Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Research Article

Received on: 10-06-2015
Accepted on: 13-06-2015
Published on: 15-06-2015

Corresponding Author:

***Kashish Aziz,**
Department of Pharmaceutics,
JamiaHamdard,
New Delhi (India) 110062
Mob No. 09818337912.

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*Email Id-drkashish27@gmail.com

Formulation and Evaluation of Cefpodoxime Proxetil Solid Dispersion: An Approach for Dissolution Enhancement of Cephalosporin

Kashish Aziz*[1], Babar Iqbal[1], Azim Akhtar[2], Kanchan Kohli[1], Sanjula Baboota[1], Abdul Mateen[2]

ABSTRACT

Cefpodoxime Proxetil is an broad spectrum, third generation cephalosporin drug used in the treatment of skin infections, upper respiratory tract and urinary tract infections. Furthermore it shows low aqueous solubility, poor dissolution and hence low oral bioavailability. In present study an attempt has been made to enhance the aqueous solubility of Cefpodoxime Proxetil and hence its availability in aqueous media. Solid dispersion (SD) of Cefpodoxime Proxetil using soluplus as carrier was prepared by solvent evaporation method. The prepared solid dispersion was characterized using FTIR, SEM, DSC and evaluated for *In vitro* drug release. FTIR and DSC results indicated chemical compatibility between drug and carrier. Moreover DSC thermogram of SD and pure drug suggested the change in crystallinity of Cefpodoxime Proxetil. SEM showed that the physical structure of Cefpodoxime Proxetil was modified from crystalline to amorphous. Dissolution rate of Cefpodoxime Proxetil, physical mixture and SD were found 46.3%, 65.04% and 91.04 % respectively Which concluded a significant improvement in *in vitro* drug release profile. Solid dispersion of Cefpodoxime Proxetil and soluplus prepared in 1:10 ratio by solvent evaporation method resulted in enhancement of aqueous solubility of Cefpodoxime Proxetil and hence improved dissolution.

Key-words: Cefpodoxime Proxetil, Solid Dispersion, Soluplus and BCS class-II

Cite this article as:
Kashish Aziz, Babar Iqbal, Azim Akhtar, Kanchan Kohli, Sanjula Baboota and Abdul Mateen, Formulation and Evaluation of Cefpodoxime Proxetil Solid Dispersion: An Approach for Dissolution Enhancement of Cephalosporin, Asian Journal of Pharmaceutical Technology & Innovation, 03 (12); 2015. www.asianpharmtech.com

1 Department of Pharmaceutics, JamiaHamdard New Delhi (India) 110062
2 Unicure India Ltd. Noida (India) 201301

INTRODUCTION:

Drug release is a crucial and limiting step for oral bioavailability, particularly for BCS class II drugs, therefore by improving the drug release profile of these drugs, it is possible to enhance their bioavailability[1-2]. Cefpodoxime Proxetil is broad spectrum, third generation cephalosporin drug and prescribed for the treatment of skin infections, upper respiratory tract and urinary tract infections. Moreover it is orally absorbed drug and has only 50% oral bioavailability[3]. Poor oral bioavailability of Cefpodoxime Proxetil are mainly attributed due to its low water solubility, gelation particularly in acidic pH and pre-absorption luminal metabolism[3-7]. Due to poor water solubility, dissolution is rate limiting step for its absorption. However methods like complexation, lipid based systems, micronization, nanonization, co-crystals, solid dispersions and solubilization etc. have been investigated to enhance the dissolution and thereby oral bioavailability of poorly water soluble drugs[8]. Solid dispersion (SD) is one of the most successful techniques to improve dissolution rate of poorly aqueous soluble drugs and it can be defined as dispersion of one or more pharmaceutically active ingredient(s) in an inert carrier or matrix[1]. Moreover, dispersed compounds may be in individual molecule unities or in clusters, such as in particles[9]. Furthermore, drug release is driven by the polymer properties; it is simple, economic and advantageous[1]. SDs can be prepared by fusion-melt method, Kneading method, solvent evaporation method and hybrid fusion-solvent evaporation method[9-11]**.** Soluplus is a novel polymer with amphiphilic properties. It is a graft copolymer of polyvinyl caprolactum (57%)-polyvinyl acetate (30%) - poly ethylene glycol (PEG 6000-13%). Several reports on the use of soluplus in solid dispersion as a carrier have been published so far. In addition to its use as polymeric matrix for SD it can also be used to solubilize poorly soluble drugs in aqueous media[12]. In the present study an attempt was made to enhance the aqueous solubility and hence dissolution of Cefpodoxime Proxetil followed by selecting soluplus as carrier using solvent evaporation method. Prior to development of SD, the proportion of drug & carrier was optimized by preparing physical mixtures obtained by simple mixing and evaluated for *in vitro* drug release in 45 min. SD was characterized using FTIR, SEM, DSC & *in vitro* studies.

MATERIALS AND METHODS

1.0 Material

Cefpodoxime Proxetil was received as gift sample from Ranbaxy Research Laboratory (Gurgaon ,India). Soluplus was received from BASF (Ludwigshafen, Germany). Solvent and reagents used were all of analytical reagent grade.

2.0 Optimization of Cefpodoxime Proxetil concentration for SD

Physical mixtures were prepared by simple mixing of drug and soluplus in ratio 1:1, 1:3, 1:5, 1:7 and 1:10. Drug release profile in 30 minutes was determined by performing *in vitro* dissolution using USP apparatus –II (paddle apparatus)in glycin buffer (pH 3) at 37± 0.1^{0}C with 75 rpm[13]

3.0 Preparation of SD

Solid Dispersion of Cefpodoxime Proxetil was prepared by solvent evaporation method. Cefpodoxime Proxetil and Soluplus were accurately weighed and dissolved in methanol followed by solvent evaporation. Dried film so obtained was passed through sieve no. 30 and further dried at 25°C temperature until a constant weight was obtained[14].

CHARACTERIZATION OF SD

1.0 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) analysis of Cefpodoxime Proxetil, soluplus and SD were performed using a DSC Q 1000 (Perkin Elmer pyres 6 DSC, Massachusetts, United States) to characterize the thermal behaviour of the pure drug, carrier and SDs. Samples were accurately weighed into aluminium pans, then hermetically sealed with aluminium lids and heated 50 to 200 ^{0}C at a heating rate of 10 ^{0}C/min under constant purging of nitrogen (20 mL/min)[7].

2.0 Infrared (IR) Spectroscopy

IR spectroscopy of solid dispersion of Cefpodoxime Proxetil, soluplus and SD was recorded using Perkin Elmer FTIR spectrophotometer (Shimadzu, Kyoto, Japan). The spectrum was recorded in the range of 400-4000 cm^{-1}. The

procedure consisted of dispersing the sample in KBr followed by gentle mixing. The spectrum was scanned at a resolution of 0.15 cm^{-1} and scan speed was 16 scans/s[15].

3.0 Scanning Electron Microscopy (SEM)

Scanning electron microscope (Zeiss EVO-50, Oberkochen, Germany) was employed for analysis of surface morphology of SD and physical mixture (PM). Samples were mounted on alumina stubs using double adhesive tape, coated with gold in Hitachi HUS-GB vacuum coating unit and observed at a voltage of 10 KV.

***4.0 In vitro* release**

Dissolution studies of Cefpodoxime Proxetil, soluplus and SD were performed using hard gelatin capsule. *In vitro* release studies were carried out using USP paddle apparatus in glycin buffer (pH 3) at 37± 0.1^{0}C with 75 rpm. At predetermined time interval, 5 ml samples were withdrawn and replaced with equal volume of fresh media. Samples were filtered through 0.22 µm nylon syringe filter and appropriately diluted with glycin buffer (pH 3). Diluted samples were assayed for drug concentration using UV spectrometry (Shimadzu, Kyoto, Japan) at 258nm. Dissolution tests were performed in triplicate and percentage of the drug dissolved at different time intervals was estimated[16].

RESULT AND DISCUSSION

1.0 Result of optimization of adsorbent carrier concentration

Result of *in vitro* drug release of physical mixture of Cefpodoxime Proxetil and soluplus are shown in table -1 which indicated that drug release is increased with soluplus content and maximum dissolution was observed at 1: 10 ratio. However there was no significant change in dissolution rate beyond the 1: 7ratio (**Fig-1)**.

Table-1 Percent drug released from the physical mixture of Cefpodoxime Proxetil and soluplus

Cefpodoxime Proxetil: soluplus	Mean % drug released ± SD (n = 3)
1:1	09.01 ± 1.5
1:3	21.41 ± 7.2
1:5	46.12 ± 7.4
1:7	57.34± 4.5
1:10	57.81 ± 2.0

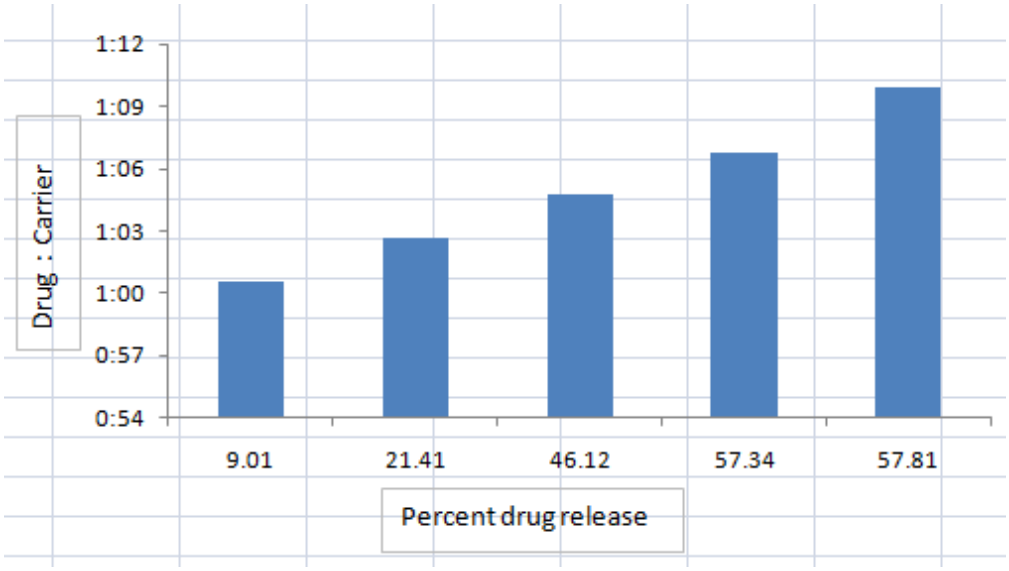

Figure-1: Percent drug released from the physical mixture of Cefpodoxime Proxetil and soluplus

2.0Result of DSC study

The DSC curve shows that a sharp endothermic peak appeared at about 100^{0}C for Cefpodoxime Proxetil. A broad endothermic peak was observed at about 322^{0}C for soluplus (**fig-2**). The results suggested the formation of the eutectic solid dispersion. Slightly broaden peak of Cefpodoxime Proxetil in thermogram of SD suggested a change in crystallinity of drug.

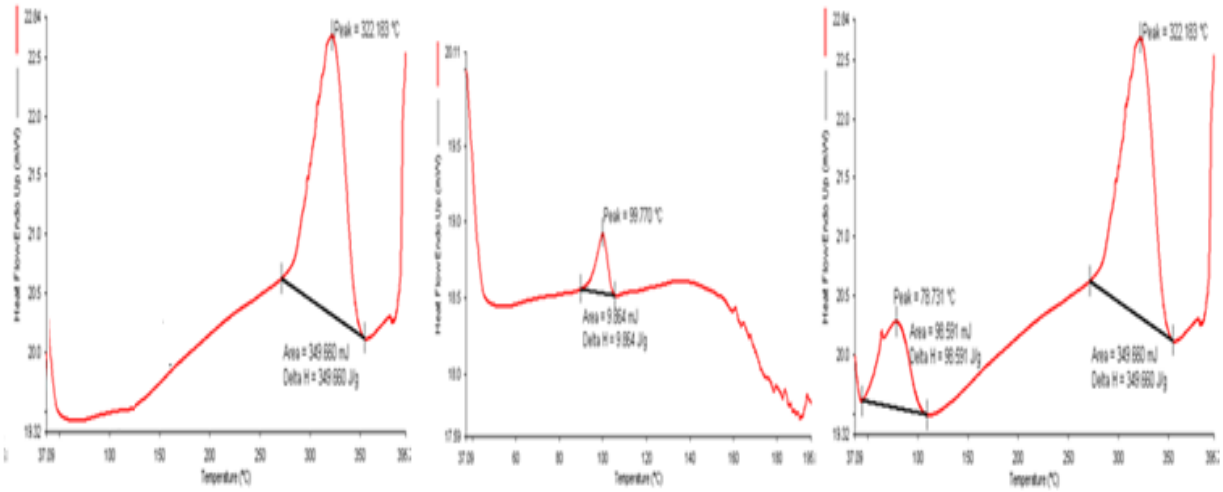

Figure-2: DSC thermograms of Soluplus, Cefpodoxime Proxetil and SD.

3.0Result of FTIR study

In FTIR spectra of Cefpodoxime Proxetil, soluplus and SD were revealed characteristic peak at 3311 cm^{-1} indicating free O-H stretching. This peak was not found in the spectra of SD of CEFPO. Although characteristic stretching of the CEFPO was present in the FTIR spectra of the physical mixture where as these bands were found missing in the FTIR spectra of the SD. The SD showed the characteristics stretching of soluplus at 1738, 1637, 1538-1445, 1372 and 1241 cm^{-1}. The missing of characteristic stretching showed the successful formation of solid dispersion.

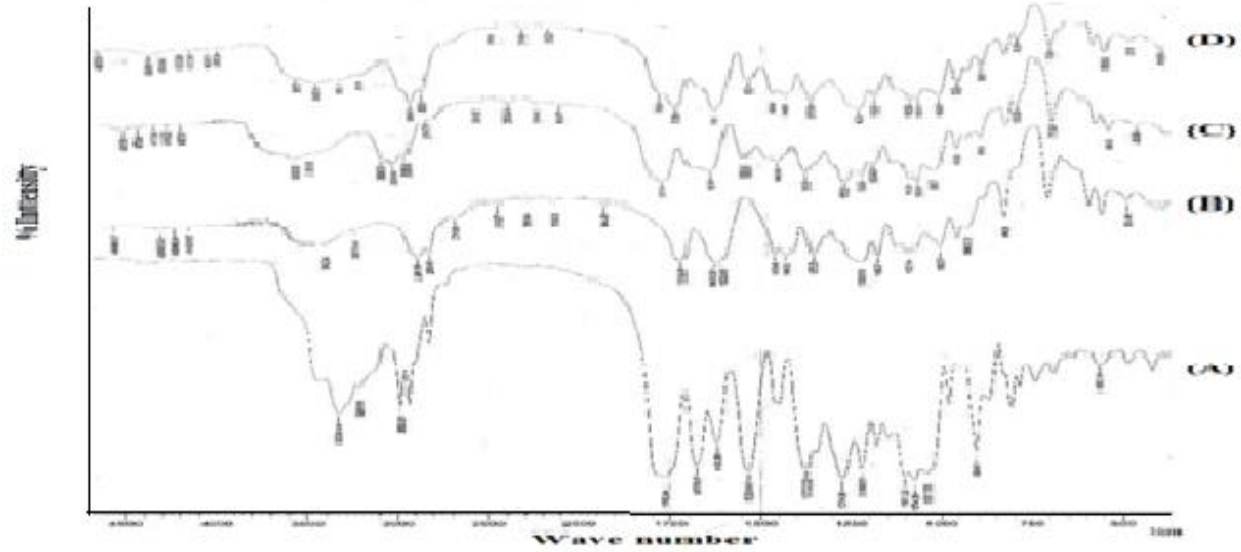

Figure -3: Comparative evaluation of FTIR spectra of pure CEFPO (A), pure soluplus as a carrier (B), physical mixture of CEFPO-soluplus (C) and SDs of CEFPO (D)

4.0 Result of SEM study

The surface morphology of solid dispersion and physical mixture (PM) observed by scanning electron microscopy shown in figure -4. SEM of SD showed fine crystals of drug entangled in polymeric matrix as compared to physical mixture in which cluster drug particles are deposited on carriers. It may be one of the causes for increased in solubility of Cefpodoxime Proxetil

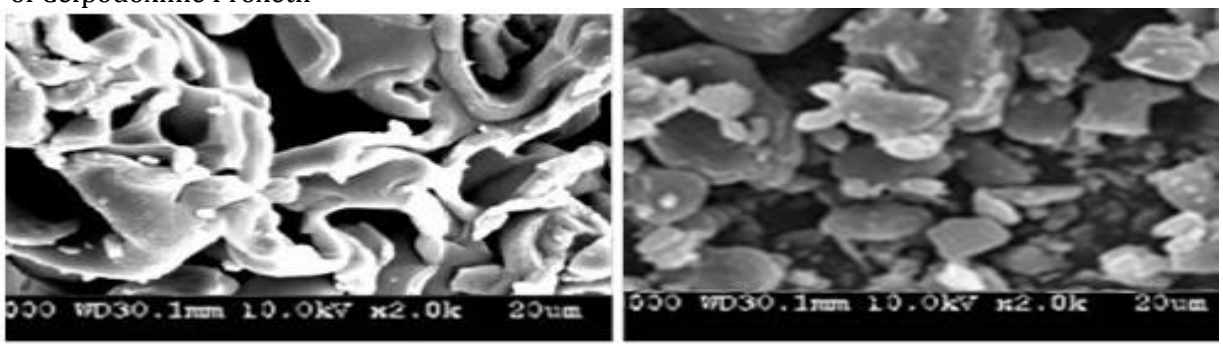

Figure-4: SEM of Cefpodoxime Proxetil and soluplus (1:10) formulations. A- Solid dispersion and B- Physical mixture

5.0 Result of *In vitro* dissolution study

The dissolution rate of Cefpodoxime Proxetil, physical mixture and solid dispersion were found 46.3%, 65.04% and 91.04% respectively. Result revealed that dissolution of Cefpodoxime Proxetil in solid dispersion is improved significantly as compared to pure drug and physical mixture **(Table-2).**

Table-2 Cumulative percent *in vitro* drug release (± SD, n=6)

Time (min)	Cefpodoxime Proxetil Mean cumulative % drug released	Physical Mixture Mean cumulative % drug released	SD Mean cumulative % drug released
5	07.12 ± 0.65	10.38 ± 0.74	21.38 ± 0.74
10	14.09 ± 0.74	19.58 ± 0.59	45.58 ± 0.59
15	29.03 ± 3.6	36.43 ± 0.59	65.43 ± 0.59
30	38.67 ± 1.2	52.88 ± 1.2	87.88 ± 1.2
45	46.3 ± 0.89	65.04 ± 3.5	91.04 ± 3.5

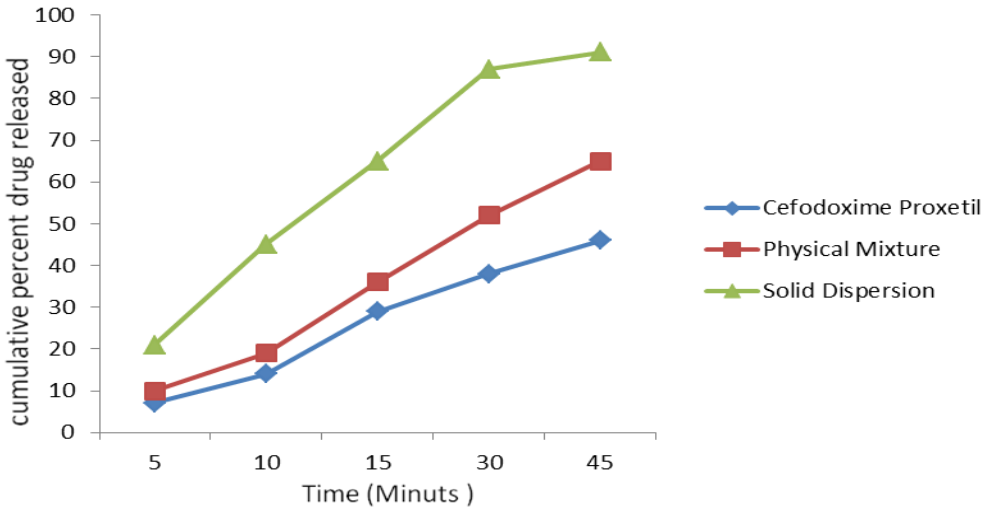

Figure-5: Dissolution release profile of Cefpodoxime Proxetil, physical mixture and solid dispersion

Conclusion

Solid dispersion of Cefpodoxime Proxetil using soluplus as carrier was successfully prepared by solvent evaporation method. SD, pure drug and physical mixture were comparatively evaluated for cumulative percent *in vitro* drug release.There was a significant improvement in the *in vitro* dissolution rate of drug as compared to pure drug and physical mixture.

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Abbreviation used

SD: Solid Dispersion
SEM: Scanning Electron Microscopy
DSC: Differential Scanning Calorimetry
FTIR: Fourier Transform Infrared
nm: nanometer
°C: Celsius
KBr: Potassium Bromide
BCS: Biopharmaceutical Classification System
CEFPO: Cefpodoxime Proxetil