Solubility and Dissolution Improvement of Fenofibrate by β-Cyclodextrin Complexation

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ABSTRACT

Fenofibrate is an antihyperlipidaemic drug practically insoluble in water and exhibits an exceedingly slow dissolution rate and poor bioavailability. The present study has emphasized on improving the solubility and dissolution rate of drug by complexation with β-Cyclodextrin (β-CD). The phase solubility studies indicated the formation of 1:1 M complex in solution. The value of apparent stability constant $K_C$ was found to be 158.4535M¹ suggesting drug formed more stable complex with β-Cyclodextrin. The inclusion complexes were prepared by physical mixture, kneading and co-precipitation method. Prepared complexes were characterized by Fourier transform infrared (FTIR) spectroscopy, Differential scanning calorimetry (DSC) studies, which indicated formation of 1:1 M complex. The fenofibrate: β-CD (1:1 M) complex prepared by kneading method exhibited higher dissolution rate and dissolution efficiency values in 20 mM SLS. The mean dissolution time of fenofibrate decreases significantly with cyclodextrin complexation.

Keywords: Solubility, Fenofibrate, Cyclodextrin, Dissolution, Kneading

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INTRODUCTION
Cyclodextrins are cyclic oligosaccharides consisting of a lipophilic central cavity and a hydrophilic outer surface. Because of such characteristic, cyclodextrin forms inclusion complexes both in solution and solid state, in which each guest molecule is surrounded by the hydrophobic environment of the cyclodextrin cavity. This can lead to the alteration of physical, chemical and biological properties of the guest molecules and can eventually have considerable pharmaceutical potential. Out of three parent cyclodextrins, β- cyclodextrin (β-CD) appears most useful as pharmaceutical complexing agent because of its complexing ability, low cost and other properties. There are two types of complex cyclodextrin form with guest molecules, type (A)_2 that forms in solution and type (B)_3 which forms in solid complex. The various methods can be used to complex drug with β-CD like kneading, co-precipitation, spray drying, freeze drying or roll mixing. Therefore, β-CD was selected to form inclusion complex with finofibrate to enhance its solubility and consequently dissolution.

Fenofibrate, propan-2-yl 2-[4-(4-chlorobenzoyl) phenoxy]- 2- methylpropanoate is a fibric acid derivative useful as antilipidemic agent. Fenofibrate is a hypolipemiant drug that reduces the amount of lipids (fats) in the blood. Fenofibrate is a white crystalline powder, practically insoluble in water (log P=5.24). Fenofibrate exhibits slow GI absorption rate and consequently dissolution. The primary objective of the present study was to enhance solubility and dissolution rate of fenofibrate by complexation with β-Cyclodextrin.

MATERIALS AND METHODS
Materials:
Fenofibrate and β-cyclodextrin were obtained as gift samples from Shreya Life Sciences (Aurangabad), Wockhardt Ltd. (Aurangabad) respectively. All other reagents were of analytical grade.

Phase solubility studies:
Phase solubility studies were performed according to the method reported by Higuchi and Connors. An excess of drug was added to 5ml portions of distilled water in series of vials each containing variable amount of β-CD (2mM to10mM). All the above solutions were subjected to sonication for 30min and then kept aside for 24 hrs to attain saturation equilibrium. These saturated systems were carefully filtered through Whatmann filter paper (No.41). The filtered samples were diluted suitably and assayed for fenofibrate, by measuring the absorbance at 287 nm. Solubility of fenofibrate in every β-CD solution was calculated, and phase solubility diagram was drawn between solubility of fenofibrate and different concentrations of β-CD. The apparent stability constant (Kc) was calculated by using formula.

\[
\text{Stability constant (Kc)} = \frac{\text{Slope}}{\text{So}(1 - \text{Slope})}
\]

Where, So= Aqueous solubility of fenofibrate

The Gibbs free energy of transfer (ΔGtr) of fenofibrate from pure water to the aqueous solution of carrier was calculated as

\[
\Delta G_{tr} = 2.303 \text{RT LogSo/S}
\]

Where So/ Ss is the ratio of molar solubility of fenofibrate in aqueous solution of β-CD to that of the same medium without β-CD.

Preparation of solid complex:

Physical mixture:
The physical mixture fenofibrate:β-CD (1:1) was prepared and then passed through sieve (No.72) with minimum abrasion.

Kneading method
Solid complexes of Finofibrate- β-CD were prepared in 1:1 molar ratio following kneading method. Stochiometric quantities (1:1) of fenofibrate: β-CD were accurately weighed. β-CD was added to the mortar, and a small amount of ethanol: water (1:1v/v) was added while triturating to get slurry like consistency. Then slowly drug was incorporated into the slurry, and trituration was continued further for 45 minutes. The slurry was then dried at 50°C
for 24 hours, pulverized and passed through sieve No. 72 and stored in desiccators until further use.

**Co-precipitation method:**
Fenofibrate and β-CD with 1:1 molar ratio was accurately weighed. Saturated solution of β-CD was prepared and fenofibrate solution in methanol was added slowly to form suspension. The suspension was stirred at 40 °C for 30 minutes and the stirring was continued at room temperature for 30 minutes. The obtained masses were filtered through Whatmann filter paper no.41 and dried at 50 °C in an oven for 24 hours. The dried complexes were pulverized and passed through sieve No. 72 and stored in desiccators until further use.

**Characterization of inclusion complexes**

**Fourier transformation infrared spectral studies (FT−IR)**
FR−IR spectra of Finofibrate and inclusion complex prepared by physical mixture and kneading method in different molar ratios were recorded using FT−IR spectrophotometer−4100 (Jasco, Japan) KBr pellet method.

**Differential scanning calorimetry (DSC)**
The samples were subjected to DSC studies using (Shimadzu DSC-60 thermal analyzer). Samples were sealed in 40 µl aluminium pans, lids were pierced and DSC thermograms were recorded at heating rate of 10 °C/min from 20 °C to 300 °C using nitrogen atmosphere.

**Dissolution studies**
The in vitro dissolution studies of pure drug, physical mixture and complexes were carried out in 900 mL of 20mM SLS, using USP digital dissolution test apparatus (Electro lab, Mumbai) with paddle stirrer. In the present study samples equivalent to 145 mg of Finofibrate were taken. The paddle was rotated at 75 rev./min and a temperature of dissolution medium was maintained at 37±0.5°C. Samples of dissolution media were withdrawn at different time intervals, filtered through Whatman filter paper no.41 and assayed for Finofibrate using spectroscopic method by measuring the absorbance at 287 nm.

**RESULTS AND DISCUSSION**

**Phase solubility studies**
The phase solubility diagram for the complex formation between Fenofibrate and β-CD is shown in Figure 1.

The aqueous solubility of the Finofibrate increases linearly with a slope 0.001 (r = 0.99899), as a function of β-CD concentration. The phase solubility diagram (Figure 1) can be classified as A_L-type. It is assumed that increase in solubility observed was due to the formation of 1:1 M inclusion complex. The apparent stability constants, \(K_{1:1}\) obtained from the slope of the linear phase solubility diagram was 158.4535M\(^{-1}\) for β-CD. The \(K_{1:1}\) value suggested that fenofibrate formed more stable complex with β-CD. An indication of the process of transfer of fenofibrate from pure water to the aqueous solution of β-CD may be obtained from the values of the Gibbs free energy change (Table 1).

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Concentration of β-CD (mM)</th>
<th>Concentration of fenofibrate (mM)</th>
<th>((\Delta G_{tr})) (J/Mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.007012</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.02226</td>
<td>-535.777</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0.03308</td>
<td>-596.748</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.03948</td>
<td>-671.446</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>0.04856</td>
<td>-729.104</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>0.05863</td>
<td>-782.725</td>
</tr>
</tbody>
</table>

Table No 1: Effect of β-CD and Gibbs's free energy on Finofibrate solubility

The values of Gibbs free energy (\(\Delta G_{tr}\)) associated with the aqueous solubility of fenofibrate in presence of β-CD were all negative at various concentrations, indicating the spontaneous nature of the drug solubilization. The values decreased by increasing β-CD concentration, demonstrating that the solubilization is more favorable as concentration of β-CD increased.

**Dissolution studies**
The dissolution characteristics of Finofibrate and Finofibrate - β-CD inclusion complex system are given in Table 2.
The dissolution data was evaluated on the basis of dissolution efficiency at 60 min (DE_{60})\textsuperscript{15}. The values of dissolution efficiency of all physical mixtures, kneaded and co-precipitated products were compared with the pure drug at 60 min, which gave a comprehensive picture of the dissolution efficiency of various systems with β-CD. The value of %DE_{60} for the pure drug was increased from 12.65% in physical mixtures to 76.20% in kneaded product and 30.35% in co-precipitated products. The dissolution efficiency (DE_{60}) of Fenofibrate prepared by kneading method was found to be significantly higher when compared to dissolution efficiency of complexes prepared by physical mixture, co-precipitation and pure drug. The results of dissolution study indicate improved dissolution rate of Fenofibrate with cyclodextrin complexes by both the techniques.

The enhanced dissolution rate may be attributed to several factors. Such factors are the strong hydrophilic character of β-CD, which improves the water penetration and the wettability of the hydrophobic Fenofibrate and the optimal dispersion of fenofibrate to β-CD. The lower degree of crystallinity, intermolecular hydrogen bonds and the molecular dispersion of fenofibrate on β-CD leads to partial miscibility, improving the hydrophilic characteristics of the drug substance via interactions with β-CD\textsuperscript{16}. Kneading showed higher dissolution than co-precipitation, this could be attributed to the improved wetting provided by cyclodextrins in kneading than coprecipitation, as earlier reported by Mukne et al for triamterene\textsuperscript{17} and Deshmukh et al for Ziprasodine\textsuperscript{18}.

**Kinetic assessment of dissolution data for fenofibrate: βCD complexes**

The best fit model for plane drug, physical mixture and kneaded product was peppas with ‘r’ values 0.9767, 0.9951, 0.9871. Plane drug shows ‘n’ > 1 indicating super case II transport. While, PM1 and B1 shows 0.5 < ‘n’ < 1 indicating anomalous transport means more than one type of release phenomenon could be involved. Co-precipitated product shows zero order release.

**FT-IR studies**

The IR spectra of pure drug and complexes are shown in Figure 3.

![FTIR Spectra](image)

**Figure 2: FTIR Spectra of**

A) Pure drug  B) β-CD C) Physical mixture D) Kneading product E) Co-precipitated product

IR spectrum of Fenofibrate is characterized by absorption of ester group at 1727.91 cm\textsuperscript{-1}. The ester group stretching band at 1727.91 cm\textsuperscript{-1} broadens and shifts towards higher wave numbers, indicating change in the intermolecular H-bonds of the drug upon complexation. Similar modifications are seen in the combination signal of the ester group which point out change in the interaction of this group when the complex is formed. In addition, the bands at 1050-1340 cm\textsuperscript{-1}, corresponding to antisymmetric vibrations of the aryl ether group and C-O stretching of esters broaden in some cases and in others peaks vanishes upon complexation. The decreased intensity and vanishing of the band associated to the out of plane bending of the aromatic C-H bonds at 824-844 cm\textsuperscript{-1} is the evidence for the inclusion of the benzene ring.

Finally, the C-H stretching seen at 3032-3052 cm\textsuperscript{-1} is not seen in the complexes indicating that complexation has occurred.

**DSC studies**

DSC thermogram of β-CD showed a broad endotherm in the range of 110–140°C, which can be attributed to the release of water molecule from the cavity (desolvation). The

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mean percentage of drug dissolved (±SD)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>(0.494, 2.423) (7.992, 3.125) (0.12) (1.05) (1.02) (0.50)</td>
</tr>
<tr>
<td>10</td>
<td>(0.916, 3.298) (12.726, 5.535) (0.06) (1.43) (0.64) (0.61)</td>
</tr>
<tr>
<td>15</td>
<td>(1.684, 4.331) (18.328, 7.822) (0.37) (1.87) (1.15) (0.53)</td>
</tr>
<tr>
<td>20</td>
<td>(2.392, 5.600) (21.262, 9.978) (0.41) (2.73) (3.83) (1.17)</td>
</tr>
<tr>
<td>30</td>
<td>(2.587, 7.232) (45.297, 14.309) (0.42) (3.03) (3.79) (2.34)</td>
</tr>
<tr>
<td>45</td>
<td>(3.760, 9.806) (58.973, 23.757) (0.95) (3.77) (3.41) (2.27)</td>
</tr>
<tr>
<td>60</td>
<td>(4.771, 12.657) (76.204, 30.354) (0.90) (3.32) (2.95) (2.10)</td>
</tr>
<tr>
<td>75</td>
<td>(6.348, 14.074) (89.611, 38.249) (0.49) (4.53) (2.07) (1.85)</td>
</tr>
<tr>
<td>90</td>
<td>(7.974, 15.259) (99.045, 45.805) (1.27) (4.01) (0.60) (1.60)</td>
</tr>
<tr>
<td>105</td>
<td>(8.434, 16.695) (100.328, 51.560) (0.82) (4.11) (1.88) (1.56)</td>
</tr>
<tr>
<td>120</td>
<td>(13.299, 18.042) (62.463, 21.262) (2.76) (3.92) (0.61) (0.64)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Mean percentage of drug dissolved (±SD)

**Table No 2: Dissolution profile of Fenofibrate in 20 mM SLS**

DSC curve of Finofibrate showed a broad endothermic peak in the range of 80–90 °C owing to the melting point of the drug. The peak of Finofibrate showed changes in terms of peak area and ΔH (heat of fusion) value in case of the complexes (Table 3) as compared to the physical mixture comprising of drug: β-CD in the same ratio. This suggested that the presence of β-CD resulted in complexation of Finofibrate. The change in peak height and broadening of peaks (Figure 4) may be attributed to loss in crystallinity.

![Figure 2](image-url)

**Figure 2** DSC thermograms of A) Fenofibrate B) β-CD C) Physical mixture D) Kneaded Complex E) Co-precipitation complex

**CONCLUSION**

The results of the study indicated the formation of Finofibrate and β-CD complexes in 1:1 ratios in solution with stability constant of 158.4535M⁻¹. Inclusion complexes of Finofibrate and β-CD (1:1) prepared by kneading method exhibited higher rate of dissolution and higher dissolution efficiency values compared to corresponding values for physical mixture, pure drug and co-precipitation. Improved dissolution observed in case of kneading method may be due to the formation of solid inclusion complexes, with better interaction of drug and β-CD during kneading process and improved wetting provided by β-CD. It is concluded that Finofibrate - β-CD complexation results in an increase in solubility and dissolution rate of drug, suggesting a possible enhancement of its oral bioavailability.

**ACKNOWLEDGEMENT**

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**REFERENCES**