

DEVELOPMENT, CHARACTERIZATION AND SOLUBILITY STUDY OF SOLID DISPERSION OF CEFPODOXIME PROXETIL BY SOLVENT EVAPORATION METHOD

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ABSTRACT: Cefpodoxime Proxetil (Poorly water soluble drug), when prepared as solid dispersion showed improved solubility and dissolution. So the main purpose of this investigation was to increase the solubility and dissolution rate of Cefpodoxime Proxetil by the preparation of its solid dispersion with urea using solvent evaporation method. Physical mixtures and solid dispersions of Cefpodoxime Proxetil were prepared by using urea as water-soluble carrier in various proportions (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 by weight), by employing solvent evaporation method. The drug release profile was studied and 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 intact drug. FT- IR spectra revealed no chemical incompatibility between drug and urea. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC) and Powder X-Ray Diffraction (PXRD).

KEYWORDS: Cefpodoxime Proxetil; Urea; Solvent Evaporation Method; Solid dispersion.

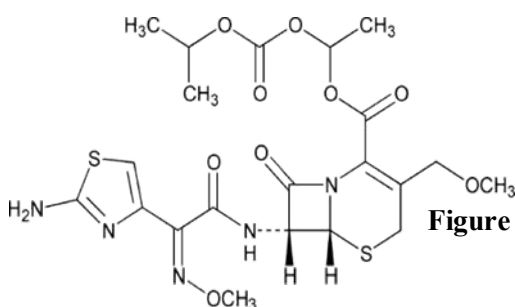
INTRODUCTION

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) (Figure 1) is the orally active ester prodrug of third generation Cephalosporin. Cefpodoxime Proxetil 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 solubility in biological fluids that results into poor bioavailability after oral administration. It shows erratic dissolution problem in gastric and intestinal fluid due to its poor water solubility. Rate of absorption and/or extent of bioavailability for such insoluble drugs are controlled by rate of dissolution in gastrointestinal fluids ⁽¹⁾. The peak plasma concentration (C_{max}) and the time taken to reach C_{max}

(t_{max}) depend upon extent and rate of dissolution of drug respectively. The effort to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development. Several methods have been introduced to overcome this problem like solid dispersions, complexation, Zydis technology, and by the use of hydrophilic carriers.

Solid dispersion, which was introduced in the early 1970s ⁽²⁾, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles ⁽²⁾. Solid dispersion technique has been used for a wide variety

of poorly soluble drugs such as nimesulide ⁽³⁾, ketoprofen ⁽⁴⁾, tenoxicam ⁽⁵⁾, nifedipine ⁽⁶⁾, nimodipine ⁽⁷⁾, ursodeoxycholic acid ⁽⁸⁾, and albendazole ⁽⁹⁾. Various hydrophilic carriers, such as polyethylene glycols ⁽¹⁰⁾, polyvinylpyrrolidone ⁽¹¹⁾, hydroxypropyl methylcellulose ⁽¹²⁾, gums ⁽⁶⁾, sugar ⁽¹³⁾, mannitol ⁽¹⁴⁾, and urea ⁽⁸⁾, have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.



1: Chemical structure of Cefpodoxime Proxetil

Solid dispersion can be prepared by various methods such as solvent evaporation and melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. According to this method, a drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. 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. Cefpodoxime Proxetil-urea systems, prepared by solvent evaporation method,

showed an improvement in dissolution rates of the drug from the solid dispersions as compared with the pure drug and physical mixtures. This study presents formulation of solid dispersions of Cefpodoxime Proxetil with urea as the hydrophilic carrier.

MATERIALS AND METHODS

Materials

Cefpodoxime Proxetil was obtained as generous gift from FDC Limited, Mumbai. Urea (Analytical grade) was purchased from Qualikems Fine Chemicals Pvt. Ltd., New Delhi. All other chemical reagents were of analytical grade.

Methods

Preparation of Physical Mixture

Accurately weighed amount of Cefpodoxime Proxetil and urea (carrier) in various drug-to-carrier weight ratios were thoroughly blended in glass mortar for 5 min. The composition of various batches is shown in Table 1. The products were kept in desiccator for further study.

Preparation of Solid Dispersion

The solid dispersions of Cefpodoxime Proxetil and urea (carrier) in various drug-to-carrier weight ratios were prepared by solvent evaporation method. The 100 mg of Cefpodoxime Proxetil was dissolved in 20 ml of methanol in a beaker and carrier was added and mixed to dissolve at 40°C on a hot plate to get a clear solution. Then the solvent was allowed to evaporate in hot air oven at 40°C ± 5°C. The process of evaporation was opted until the constant weight was obtained. Solid Dispersions prepared were crushed, pulverized and sifted through mesh number 80 and stored in desiccators.

Table 1: Composition of Batches Containing Cefpodoxime Proxetil and Urea

Batches for Physical Mixture	Cefpodoxime Proxetil (mg)	Urea (mg)	Drug : Carrier Ratio	Batches for Solid dispersion
PM1	100	100	1:1	SD1
PM2	100	200	1:2	SD2
PM3	100	300	1:3	SD3
PM4	100	400	1:4	SD4
PM5	100	500	1:5	SD5
PM6	100	600	1:6	SD6
PM7	100	700	1:7	SD7

Estimation of Cefpodoxime Proxetil

Cefpodoxime Proxetil was estimated at 232 nm using UV spectrophotometer (Systronics Double Beam Spectrophotometer 2202). Standard curve for the estimation was prepared in 15% v/v methanolic phosphate buffer pH 6.8 in concentration range of 2-30 µg/ml. In this concentration range good linearity was observed with the correlation coefficient (R^2) 0.9987. The graph obeyed the Beer-Lambert's law in the selected concentration range.

Characterization of Samples

Fourier Transform Infrared Spectroscopy

All prepared solid dispersions were subjected to FTIR spectroscopic studies to determine drug-carrier interaction. FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using Fourier Transform IR spectrophotometer (Perkin Elmer, RXI FTIR System). Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 2 cm^{-1} .

Differential scanning calorimetric studies

Differential scanning calorimetry (DSC) measurements were carried out on a scanning calorimeter (DSC Q10 V9.0 Build 275, Universal V4.1D TA Instruments). The instrument was calibrated using indium as standard. Samples (5-10 mg) were placed in sealed aluminium pans and heated from 70°C to 160°C at a rate of 10°C/min under nitrogen atmosphere (60 ml/min), with empty pan as reference.

X-Ray Diffraction Studies

The powder x-ray diffraction (XRD) was performed by X'pert Pro with Spinner PW3064 using Ni-filtered, $\text{CuK}\alpha$ radiation, a voltage of 45 kV, and a current of 40 mA with a scintillation counter. The instrument was operated in the continuous scanning speed of 4°/min over a range of 5°C to 40°C.

Drug Content

Solid dispersions equivalent to 100 mg of Cefpodoxime Proxetil were weighed accurately and dissolved in a suitable quantity of methanolic phosphate buffer pH 6.8. The solutions were filtered and drug content was determined at 232 nm by UV spectrophotometer (Systronics Double Beam Spectrophotometer 2202) after suitable dilution. The percentage yield of each formulation was also calculated.

Saturation Solubility

To evaluate the increase in solubility of Cefpodoxime Proxetil, physical mixture and solid dispersions, saturation solubility measurements were conducted. The known excess (approximately 50 mg) of Cefpodoxime Proxetil was added to 100 mL of phosphate buffer (pH 6.8). Samples were rotated at 20 rpm in a water bath ($37.0 \pm 0.5^\circ\text{C}$) for 48 hours. The samples were then filtered, suitably diluted, and analyzed by UV spectrophotometer at 232 nm.

Dissolution Studies

The dissolution studies were performed using a US Pharmacopeia XXIV type II dissolution test apparatus. The samples equivalent to 100 mg Cefpodoxime Proxetil were placed in a dissolution vessel containing 900 mL of phosphate buffer (pH 6.8) maintained at $37.0 \pm 0.5^\circ\text{C}$ and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration, concentration of Cefpodoxime Proxetil was determined spectrophotometrically at 232 nm.

RESULT AND DISCUSSION

Fourier Transform Infrared Spectroscopy

FT-IR studies were done to detect the possible interactions between the Cefpodoxime Proxetil and urea. The characteristic peaks of Cefpodoxime Proxetil, urea and physical mixtures are presented in Table 2. 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 Cefpodoxime Proxetil and urea.

Table 2: FT-IR peaks of pure Cefpodoxime Proxetil, urea and physical mixture of Cefpodoxime Proxetil and urea.

Description	Characterization (cm^{-1})
Cefpodoxime Proxetil	2937.8, 1676.6, 1274.6 and 1075.7.
Urea	3335.8, 1150.6, 787.1 and 556.9.
Cefpodoxime Proxetil and Urea	3335.8, 2937.8, 1676.6, 1274.6, 1150.6, 1075.7, 787.1 and 556.9.

Differential Scanning Calorimetric Studies

Differential scanning calorimetry shows sharp endothermic fusion peak at 126.8°C, which is corresponding to the melting point of Cefpodoxime Proxetil [Figure 2].

X-Ray Diffraction Studies

The diffraction spectra of Cefpodoxime Proxetil and urea show numerous distinct peaks indicating that both are present in a highly crystalline state. The XRD

pattern of solid dispersion of sample SD5 exhibits all the characteristic diffraction peaks of urea and crystalline Cefpodoxime Proxetil, but of lower intensity. This study reveals that some Cefpodoxime Proxetil still exists in the crystalline state in the solid dispersion.

Drug content and saturation solubility

The drug content and saturation solubility were determined and results were presented in Table 3.

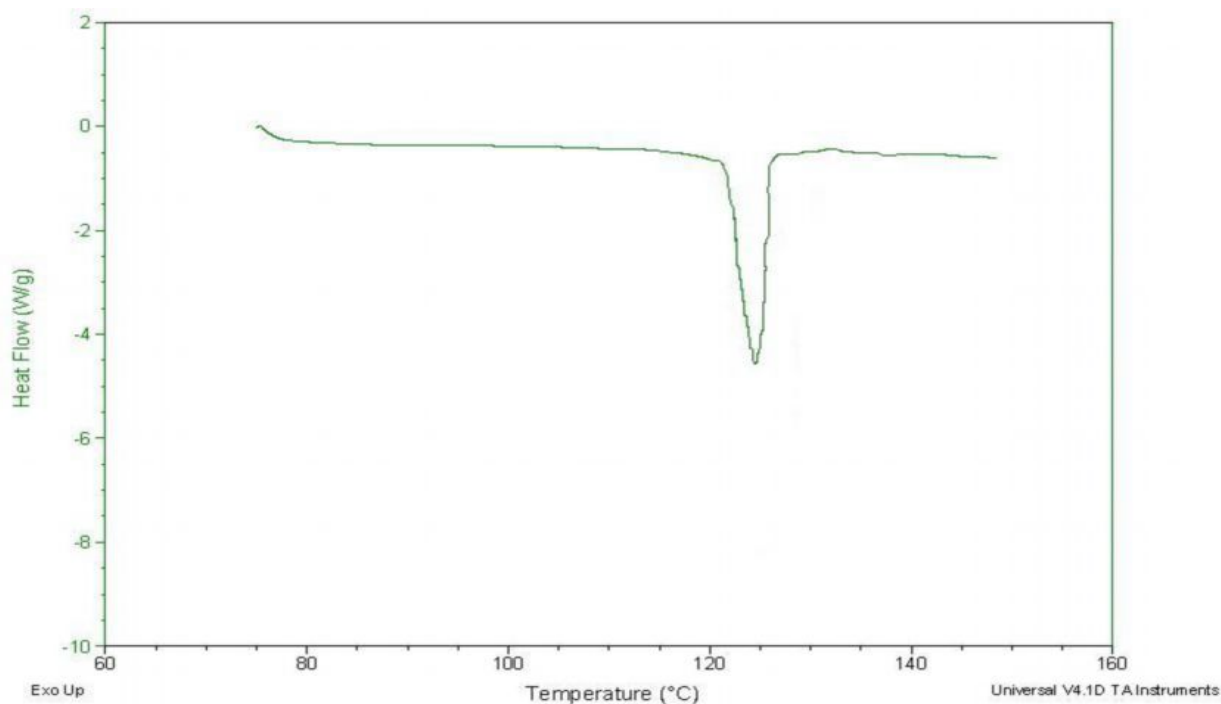


Figure 2: Differential scanning calorimetry of Cefpodoxime Proxetil.

Table 3: Drug content and saturation solubility of different formulations.

Product Name	Drug Content (%) [*]	Saturation Solubility (µg/ml)
Pure Drug	--	72.11±(1.56)
SD1	95.23±1.21	141.67±(1.88)
SD2	97.15±1.29	150.29±(2.34)
SD3	94.75±2.01	154.45±(1.81)
SD4	96.64±1.45	161.48±(1.92)
SD5	99.12±1.76	167.23±(1.72)
SD6	96.49±1.93	170.34±(1.32)
SD7	95.78±1.41	171.92±(2.52)
PM5	96.39±2.11	121.78±(2.71)

^{*}Values represent mean of three individual experiments.
Data in parenthesis represent S.D.

Dissolution Studies

The dissolution rate of pure Cefpodoxime Proxetil was very poor and during 120 min a maximum about 32.56% of the drug was released. The reason for the poor dissolution of pure drug could be poor wettability and/or agglomeration or particles size. It was found that the dissolution rate of the drug increased according to increasing amount of hydrophilic carrier (urea) in physical mixture batches. This was due to the increase in solubility of drug by the presence of hydrophilic carrier surrounding the drug particles. Figure 3 shows comparative release profile of various solid dispersions of Cefpodoxime Proxetil with urea, physical mixture containing 1:5 ratio of drug: urea and pure drug. From release profile it can be seen that dissolution of Cefpodoxime Proxetil in solid dispersions increase with increase in urea up to 1:5

ratio of drug: urea. This increase in the dissolution rate may due to increase in drug wettability, solubilization of drug by carriers. After this particular ratio with further increase in the amount of urea, the dissolution rate was decreased. The decrease in dissolution may be due to the higher amounts of carrier takes time to dissolve. It was found that the drug release from physical mixture is greater than that of the pure drug and slower than that of solid dispersions. From the results, it was conclude that the dissolution rate of Cefpodoxime Proxetil increased by preparing solid dispersion with urea.

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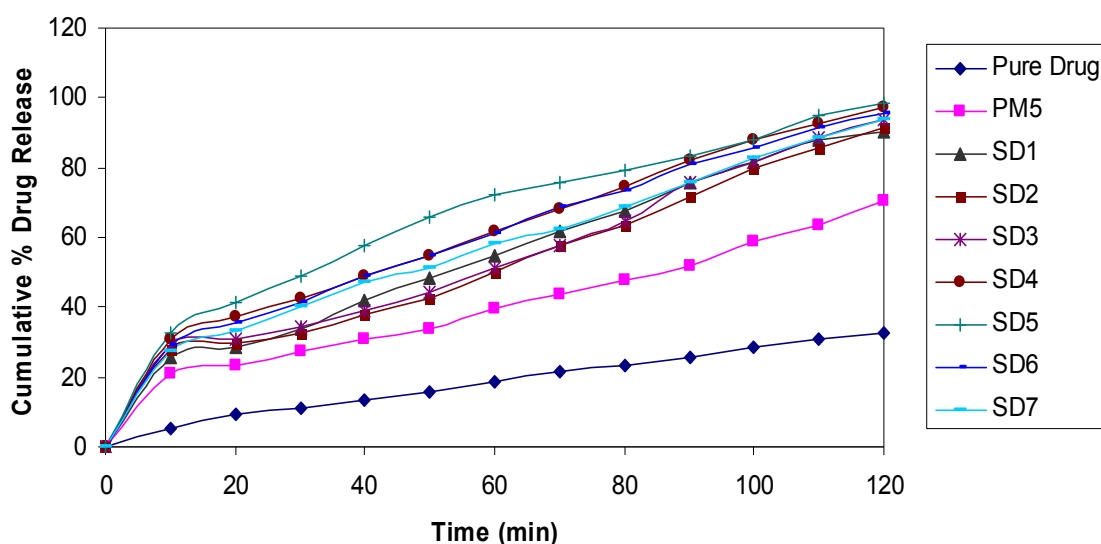


Figure 3: Comparative *in vitro* release profiles of Cefpodoxime Proxetil from solid dispersions and physical mixture containing urea.

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