hence, it could be presumed the formation of inclusion of 1, 2-disubstituted benzene ring and carboxylic acid group of TLM in the cyclodextrin complexes.

Powder X-ray diffraction analysis
Powder X-ray diffraction spectroscopy (PXRD) has been used...
to assess the degree of crystallinity of the given sample. When complexes of drug and CDs are formed, there was increase in amorphousness and consequently solubility of drug. The PXRD spectra of all the samples are shown in Figure 4. TLM spectra depict a major peak at 2θ values of 6.8, 9.7, 14.23, 14.2, 15.1, 16.2, 18.3, 20.7, 22.3, and 25.1, while β-cyclodextrin spectra showed major peaks at 2θ values of 5.07, 8.87, 9.65, 11.87, 13.61, 17.16, 19.83, 21.06, 26.76, and 29.93. Due to the amorphous nature of HPβ-CD, no major peaks were detected in its spectra. Degree of crystallinity was decreased to a maximum extent in the case of complexes prepared using HPβ-CD and β-CD. Hence, from present structural data of complexes, it can be confirmed that inclusion of TLM in CDs cavity has been occurred.

**Differential scanning calorimetry analysis**

DSC analysis has largely been used to detect all processes in which energy is required or produced. The thermograms of all samples are presented in Figure 5. The TLM showed a melting peak at 265.45-268.82°C. In the thermogram of the β-CD and HPβ-CD, a peak between 75°C and 125°C was due to loss of water from CDs molecules. In the thermogram of all samples, peaks due to β-CD and HPβ-CD were observed at the same position i.e. between 75 and 125°C. Peak of TLM at 265-268°C was present at the same position i.e. near to 265°C in PMB, COB, PMH, and KNB. In the case of KNH and COH, intensity of TLM peak decreases and this may be attributed to trapping of TLM in the CDs cavity. This further confirms that the kneading method is the best method for the preparation of inclusion complexes.

**Dissolution studies**

The dissolution studies were carried out with TLM and its complexes and physical mixture using dissolution medium phosphate buffer pH 7.5. DP_{30} min (percent drug dissolved within 30 min), time to dissolve 50% drug (t_{50}%), and mean dissolution time (MDT) are reported in Table 3.

The data revealed that the onset of dissolution of pure TLM was very low (51.27% within 30 min). COH, KNH, COB, and KNB significantly enhanced dissolution rates within 30 min as compared to pure TLM, PMB, and PMH; see Figure 6. It is evident that the dissolution rate of pure TLM is very low (60.34% in 45 min.). Inclusion complexes KNB, COB, KNH, and COH significantly enhanced the dissolution rate of TLM (75-81% within 45 min). The likely factors responsible for the improvement in dissolution rates of complexes and PM’s are: reduction of crystal size, solubilization effect of carrier, improved wettability, etc.\[22\] MDT of TLM was 12.45 min in dissolution medium. The MDT values of TLM decreased to a greater extent after preparing the complex of TLM with CDs i.e. 10.99 min, 10.72 min 10.79 min, and 10.68 min for COB, KNB, COH, and KNH, respectively. Complexes prepared by co-evaporation and kneading methods exhibited enhanced dissolution profile and lower MDT values and were taken as an important paradigm for the formulation studies.
Calculated $f_2$ values [Table 4] indicate that the release profile of COH and KNH is significantly different from pure TLM ($f_2$ values 27.25 and 25.21) which explains that complexes with HP-$\beta$-CD gives better dissolution results than $\beta$-CD.

**Formulation studies**

The complexes prepared by the kneading and co-evaporation method (KNH and COH) were studied for physical properties to judge its tableting suitability. In general, compressibility index values up to 15% and angle of repose between 25° and 30° often shows good to excellent flow properties. Percent compressibility, angle of repose for complexes, and physical properties of tablets evaluated using these complexes are shown in Table 5. These values indicated good compressibility and flow properties, making these samples suitable for tableting. The tablets prepared using complexes showed faster and reproducible release as compared to the tablets containing pure TLM and no CDs. Tablets prepared using COH and KNH showed 79.38 and 81.04% release in 45 min with $t_{50}$ of 12.36 min and 11.44 min, respectively [Figure 7], exhibiting better dissolution profiles as compared to tablets prepared using TLM alone and marketed TLM tablet (Telsar®). These results clearly point out advantage of improved aqueous solubility of TLM in a complex form, which can be formulated as tablets with a better dissolution pattern. Release profiles of TLM from tablets containing TLM alone are significantly different from tablets containing COH and KNH, as the $f_2$ values were 34.43 and 32.24, respectively. MDT of TLM from tablets containing COH and KNH were (12.34 and 11.91 min) significantly lower than that of tablets containing only TLM [Table 3].

<table>
<thead>
<tr>
<th>Sample</th>
<th>DP$_{30\text{ min}}$</th>
<th>$t_{50%}$ (min)</th>
<th>MDT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure IRB</td>
<td>51.27</td>
<td>27.93</td>
<td>12.45</td>
</tr>
<tr>
<td>PMB</td>
<td>64.87</td>
<td>14.2</td>
<td>11.71</td>
</tr>
<tr>
<td>PMH</td>
<td>67.09</td>
<td>11.49</td>
<td>11.44</td>
</tr>
<tr>
<td>COB</td>
<td>78.61</td>
<td>9</td>
<td>10.99</td>
</tr>
<tr>
<td>COH</td>
<td>85.12</td>
<td>8.6</td>
<td>10.79</td>
</tr>
<tr>
<td>KNB</td>
<td>84.66</td>
<td>8.89</td>
<td>10.72</td>
</tr>
<tr>
<td>KNH</td>
<td>89.72</td>
<td>8.37</td>
<td>10.68</td>
</tr>
<tr>
<td>TLM Telsar® Tab</td>
<td>95.07</td>
<td>50.67</td>
<td>12.47</td>
</tr>
</tbody>
</table>

Fitted 3D surface plot showing the effect of factor levels on the response variables. Therego figure 3b: DSC thermograms of telmisartan, HP-$\beta$-CD and its complexes (A) TLM, (B) HP-$\beta$-CD, (C) PMH, (D) COH, (E) KNH

**Figure 6:** In vitro dissolution profiles of telmisartan, its physical mixture and complexes in Phosphate buffer pH 7.5
Table 4: f₂ values for comparison between release profiles of telmisartan from complex and PM’s in phosphate buffer pH 7.5

<table>
<thead>
<tr>
<th>Sample</th>
<th>PMB</th>
<th>PMH</th>
<th>COB</th>
<th>COH</th>
<th>KNB</th>
<th>KNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure IRB</td>
<td>49.6</td>
<td>45.08</td>
<td>32.15</td>
<td>27.25</td>
<td>28.12</td>
<td>25.21</td>
</tr>
<tr>
<td>PMB</td>
<td>—</td>
<td>78.62</td>
<td>44.74</td>
<td>36.66</td>
<td>38.06</td>
<td>33.63</td>
</tr>
<tr>
<td>PMH</td>
<td>—</td>
<td>—</td>
<td>49.35</td>
<td>39.73</td>
<td>41.71</td>
<td>36.25</td>
</tr>
<tr>
<td>COB</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>61.52</td>
<td>66.75</td>
<td>53.14</td>
</tr>
<tr>
<td>COH</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>83.65</td>
<td>75.24</td>
</tr>
<tr>
<td>KNB</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>67.91</td>
</tr>
</tbody>
</table>

Table 5: Physical properties of complexes and tablets of telmisartan

<table>
<thead>
<tr>
<th>Physical property</th>
<th>Pure IRB</th>
<th>COH</th>
<th>KNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Compressibility</td>
<td>7.5</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Angle of repose (°)</td>
<td>27.93±0.39</td>
<td>26.71±0.37</td>
<td>26.73±0.87</td>
</tr>
<tr>
<td>Hardness (Kg/cm²) (a)</td>
<td>3.2±0.10</td>
<td>4.2±0.10</td>
<td>4.2±0.21</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.08</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>16</td>
<td>16.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Width (mm)</td>
<td>7.1</td>
<td>7.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>4.5</td>
<td>4.6</td>
<td>4.5</td>
</tr>
</tbody>
</table>

(a) n=3

Figure 7: Release profiles TLM from conventional tablets containing only TLM and tablets containing KNH and COH in phosphate buffer of pH 7.5

CONCLUSION

Solubility studies showed a significant, linear increase in the aqueous solubility of TLM with increasing concentrations of β-CD and HPβ-CD. The highest improvement in solubility and in vitro drug release were observed in inclusion complex prepared with HPβ-CD by the kneading method. Improvement in solubility and drug release of TLM were more with HPβ-CD as compared to β-CD. The findings suggest that prepared complex with HPβ-CD showed greater dissolution profile of TLM. Further similar improved dissolution with tablets was formulated with the HPβ-CD inclusion complex of TLM.

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