The aim of this study was to enhance the solubility and bioavailability of cefpodoxime proxetil (CFP) through complexation with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD). CFP is a poorly water soluble antibiotic drug. Reportedly, it has slow, erratic, and complete absorption after oral administration. This present report describes the study of the phase solubility diagram, preparation of the inclusion complex, In-Vitro dissolution study of optimized ratio. An AL-type phase solubility diagram indicated a 1:1 complex of CFP-HP-β-CD with the constant of complex formation of 188.35 M⁻¹ at 37°C. The complex formation was confirmed by DSC, IR. The extent of absorption of the complex was determined in rats and was compared with that of pure drug. The pure CFP shows 9.7% Corrected cumulative Drug release (CCDR) in hr while kneded drug complex with HP-β-CD shows 53.06% CCDR. The solubility and dissolution rates of CFP were significantly increased by Hydroxypropyl cyclodextrin complexes.

**Keywords:** Cefpodoxime proxetil, Hydroxy propyl β Cyclodextrin, Phase Solubility Diagram, Inclusion Complex.
Hydroxypropyl beta cyclodextrin have extensively been used to increase the solubility, dissolution rate\textsuperscript{4, 5}, and bioavailability of poorly water soluble drugs\textsuperscript{21}. The ability of cyclodextrin to modify these characteristics has been attributed to the formation of inclusion complex between cyclodextrin and ‘guest’ drug molecules. 2-Hydroxypropyl-β-cyclodextrin [HP β CD] is an amorphous mixture of modified β-cyclodextrin (βCD). It has the ability to form inclusion complexes but does not have the limitations associated with crystalline cyclodextrin such as renal toxicity. Further, the aqueous solubility of HP β CD is far greater than that of the parent β CD which results in vastly improved solubility of numerous compounds. Cefpodoxime Proxetil\textsuperscript{22-23} (CFP) is a major antibiotic drug for the treatment of different form of seizures. The drug is practically insoluble in water and has poor wettability properties. It is absorbed slowly and erratically after oral administration. Reportedly, it has an oral bioavailability\textsuperscript{8} of less than 50%. These properties of CFP led to the belief that it can be a good candidate for complexation with HP β CD to increase solubility and bioavailability. The primary objective of the present study is to investigate the possibility of improving the aqueous solubility and oral bioavailability of CFP via complexation with HP β CD. The formation of such complex was confirmed by a variety of techniques such as solubility determination, Infrared spectrophotometry (IR)\textsuperscript{9}, Differential scanning calorimetry (DSC)\textsuperscript{10}. The work also included determination of the in vitro dissolution profiles of pure drug, physical mixture and CFP : HP β CD complex system.

**MATERIALS AND METHODS**

Materials

Cefpodoxime proxetil was a gift from Cadilla pharmaceuticals Pvt Ltd. HPβCD were kindly supplied by Roquett Pharma. Ethanol, methanol, and water were obtained from S.D.Fine Labs, and all were of HPLC grade. All other chemicals were of analytical reagent grade.

Methods

The standard curve of CFP was prepared in distilled water dissolved by HP-β-CD.
Preparation of stock solution

50 mg of CFP was accurately weighed in to 50 ml volumetric flask and dissolved in small quantity of water. The volume was made up with water to 50 ml to produce a stock solution having a concentration of 1 mg/ml. 100 mg of HP-β-CD was added to solubilize the drug with sonication.

Preparation of standard solution

An aliquot of 5 ml of the stock solution was diluted to 50 ml to get a standard solution having a concentration of 100 mcg/ml using water.

Preparation of the working standard solution

Standard solutions ranging in concentrations from 2 to 10 mcg/ml were prepared by appropriately diluting the stock solution with water. The absorbance of each working standard solution was measured at 263 nm (Shimadzu UV spectrophotometer) using water having same concentration of HP-β-CD as a blank so as to nullify any absorbance that may be exhibited by the HP-β-CD molecule. Data was collected in triplicates and statistically analyzed.

Phase Solubility Study

Phase-solubility studies were performed according to the method reported by Higuchi and Connors (1965). Exactly 50 mg of CFP was weighed into 20 ml scintillation vial, to which were added 10 ml of water containing different concentrations of HPβCD (5-100 mM). Different ratios prepared were ratios are 1:0, 1:0.5, 1:1, 1:2. (CFP: HP-β-CD).

The sealed vials were shaken for 2 days at a controlled temperature of 37 ± 0.5°C. After 2 days, an aliquot was withdrawn and filtered through a 0.45micron millipore filter. The concentration of CFP in each aliquot was determined spectrophotometrically at 263 nm to have a standard plot.

Kneading Method

Solid inclusion complex of Cefpodoxime proxetil (CFP) and HP-β-CD were prepared in molar ratio by following kneading method. HP-β-CD was mixed in a glass mortar along with water to obtain a homogeneous paste. The drug was slowly added to the paste and the mixture triturated for 1 hr. During the process the water
content of the paste was empirically adjusted to maintain the consistency of the paste. The paste was dried at 45 °C for 48 hrs, pulverized and passed through sieve No.100.

Physicochemical properties

IR spectroscopy of the KBr pellet was performed using a FTIR spectrophotometer (SHIMADZU). The above scans were performed on CFP, HPβCD, and the complex.

Dissolution rate

Dissolution studies were performed using the U.S.P. dissolution apparatus (paddle method) in 900 ml water as the dissolution medium. The stirring rate was 70 rpm and temperature was maintained at 37 ±0.5 °C. Dissolution samples were passed through 30 meshe and retained on 80 mesh USP standard and contained the equivalent of 100 mg cefpodoxime proxetil.

RESULTS AND DISCUSSION

The absorbance data for standard calibration curves are given in table-1. The standard calibration curve yields a straight line, which shows that the drug follows Beer’s law in the concentration range at 2 to 10 mcg/ ml.

Table 1.

Absorbance Data

<table>
<thead>
<tr>
<th>Concentration (mcg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.055±0.25</td>
</tr>
<tr>
<td>4</td>
<td>0.117±1.08</td>
</tr>
<tr>
<td>6</td>
<td>0.164±1.22</td>
</tr>
<tr>
<td>8</td>
<td>0.221±1.36</td>
</tr>
<tr>
<td>10</td>
<td>0.273±1.05</td>
</tr>
</tbody>
</table>
Figure 1: Standard Calibration Curve in Water

Figure 2. Phase solubility diagram

The phase solubility diagrams shown in Fig. 1 can be classified as type A_L according to Higuchi Connors Phase solubility diagram of CFP and HP-β-CD systems in distilled water at 37°C.

Because the straight line had a slope less than unity, it was assumed that the increase in solubility observed was due to the formation of a 1 : 1 complex. The observed rate constants for the formation of the complex (K_F) were calculated for HPβCD Equation 1^{13-15} and were found to be 188 M^{-1}. 

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\[ K_{ab} = \frac{\text{slope}}{S_0(1-\text{slope})} \]  

As observed from Fig. 2 a considerable increase in solubility of CBZ was obtained with HP\(\beta\)CD.

The IR spectra of the inclusion complex (Fig. 5) did not show any significant differences from the respective spectra of the pure compounds. The absorption peaks characteristic of the carbonyl group\(^{16}\) of CFP in the range 1735-1760 cm\(^{-1}\) and the amino groups\(^{17,18}\) in the range 3200-3600cm\(^{-1}\) have disappeared from the spectrum of the inclusion complex. These spectral changes may have resulted from the inclusion of CFP within the cavity of HP\(\beta\)CD.

![Figure 3. FTIR of Cefpodoxime Proxetil](image-url)
Figure 4. FTIR of HP-β-CD

Figure 5. FTIR of Inclusion complex
Figure 6 shows the dissolution profiles\textsuperscript{6,7} of CFP from complex, physical mixture, and powders. It is evident that the release of CFP was significantly enhanced by complexation. Within 1 hr, the percentage of drug released was approx 10 and 50 % for the powdered drug and the complex samples, respectively. Additionally, in this study, improved wettability of CFP in the samples of Complex was observed. The enhanced dissolution rate is probably due to increased solubility, decreased crystallinity and improved wettability.

Figure 6. \textit{In Vitro} dissolution Study of Inclusion complex, physical mixture and pure drug

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{in_vitro_dissolution.png}
\caption{In-Vitro dissolution Study}
\end{figure}

CONCLUSION

The above data clearly indicate that the inclusion complex makes the drug more soluble. This enhancement in drug solubility is due to fast dissolution rate of the complex. Thus, HP\(\beta\)CD could be a useful additive to solid Cefpodoxime proxetil. Formulations having Inclusion Comlexation with HP-\(\beta\)-CD result in a more rapid absorption and improved bioavailability of the drug.


6. Indian Pharmacopoeia, Volume -III, the Indian Pharmacopoeia Commission, Ghaziabad, Govt. of India, Ministry of Health and Family Welfare. 2007: 232-233

7. United state pharmacopoeia 30- National formulary 25, United state pharmacopoeial convention.


15. Rajeswari Challa: Cyclodextrins in Drug Delivery: An Updated Review Submitted: June 11, 2004; Accepted: January 26, 2005; Published: October 14, 2005.


