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Fabrication and Characterization of Cefopodoxime Proxetil Solid Dispersion for Solubility Enhancement

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ABSTRACT

Cefopodoxime Proxetil belongs to BCS class IV and used in treatment of upper respiratory tract and urinary tract infections. Solid dispersions (SDs) are one of the most promising strategies to improve the solubility, dissolution and ultimately oral bioavailability of such poorly water soluble drugs. The main objective of the present research was to formulate Cefopodoxime Proxetil solid dispersion employing two methods namely hot melt granulation and solvent evaporation method. The PEG 4000 and PEG 6000 were used as carrier in varied proportion (1:1, 1:2, 1:3 and 1:4 w/w). Results of FT-IR spectra revealed no potential chemical incompatibility between drug and excipients. Enhancement in the percent drug released and dissolution rate was observed in SD of PEG 6000 as to PEG 4000 and pure drug. Drug release kinetics studies revealed that the drug release from the formulations followed non-fickian diffusion and the best fitted model for drug release for Korsmeyer Peppas Model. No sharp peaks were observed in both solid dispersions (comprising PEG 4000 & PEG 6000) in PXRD spectra revealing the formation of amorphous product. Similar results were observed in DSC studies indicating disappearance of sharp fusion endothermic peak i.e. conversion of crystalline form into amorphous form. These results were further supported by SEM studies showing disappearance of crystal habit in these formulations.

Keywords: Solid dispersions (SDs), dissolution, hot melt granulation method, solvent evaporation method.

INTRODUCTION

Solubility is one of the important parameters to deliver the oral dosage forms to a target site with desired concentration in systemic circulation for achieving required pharmacological response. [1] But, more than 90% of drugs developed or approved in pharmaceutical industry have poor solubility, poor permeability, or both. [2-4] Such poorly water-soluble drugs often require high doses in order to reach with optimum therapeutic plasma concentrations at target site after oral administration.

Cefopodoxime Proxetil (CP) is an orally absorbed, broad spectrum, third generation cephalosporin ester implicated in treatment of skin infections, upper respiratory tract and urinary tract infections. It belongs to BCS class IV (i.e. low solubility and low permeability). When administered orally, it shows poor gastrointestinal absorption because of its low dissolution rate in aqueous media and poor permeability. [3] However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. Increased efforts is been done for the development of pharmaceutical formulations with enhanced oral bioavailability of API by enhancing its solubility as well permeability.

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There are numerous approaches available and reported in literature to enhance the solubility of such poorly water-soluble drugs like particle-size reduction which includes micro sizing and nanosizing, salt formation, solubilization, and complexation with β cyclodextrins. [5] All these methods suffer from one or the other drawbacks. The formulation of drugs having low aqueous solubility using solid dispersion method has been an active area of research to overcome the problem associated with above mentioned methods. [6]

Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. [7] The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles by various methods such as melting method, hot melt granulation, hot melt extrusion and solvent evaporation method. [8] The main objective of the present investigation was to enhance the solubility and dissolution rate of Cefopodoxime Proxetil by formulating its solid dispersions into a oral dispersible tablets. [9]

In the present work study the solid dispersion of CP was formulated by employing two methods namely hot melt granulation and solvent evaporation method. Solid dispersions of Cefopodoxime Proxetil were developed with different water soluble carriers i.e. PEG 4000 and PEG 6000 in the proportion of 1:1, 1:2, 1:3 and 1:4 w/w. PEG is freely soluble in water and releases the entrapped drug as fine colloidal particles in presence of aqueous media. [10]

Table 1: Formulation codes of CP solid dispersions with different carriers prepared in varying proportions employing different methods.

Carrier	Ratios (w/w)	Formulation prepared by different methods	
		Hot melt granulation	Solvent evaporation
PEG 4000	1:1	CPEhg1:1	CPEse1:1
	1:2	CPEhg1:2	CPEse1:2
	1:3	CPEhg1:3	CPEse1:3
	1:4	CPEhg1:4	CPEse1:4
PEG 6000	1:1	CPGhg1:1	CPGse1:1
	1:2	CPGhg1:2	CPGse1:2
	1:3	CPGhg1:3	CPGse1:3
	1:4	CPGhg1:4	CPGse1:4

MATERIALS AND METHODS

Preparation of Physical mixtures

Drug and carriers (PEG 4000 and PEG 6000) are accurately weighed and mixed in different ratios (1:1, 1:2, 1:3, 1:4 w/w) are thoroughly blended in pestle and mortar for 5 min., and then carefully sieved through 22 mesh sized sieve. The prepared mixtures were kept in desiccators before further study. [11]

Preparation of Solid Dispersions: Solid dispersions were formulated using various water-soluble carriers *viz.* PEG 4000 and PEG 6000 in varying proportions (1:1, 1:2, 1:3, 1:4 w/w) by solvent evaporation and hot melt granulation method. [12]

Solvent Evaporation Method: Drug was accurately weighed and dissolved in 20 ml of methanol using magnetic stirrer and after complete solubilization in methanol, the carrier (PEG) was added. The solution was heated to 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. The process of evaporation was opted until the constant weight was obtained. Solid dispersions prepared were crushed, pulverized and sifted through mesh no. 22 to get the uniform particle size of solid dispersion. Different code names were given to different ratios (Table 1). [13]

Hot Melt Granulation: Each carrier (PEG 4000 and PEG 6000) were accurately weighed and melted in a china dish on a water bath maintained at their respective melting temperatures. The CP was added to the molten carriers and mixed thoroughly with a glass rod for 10 min. The mixture was cooled rapidly by placing the china dish in an ice bath to get uniformly solidified dispersion. The prepared solid dispersion was sieved and stored in vacuum desiccator. [14]

Evaluation of Prepared Solid Dispersions

Drug Excipient compatibility Studies by FTIR Spectroscopy

To check any interaction between the drug, carriers and excipients, FTIR studies was carried out on drug (Cefopodoxime Proxetil), physical mixtures as well as on treated sample. Figure 1 shows the FTIR spectra of CP, physical mixtures and treated samples of drug with different carriers *viz* PEG 4000 and PEG 6000 in the proportion of 1:1 w/w.

Determination of Percent Yield: The percent yield was calculated using the equation 1.

$$\text{Percent yield} = \frac{\text{Total recoverable weight}}{\text{Total theoretical weight}} \times 100 \quad (1$$

Determination of Percent Drug Content: Drug content was calculated by dissolving solid Dispersion containing drug equivalent to 10 mg of Cefopodoxime Proxetil in 10 ml of methanol, filtering and analyzing at 235 nm by UV spectrophotometer. [15] The percent drug content was calculated using the equation 2.

$$\text{Percent drug content} = \frac{\text{Absorbance of sample}}{\text{Absorbance of reference}} \times 100 \quad (2)$$

***In vitro* Dissolution studies:** The best method was selected out of three methods applied to prepare solid dispersion on the basis of percent drug release. On all the selected formulations, dissolution studies were performed using USP apparatus type II (equipped with paddle). SDs powder equivalent to 100 mg drug was put in 900 ml of serum gastric fluid 0.1 N HCl without enzyme as dissolution media. The rotation speed of paddle was set at 75 rpm and the temperature maintained at 37 +/- 0.5°C. In all experiments, 10 ml of dissolution sample was withdrawn at 5, 10, 15, 20, 30, 45, 60 minutes and replaced with an equal volume of fresh medium to maintain the sink conditions. The filtered samples were analyzed by UV spectrophotometer at 235 nm. Appropriate correction for drug and volume losses during each sampling was applied by using equation 3.

$$C_i = A_i\left(\frac{V_s}{V_t}\right).\sum_{i=1}^{n-1} A_i\left[\frac{V_t}{V_t - V_s}\right] \quad (3)$$

Where, C_i is the corrected absorbance of i^{th} observation, A_i is the observed specific absorbance, V_s is the sample volume, and V_t is the total volume of dissolution medium.

Determination of Dissolution Parameters: Percent released at three time points (PD_{10}, PD_{30} and PD_{60}) was calculated from the dissolution data.

Kinetic Modeling: *In vitro* drug release data of formulation amongst each carrier which showed ceiling aptness in dissolution characteristics was fitted to various release kinetic models (Table 2) *viz* Zero order, First-order, Higuchi, Hixson-Crowell, Korsmeyer–Peppas model.

Table 2: Representative equations of release kinetic models

Kinetics		Equation
Zero order	:	$M_o - M_t = k_o t$
First order	:	$\ln(M_o/M_t) = k_1 t$
Korsmeyer Peppas	:	$M_t/M_\infty = kt^n$
Higuchi	:	$M_t = {}_K\sqrt{T}$
Hixson Crowell	:	$(W_o)^{1/3} - (W_t)^{1/3} = K_{1/3}t$

Where, M_o, M_t and M_∞ correspond to the drug amount taken at time equal to zero, dissolved at a particular time, t, and at infinite time, respectively. The terms, W_o and W_t refer to the weight of the drug taken initially and at time t, respectively. Various other terms viz. k_o, k_1, k, K and $k_{1/3}$ refer to the release kinetic constants obtained from the linear curves of zero-order, first-order, Korsemeyer–Peppas, Higuchi model and Hixson-Crowell cube root model respectively.

Differential Scanning Calorimetry (DSC) Studies

DSC thermograms were obtained on DSC, Q20, TA Instruments-Waters LLC, USA. The calorimeter was calibrated for temperature and heat flow accuracy using the melting of pure indium (mp 156.6°C and ΔH of 25.45 Jg^{-1}). A mass between 2-8 mg was taken into the aluminium pan, covered with lid and sealed. DSC curves were obtained under a nitrogen purge of 50 ml per minute at a heating rate of 10°C per minute with the temperature range from 50-350°C.

Powder X-Ray Diffraction (PXRD) Studies

The PXRD pattern was recorded using high power powder x-ray diffractometer (XPERT-PRO, PANalytical, Netherlands, Holand) with Cu as tube anode. The diffractograms were recorded under following conditions: voltage 40 kV, 35 mA, angular range 5 and fixed divergence slit. Care was taken to avoid crystal changes during sample preparation. Approximately 200 mg of samples were loaded into the sample holder, taking care not to introduce preferred orientation of the crystals.

Scanning Electron Microscopy (SEM)

The shape and surface characteristics of the ground mixtures were studied by SEM. The SEM analysis was carried out using a scanning electron microscope (Hitachi S-3600 N, Japan). Prior to examination, samples were mounted on an aluminum stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV.

RESULTS AND DISCUSSION

Percent Yield

Percent yield and drug content for solid dispersion formulations containing PEG 4000 were calculated using formula given in equation 2. Calculated percent yield of eight formulations of PEG 4000 prepared by HG and SE lies in range of 92.3 to 97.8 % w/w. Whereas the percent yield of PEG 6000 formulations prepared by HG and SE methods varied between 93.7 to 98.3%.

Out of all the formulations CPGse1:4 containing PEG 6000 prepared by SE have shown highest yield (98.3 %) whereas CPEhg1:1 containing PEG 4000 prepared by HG have produced minimum yield (93.7%)

Drug Content

The drug content in the SD formulations containing PEG 4000 as well as PEG 6000 is above than 86 to 96.8% as shown in Table 3. The drug content was found to be minimum (89%) for CPEhg1:1 (PEG 4000) whereas CPGse1:4% (PEG 6000) have shown maximum (96.8%) drug content. PEG 6000 containing formulations showed better results than PEG 4000 formulations because of its high molecular weight which leads to formation of fine microcrystal's and absence of drug clusters.

***In vitro* Release Studies of Formulations Containing PEG 4000**

The best method was selected out of three methods applied to prepare solid dispersion on the basis of percent drug release. On all the formulations, dissolution studies were carried out in SGF 0.1 N HCl without enzyme.

Table 3: Percent yield and drug content of solid dispersions having PEG 4000 and PEG 6000

S. No.	Formulation using PEG 4000	Percent yield (w/w) (%)	Drug content (w/w) (%)	Formulation using PEG 6000	Percent yield (w/w) (%)	Drug content w/w (%)
1.	**CPEhg1:1**	92.3	89.0	**CPGhg1:1**	93.7	93.4
2.	**CPEhg1:2**	93.5	91.4	**CPGhg1:2**	94.9	89.3
3.	**CPEhg1:3**	96.8	92.6	**CPGhg1:3**	95.8	92.0
4.	**CPEhg1:4**	97.3	94.8	**CPGhg1:4**	96.7	95.1
5.	**CPEse1:1**	94.07	93.0	**CPGse1:1**	95.3	94.3
6.	**CPEse1:2**	95.8	95.7	**CPGse1:2**	96.4	96.2
7.	**CPEse1:3**	96.2	96.5	**CPGse1:3**	97.7	96.6
8.	**CPEse1:4**	97.8.	96.8	**CPGse1:4**	98.3	98.8

Dissolution data of physical mixtures of drug with PEG 4000 in different proportions indicates the existence of ascending trend in both maximum percent release and dissolution rate i.e., CPEpm1:1 < CPEpm1:2 < CPEpm1:3 < CPEpm1:4. Maximum percent released and overall dissolution rate of CPEpm1:4 were observed to be highest (45.32%).

***In vitro* Release Studies of Formulations Containing PEG 6000**

In vitro drug release data concluded that as the increase percent release due to increased wettability and decreased surface tension of drug.

From graph (figure 1a), it is clear that dissolution profile of CP in PEG 4000 PM formulations slowly increased with time but after 45 min dissolution profile becomes constant. Results of dissolution studies of SDs indicated the existence of ascending trend in dissolution profile i.e. 1:1 < 1:2 < 1:3 < 1:4 w/w proportion of carrier. Increased solubility of CP was due to encapsulation of drug inside the diffusion layers of PEG. It followed the diffusion controlled release of the drug from the polymer matrix. The improvement of dissolution profile may be due to strong hydrophilic character. Formulations prepared by hot melt granulation as well as solvent evaporation methods revealed increased rate of dissolution with increased level of carrier in formulations in the order of 1:1 <1:2 <1:3 <1:4 w/w.

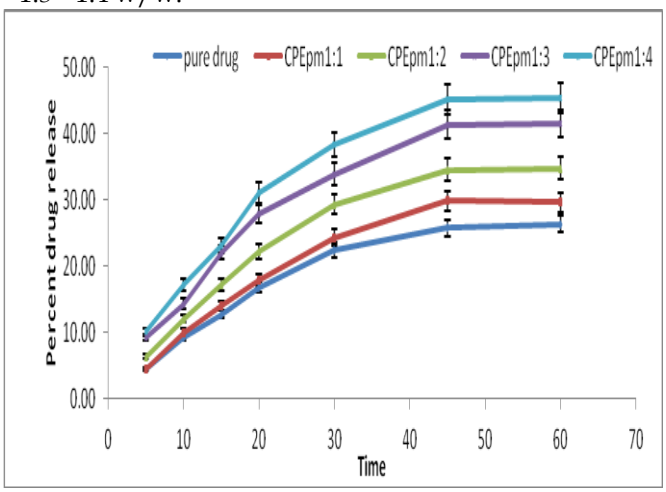


Fig. 1a: *In vitro* release graph of formulations containing PEG 6000

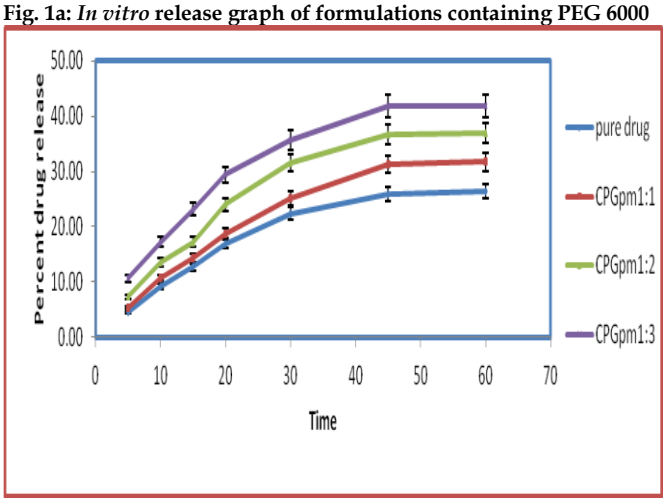


Fig. 1b: *In vitro* release graph of formulations containing PEG 6000

Similar results were found with solid dispersion formulations containing PEG 6000 as shown in figure 1 b. However, formulations prepared with 1:1 w/w PEG 6000 showed minimum release as compared with 1:2, 1:3 and 1:4 w/w carrier formulations. The order of drug release was found to be CP<PM<SD (SDhg<SDse).

Dissolution Parameters of Formulations Containing PEG 4000 and PEG 6000

For each formulation of PEG 4000, dissolution parameters (PD_{10}, PD_{30}, and PD_{60}) were calculated and presented graphically (Figure 2a). In case of physical mixture, *in-vitro* drug release increases with time as well as with increase in concentration of carriers as compared to drug. For each formulation of PEG 6000, dissolution parameters (PD10, PD30, and PD60) was calculated and presented graphically.

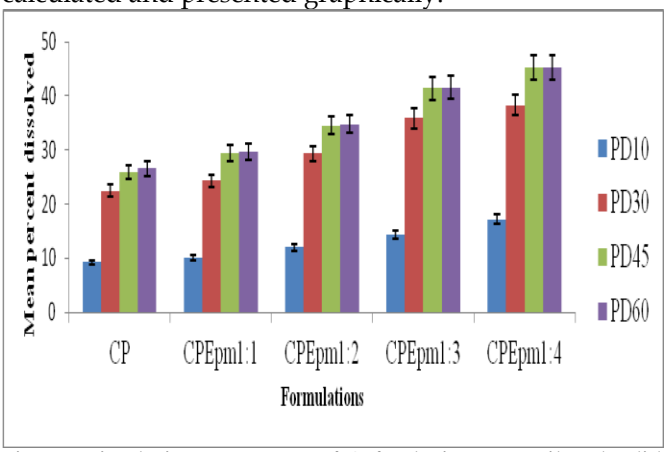


Fig. 2a: Dissolution parameters of Cefpodoxime proxetil and solid dispersion of drug with PEG 4000 formulations in different ratios

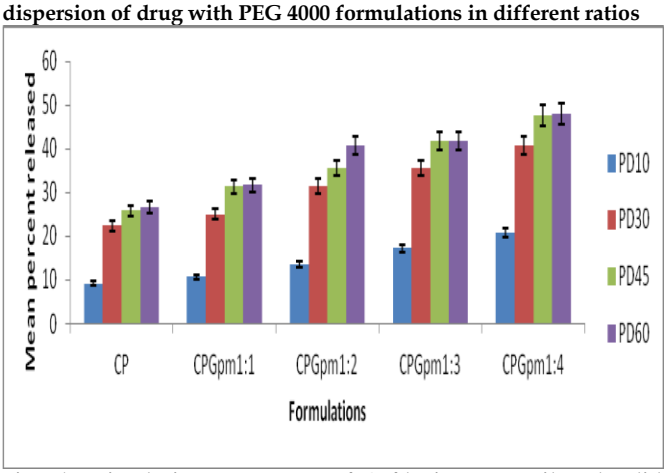


Fig. 2b: Dissolution parameters of Cefdoxime proxetil and solid dispersion containing PEG 6000 formulations in different ratios.

The solubility and dissolution studies showed improved solubility of CP through solid dispersion with PEG 6000 than with PEG 4000, due to the reason that the high molecular weight of PEG 6000 which leads to formed fine microcrystal in formulation and absence of drug clusters. The formulation containing CPGse1:4 (PEG6000) was found to be better as compared with other formulation CPGhg1:4 (Figure 2b).

Kinetic Modelling of PEG 6000 Formulation (CPGse1:4) with Best Dissolution Characteristics

Kinetic models (Zero order model, First order model, Korsmeyer Peppas model, Higuchi model and Hixson

Crowell model) was applied to best formulation (CPGse1:4).

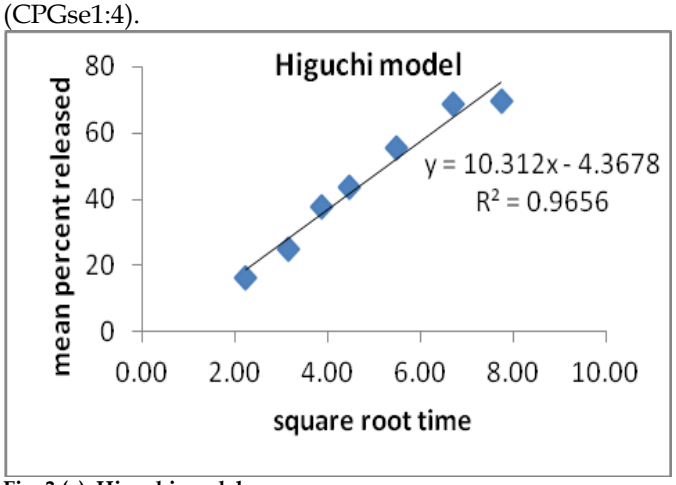


Fig. 3 (a): Higuchi model

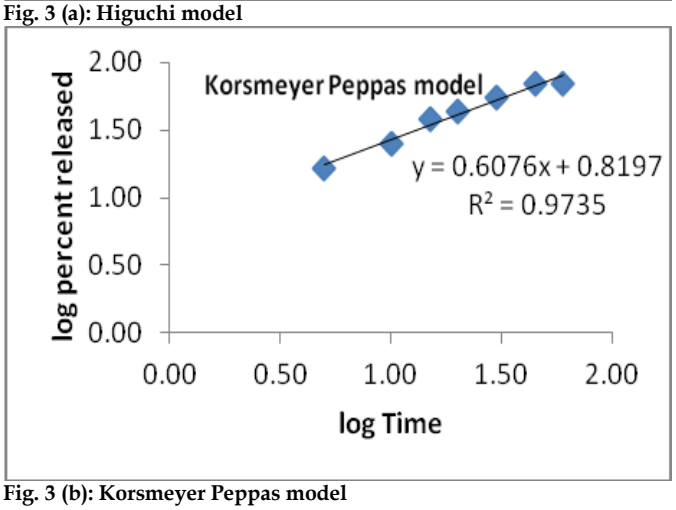


Fig. 3 (b): Korsmeyer Peppas model

Table 4: Regression parameters of CPGse1:4 obtained after fitting the data to various release models

Regression parameters	Zero order	First order	Korsmeyer peppas model	Higuchi model	Hixson crowell model
Slope	0.975	0.008	0.607	10.31	0.023
R^2	0.897	0.945	0.973	0.965	0.933

Table 4 enlists the regression parameters obtained after fitting various release kinetic models to the *in-vitro* dissolution data of CPEse1:4. The value of regression coefficient indicated that the goodness of fit for various models followed in the order of Korsmeyer Peppas > Higuchi > First order > Hixson Crowell > Zero order. By and large, the Korsmeyer Peppas model described drug release kinetics in the most befitting manner. Value of the slope of CPGse1:4 were 0.607 which depicted that it followed the non-fickian diffusion as possible mechanism of drug release.

On comparing results of all the best formulations containing PEG 4000 and PEG 6000, it was concluded that CPGse1:4 have shown highest percent release of drug from polymer matrix and were chosen for further study.

Powder X-ray Diffraction (PXRD) Studies

The powder X-ray diffraction studies were carried out on given powder of samples. PXRD pattern of CP showed characteristics diffraction peaks at (2θ) 9.63°, 11.24°, 15.90°, 16.889°, 17.56°, 18.04°, 19.74°, 22.84°, 28.68°, 33.51°, 35.17°, and 38.73°On comparing the position and the relative intensities of the major peaks of SDs prepared by using PEG 4000 and PEG 6000 with those of pure components, a distinct difference was visible which confirms the differences in the crystallinity of the different forms indicating its crystalline nature. Moreover, much reduced number of signals, with remarkably lowered intensity was observed in both SDs as shown in figure 5. This suggested that reduced crystallinity attributed to the reciprocal interactions between host and the guest in the solid state. Besides this, decrease in particle size during formulation is also responsible for the decrease in peak intensities. The increased amorphous nature among SDs having PEG 4000 and PEG 6000 indicated the entrapment of drug inside the polymer.

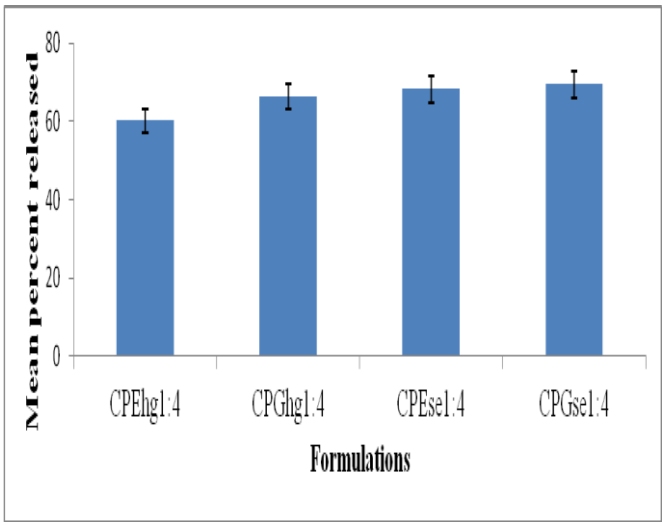


Fig. 4: Dissolution profile best formulations of PEG 4000 and PEG 6000

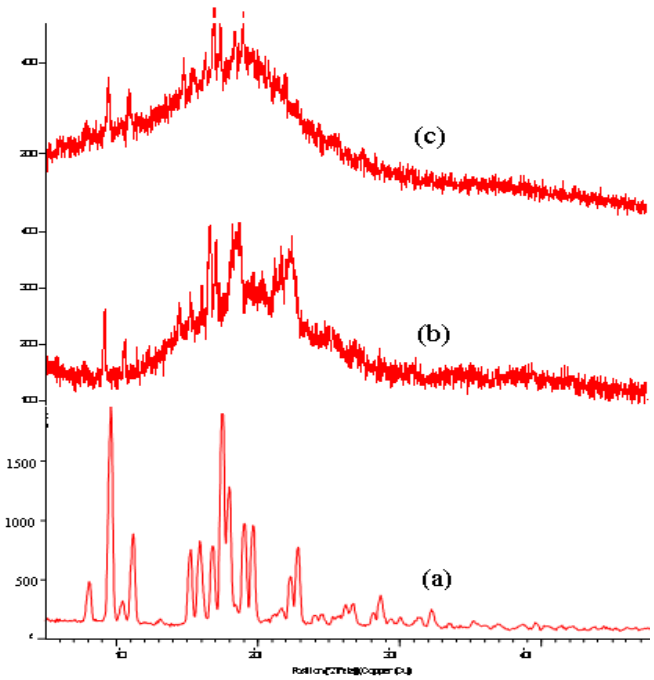


Fig. 5: X-ray diffraction pattern of (a) Cefpodoxime proxetil (b) Optimized formulation with PEG 4000 (c) and optimized formulation with PEG 6000

Differential Scanning Calorimetry (DSC) Studies

The existence of an interaction as well as detailed information about change in both the physical and energetic properties between the drug and polymers can be obtained by thermal analysis. DSC, a thermal analysis technique of choice is frequently used because of its ability to provide detailed information about both the physical and energetic properties of a substance when the guest molecules are entrapped inside the polymer matrix, their melting and boiling points usually shift to a different temperature or disappear. The DSC curve of CP showed a characteristic fusion endothermic peak at 101.13°C corresponding to its melting point. DSC thermogram of the pure drug was compared with that of the complexes which revealed important information about the complex formation. The disappearance of an endothermic peak in SDs (Figure 6) may be attributed to inclusion of drug in the polymer and formation of amorphous form.

Scanning electron microscopy (SEM)

SDs of best formulations (PEG-6000) was subjected to SEM studies which revealed a change in their surface characteristics (shape and appearance). The commercial sample (CP) was highly crystalline material and characterized by its needle shaped crystals whereas no characteristic shape of crystals was observed in solid dispersion having PEG 6000 as shown in Figure 7 which inferred that crystallinity of drug had been reduced or might be changed to amorphous state.

Infrared Spectroscopy

FTIR spectrum of CP showed a peaks at 3743 cm^{-1}, 3311 cm^{-1}, 3308 cm^{-1}, 2998 cm^{-1}, 2939 cm^{-1}, 2302 cm^{-1}, 1754 cm^{-1}, 1678 cm^{-1}, 1534 cm^{-1}& 1273 cm^{-1} were due to amide N-H stretch, alcohol/phenol O-H Stretch, alkynyl C=C Stretch, ketone C=O Stretch, amide C=O Stretch, aromatic C=C Bending, C-H stretching respectively. The characteristic peaks of the drug in the IR spectrum were retained in the treated sample when compared with physical mixture which indicated that there is no incompatibility between drug, carriers and excipients. It was observed that no significant shift in the peaks corresponding to the drug, which is an indicative of compatibility between the drug, carriers and excipients as shown in figure 8.

Solid dispersions formulations prepared using PEG 6000 as carrier followed the same trend of drug release as in SDs with PEG 4000. 2.5 times increase in the percent drug released and dissolution rate was observed (CPGse1:4) as compared to pure drug.

Out of two methods used for preparing SDS using different ratios, SE was observed to be best method and CPGse1:4 have shown highest percent drug release.

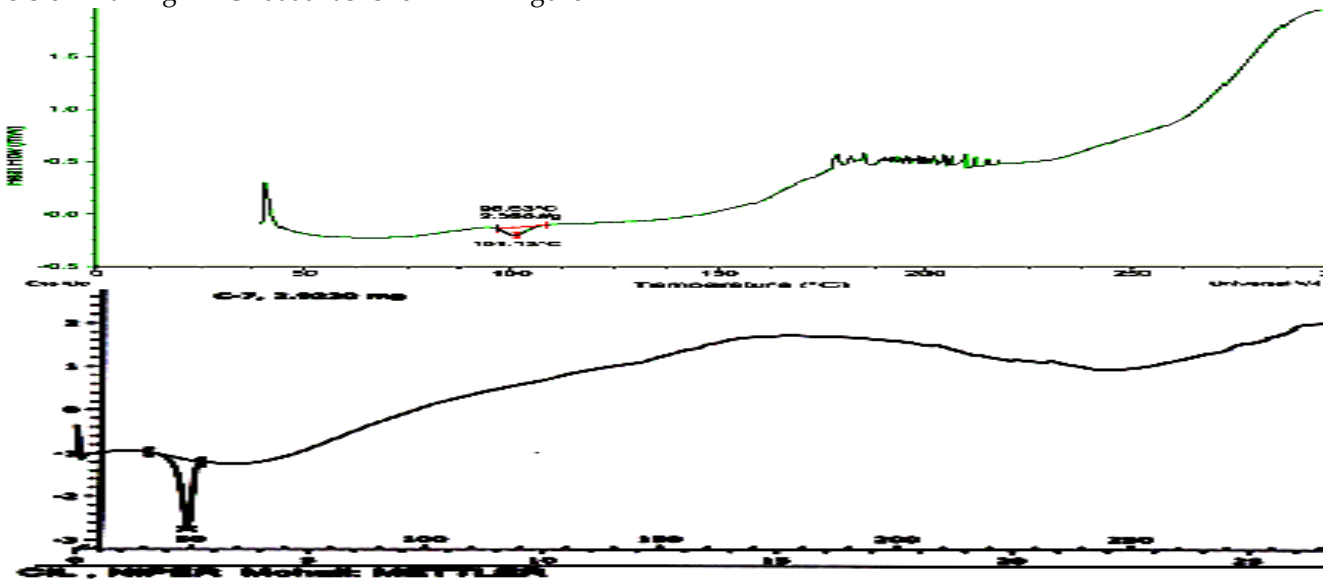
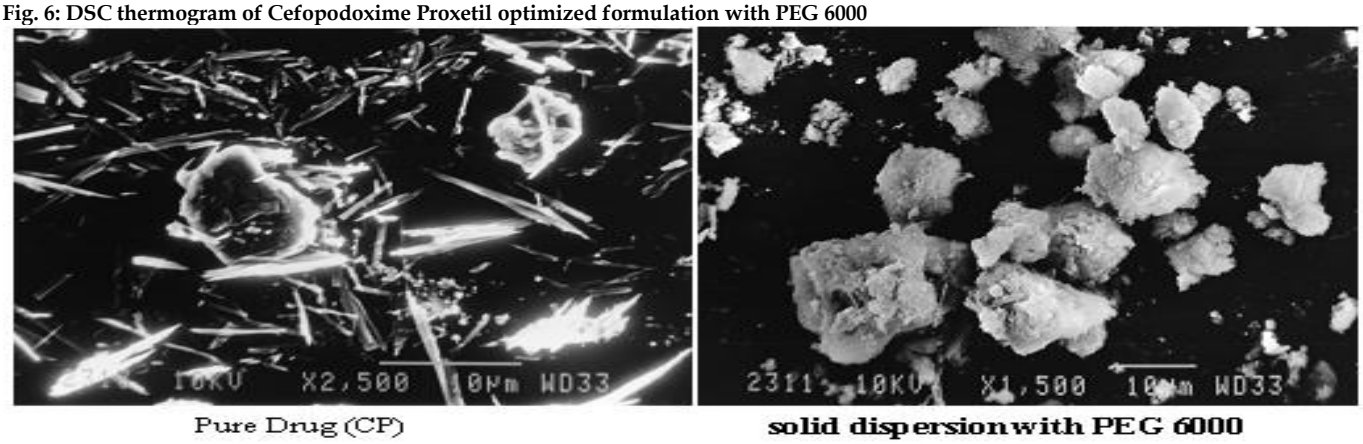


Fig. 6: DSC thermogram of Cefopodoxime Proxetil optimized formulation with PEG 6000



Pure Drug (CP) solid dispersion with PEG 6000

Fig. 7: Scanning electron photomicrographs of CP and optimized solid dispersion with PEG 6000

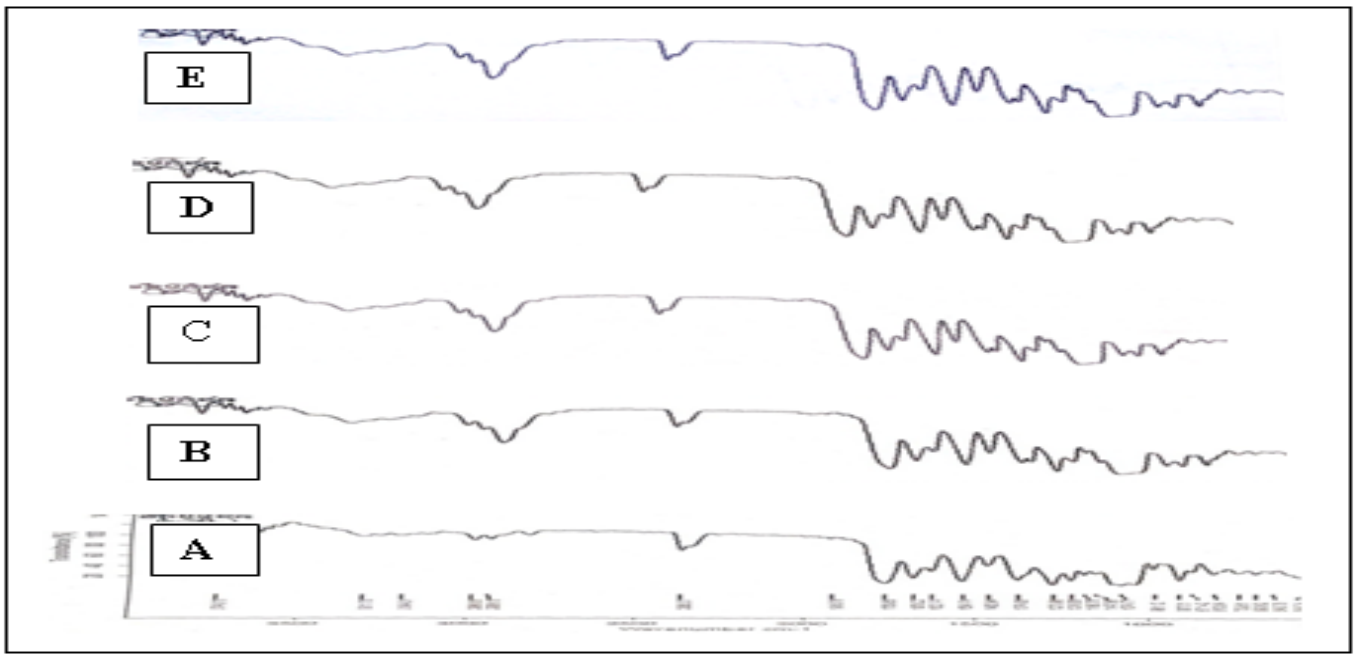


Fig. 8: FTIR Spectra of: (A) Drug (CP) (B) Physical Mixture of PEG 4000 with drug and excipients (C) Physical Mixture of PEG 6000 with drug and excipients (D) Treated sample containing PEG 4000 with drug and excipients, (C) Treated Sample containing PEG 6000with drug and excipients

This may be due to increased amount of water soluble carriers. The value of slope (0.607) indicated that it follows non-fickian diffusion and a result of kinetics release was best fitted in Korsemeyer Peppas model.

Finally, the selected SDs were further characterized by PXRD, DSC and SEM. PXRD of formulations (with PEG 6000) showed much reduced intensities in characteristic peaks of drug revealing that drug was encapsulated inside the carrier. The DSC of SDs with PEG 6000 showed the absence of melting endotherm depicting that drug was solubilized in polymeric matrix which further inferred the change of crystallinity nature of drug into an amorphous form. The SEM photographs of CP indicated the change of topography from needle shape to no characteristic shape of crystals inferring that crystallinity of drug had been reduced or changed to amorphous form.

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