DEVELOPMENT AND CHARACTERIZATION OF SOLID DISPERSIONS OF CEFPODOXIME PROXETIL WITH PEG 6000

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ABSTRACT
Solid dispersion is one of the most successful techniques to improve dissolution rate of poorly aqueous soluble drugs. Cefpodoxime Proxetil, a class IV drug as per BCS is having poor solubility and poor dissolution rate. But when prepared as solid dispersion with hydrophilic carrier showed improved solubility and dissolution rate. So the main purpose of this investigation was to increase the solubility and dissolution rate of Cefpodoxime Proxetil by preparing its solid dispersion with PEG 6000 using kneading method (KM) method. Physical mixtures and solid dispersions of Cefpodoxime Proxetil were prepared in various proportions (0.5:1, 0.75:1, 1:1, 1:0.5 and 0.75), by employing kneading method. Prepared SDs were optimized from solubility studies and dissolution rate studies. Optimized SD was further characterized for DSC and FTIR studies. From the results it was found that the dissolution rate and the dissolution parameters of the drug from the physical mixture as well as solid dispersion were higher than those of the pure drug. FTIR spectra and DSC data revealed no chemical incompatibility between drug and PEG. Hence, Solid dispersion technology can be used to improve the solubility and dissolution rate of Cefpodoxime proxetil.

KEYWORDS: Solid dispersions, Cefpodoxime proxitel, PEG 6000, kneading method (KM)

INTRODUCTION
Cefpodoxime Proxetil (1-[(isopropoxycarbonyl) oxy] ethyl ester of (Z)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid) is the orally active ester prodrug of third generation Cephalosporin (CP) (Figure 1). CP is used orally for the treatment of mild to moderate respiratory tract infections, uncomplicated gonorrhea and urinary tract infections. One of the major problems with this drug is its very poor aqueous solubility that results into poor bioavailability after oral administration. It shows erratic dissolution in gastric and intestinal fluid due to its poor aqueous solubility. Rate of absorption and/or extent of bioavailability for such drugs are controlled by rate of dissolution in gastrointestinal fluids. The peak plasma concentration (Cmax) and the time taken to reach Cmax (tmax) depend upon extent and rate of dissolution of drug respectively. The efforts to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development.1-4

Solid dispersion (SD) is one of the most successful strategies to improve dissolution rate of poorly aqueous soluble drugs. SDs can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.5-7 SD can be prepared by various methods such as solvent evaporation or melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. The mechanism by which the solubility and the dissolution rate of the drug are increased includes: reduction of the particle size of drug to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from amorphous to crystalline form, the high energetic state which is highly soluble; finally, the wettability of the drug particle is improved by the hydrophilic carrier. Hence solid dispersion technique has been introduced to overcome this problem by improving dissolution rate of poorly soluble drugs.2,5,8,9

In present work, SDs of CP were prepared by kneading method. PEG 6000 is used as hydrophilic carrier. By changing CP:PEG 6000 ratio like, 0.5:1, 0.75:1, 1:1, 1:0.5 and 1:0.75 solid dispersions were prepared by kneading (KM) method. SDs were optimized for solubility studies, and dissolution studies data. Optimized SD was further characterized for DSC and FTIR studies and also compared with physical mixture of...
same composition. CP-PEG 6000 SD system, prepared by kneading method, showed an improvement in dissolution rates of CP from the solid dispersions as compared with the pure drug and physical mixtures. Hence this study presents preparation of solid dispersions of Cefpodoxime Proxetil with PEG as the hydrophilic carrier and their characterization.

**MATERIALS AND METHODS**

**Materials**
Cefpodoxime proxetil and PEG 6000 were obtained as a gift sample from Maxim Pharmaceuticals, Pune and Colorcon Asia Ltd. (Goa, India) respectively. All other chemicals and reagents were of analytical grade.

**Methods**

**Preparation of solid dispersions by Kneading Method (KM)**
CP and PEG 6000 in the ratios of 0.5:1, 0.75:1, 1:1, 1:0.5 and 1: 0.75 were mixed and triturated well. Each one was kneaded thoroughly by using sufficient methanol and resultant mass was dried for 20 min. at 30°C and finally passed through 60 mesh. The powder fraction passing through 60 meshes was collected.

**Preparation Of Physical Mixtures (PM)**
PMs were prepared by taking CP and PEG 6000 in a ratio of optimized composition and simply mixing it well. The mixture was sieved and the powder fraction passing through 60 mesh was collected for dissolution studies.

**Evaluation Of Prepared Solid Dispersions Assay**
Solid dispersions equivalent to 10 mg of CP were weighed accurately and dissolved in a suitable quantity of methanolic 0.1 N HCl. The solutions were filtered and drug content was determined by measuring absorbance at 262 nm by UV spectrophotometer (JASCO, V-550, Japan) after suitable dilution. Standard curve for the estimation was prepared in methanolic HCl in the concentration range of 12-20 μg/ml. In this concentration range, good linearity was observed with correlation coefficient of 0.9987. The percentage yield of each formulation was calculated by referring calibration curve.

**Determination Of Saturation Solubility**
Saturation solubility was determined by using shake flask method. Excess quantities of CP and prepared SDs were added in 25 ml distilled water in conical flasks which were then put in orbital shaker at 37°C and at 100 rpm for 72 hrs. Absorbance of resulting solution was measured on UV spectrophotometer at 262 nm. Calculations were done with by referring calibration curve.

**Shake flask method**
Shake flask method same as that for saturation solubility was used with 0.1N HCl and phosphate buffer pH 6.8 as solvents.

**In Vitro Dissolution Studies**

**In vitro** dissolution studies of prepared solid dispersions were carried out in 900 mL of 0.1 N HCl as a medium using USP Apparatus 2 (paddle method) with three replicates. The paddle rotation speed was 75 rpm, and a temperature of 37 ± 1 °C was maintained. In all experiments, 5 mL of dissolution sample was withdrawn at 15, 30, 45 and 60 min, filtered using a 0.45-mm Whatman filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were analysed by UV spectrophotometry at 262 nm (JASCO, V-550, Japan). Cumulative percentages of drug dissolved from the solid dispersions were calculated by using PCP disso software. From above evaluation tests, optimized formulation was confirmed which was then subjected to following tests.

**Fourier Transform Infrared Spectroscopy**
Optimized solid dispersion and CP were subjected to FTIR spectroscopic studies. FTIR spectra were recorded on the samples prepared in potassium bromide (KBr) discs by means of hydrostatic press, using FTIR spectrophotometer (460 plus, Jasco- Japan). The scanning range was 4000 – 400 cm⁻¹ and the resolution was 2 cm⁻¹.

**Dsc Studies**
The DSC thermogram of CP and its optimized SD were recorded using Differential scanning calorimeter (DSC 823 Mettler Toledo, Japan). Approximately 1-3 mg of Cefpodoxime Proxetil or its SD containing equivalent amount of drug was heated in a closed pierced aluminum pan from 30 °C to 300 °C at a heating rate of 10°C/min under a stream of nitrogen at a flow rate of 40ml/min.

**RESULTS AND DISCUSSION**
All the prepared SDs showed assay results in between 98-100% which complies with USP specifications (Table No.1 and 2). SDs prepared in 1:1 ratio of CP and PEG 6000 showed maximum increase in Saturation solubility, pH dependent solubility and in vitro dissolution profile as compared to other ratios. Hence same composition i.e 1:1 was selected for the preparation of physical mixture. The observed increase in the solubility of CP in solid dispersions is thought to be attributable to the solubilization effect of the PEG 6000. The solubilization effect of the carriers may be found because of the formation of concentrated diffusion layer into which the drug dissolves prior to its release into the aqueous medium.
Estimation Of Cefpodoxime Proxetil
CP was estimated at 262 nm using UV spectrophotometer (Jasco V-550, Japan). Standard curve for the estimation was prepared in methanolic 0.1 N HCl in concentration range of 12-20 µg/ml. In this concentration range good linearity was observed with the correlation coefficient ($R^2$) 0.9987. The graph (Figure 2) obeyed the Beer-Lambert’s law in the selected concentration range.

Fourier Transform Infrared Spectroscopy
FTIR studies were done to detect the possible interactions between the CP and PEG 6000. The characteristic peaks of CP and PEG are retained in physical mixtures and in solid dispersion (Figure 3). It was revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of interactions in the solid state between CP and PEG.

Differential Scanning Calorimetric Studies
DSC studies revealed that, sharp endothermic fusion peak corresponding to melting point of CP observed at approximately 84°C in the thermogram of pure CP. The peak observed for the melting of CP is found to be absent in that for SDs with PEG 6000 carriers (Figure 4). The complete disappearance of drug melting peak observed in the DSC thermogram of SDs with PEG 6000 can be attributed to uniform drug dissolution in the carriers.

Dissolution Studies
The dissolution rate of pure Cefpodoxime Proxetil was very poor and during 60 min a maximum about 38.40% of the drug was released. One of the reasons for the poor dissolution rate of CP is poor wettability. It was found that the dissolution rate of the drug increased by using hydrophilic carrier (PEG) in physical mixture as well as SD batches as compared to CP. This was due to the increase in solubility of drug by the presence of hydrophilic carrier surrounding the drug particles. Figure 5 shows comparative release profile of various solid dispersions of CP with PEG 6000, physical mixture containing 1:1 ratio of CP : PEG and CP. From release profile it can be seen that dissolution of CP in solid dispersions increases as compared to pure drug and physical mixture. This increase in the dissolution rate may due to increase in CP wettability, solubilization of CP by carriers. It was found that the drug release from physical mixture is greater than that of the CP and slower than that of solid dispersions. From the results, it was conclude that the dissolution rate of CP increased by preparing solid dispersion with PEG.

CONCLUSION
From the present study it can be conclusively stated that, the aqueous solubility, pH dependent solubility and dissolution rate of CP can be increased by preparing SDs with help of hydrophilic carriers like PEG 6000. Results obtained by different characterization techniques (FTIR, DSC) clearly indicated that the kneading method leads to the formation of interaction between CP and PEG 6000 to form solid dispersions with improved dissolution rate. Hence, from present study, it can be said that, problem of low bioavailability of CP due to low solubility may be handled by preparing Solid dispersions of Cefpodoxime proxetil with hydrophilic carriers like PEG 6000.

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REFERENCES
Table 1: Composition of Batches Containing Cefpodoxime Proxetil and PEG 6000.

<table>
<thead>
<tr>
<th>Batches for SDs</th>
<th>CP (mg)</th>
<th>PEG 6000 (mg)</th>
<th>Drug : Carrier Ratio</th>
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<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>100</td>
<td>1:1</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>75</td>
<td>1:0.75</td>
</tr>
<tr>
<td>C</td>
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<td>50</td>
<td>1:0.5</td>
</tr>
<tr>
<td>D</td>
<td>75</td>
<td>100</td>
<td>0.75:1</td>
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<tr>
<td>E</td>
<td>50</td>
<td>100</td>
<td>0.5:1</td>
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Table No.2: Assay, Saturation solubility and pH dependent solubility study results

<table>
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<tr>
<th>Ratios</th>
<th>Saturation solubility in DW (mg/ml)</th>
<th>% increase</th>
<th>pH dependent solubility in HCl (mg/ml)</th>
<th>% increase</th>
<th>pH dependent solubility in PB (mg/ml)</th>
<th>% increase</th>
<th>Assay % w/w</th>
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<tr>
<td>PD</td>
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<td>SDs by KM</td>
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<td>33.23</td>
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Figure 1: Chemical structure of CefpodoximeProxetil

Figure 2: Calibration curve of CP in 0.1 N HCl
Figure 3: FTIR Studies

Figure 4: DSC Studies

Figure 5: Mean (n = 3) in vitro dissolution profiles of solid dispersions of CP

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