IJPT
International Journal of Pharmacy & Technology

ISSN: 0975-766X

Available Online through *Research Article*
www.ijptonline.com

DISSOLUTION IMPROVEMENT OF POORLY WATER SOLUBLE DRUG BY FREEZE DRYING WITH PVP K-30

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Received on: 19-01-2010 ***Accepted on: 12-02-2010***

Abstract

This study compares the physicochemical properties of cefixime (CFX) solid dispersions prepared by freeze drying method. Solid dispersions of cefixime in polyvinylpyrrolidone (PVP) K30 were prepared and characterized by intrinsic dissolution, powder X-ray diffraction, Fourier transform infrared spectroscopy and Scanning electron microscopy. CFX:PVP K30 solid dispersions showed increased dissolution rate than pure CFX. The Infrared spectroscopic studies showed interaction between CFX and PVP K30 in solid dispersions. The scanning electron microscopy studies showed decrease in particle size of binary system as compared to particle of pure drug. The amorphous state of CFX coupled with presence of interaction between drug and PVP K30. However, the antimicrobial activity of CFX was increased significantly by PVP K-30 against S. aureus and E. coli. The solid dispersion technique of CFX:PVP K-30 binary system provides a promising way to increase the solubility and dissolution rate of poorly soluble drugs.

Keywords: Binary system; Cefixime; Dissolution rate; Freeze drying; PVP K-30; Solid dispersion.

1. Introduction

A large percentage of potential drug candidates suffer from low aqueous solubility and/or low dissolution rate. This results in low drug concentrations at the absorptive sites and hence low oral bioavailability [1]. Amidon et al. classified such drugs in the Biopharmaceutical Classification

System as class II compounds. The formulation of solid dispersions of BCS II compounds either by coprecipitation of drug and carrier from a common solvent or by co-melting and quench cooling is a popular strategy to reduce the drug particle size and hence increase the dissolution rate. If a drug is molecularly dispersed into its carrier the term solid solution can be used and the dissolution of the carrier becomes the rate limiting step [1,2]. Also, the solution that is generated in this way will have a drug concentration that is far beyond its thermodynamic solubility. Consequently, the excessive amount of drug will tend to precipitate until a saturated solution is formed. Therefore, one of the rationales to select an excipient for the formulation of solid dispersions should be its influence on the stability of the supersaturated solution that is generated upon dissolution [2]. The incorporation of drugs into hydrophilic carriers has frequently been reported to increase the dissolution rate of poorly soluble drugs, often leading to improved drug bioavailability [3].

Cefixime (CFX), is the first orally active, third generation cephalosporin that is approved for therapy in the U.S. It is a semisynthetic antibiotic derived from the secretion of the mold Cephalosporin which resembles, in respect of its structure, the spectrum of organism fighting ability to the third generation cephalosporins of the cefotaxime type [4,5]. The drug is highly stable in the presence of beta-lactamase enzymes, as a result, many organisms resistant to penicillins and some cephalosporins may be susceptible to CFX. CFX is employed in the treatment of a variety of respiratory tract infections and otitis media [5].

CFX with different crystalline forms, all of which have variable dissolution leading to irregular and delayed absorption. CFX and similar drugs of low solubility and high permeability, i.e. “Class II” in the Biopharmaceutical Classification System.

Historically, water-soluble carriers such as high molecular weight polyethylene glycols and polyvinylpyrrolidones (PVP) have been the most common carrier used for solid dispersions. For solid dispersions PVP K30 (MW 2500–50,000) has been widely used. The high molecular size of the

polymers favors the formation of solid solutions. The use of new formulation technique in conjunction with PVP might reduce the rate of crystallization in carriers with low melting temperatures.

Very few comparisons of the in vitro performance of freeze drying-based solid dispersions are found in literature. Attempts have been done in this study to evaluate the physicochemical properties of the solid dispersions of CFX with PVP K30. Solid dispersions were prepared by freeze drying method and characterized by powder X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectroscopy, and Scanning electron microscopy (SEM) [6].

2. Materials and methods

2.1. *Materials*

CFX was kindly supplied by Emcure Pvt. Ltd (Pune, Maharashtra, India). Polyvinylpyrrolidone K30 was provided by Loba Chemie Pvt Ltd. (India) with a molecular weight of 50,000–55,000. All other materials used were of analytical grade.

2.2. *Methods*

2.2.1. *Preparation of solid dispersions and physical mixtures*

Physical mixtures of CFX were prepared in different ratios (Table 1) by mixing CFX with PVP K-30 for three min in a mortar until a homogeneous mixture was obtained. The resulting mixtures were sieved through a 100 μm mesh and then stored in a desiccator at room temperature until use.

Table 1: Compositions (w/w) of Different Physical Mixture of CFX with PVP K-30

Code	Ratio	CFX	PVP K- 30
A1	1:1	1	1
A2	1:2	1	2
A3	1:3	1	3

Solid dispersions of different ratios (Table 2) were prepared. CFX was dissolved in nonaqueous solvent and PVP K-300 is dissolved in water. Nonaqueous system was added to aqueous system with continuous stirring. Addition rate was maintained 6-8ml/min. Nonaqueous phase (dichloromethane) was evaporated using Rotary evaporator. This was then freeze dried after initial freezing. The freeze dried product thus obtained was passed through sieve No. 100 & stored in dessicator at room temperature [7].

Table 2: Compositions (w/w) of Different Binary system (Solid dispersion Formulations) of CFX with PVP K-30 by freeze drying method

Code	Ratio	CFX	PVP K- 30
A1	1:1	1	1
A2	1:2	1	2
A3	1:3	1	3

2.2.2. Solubility measurements of CFX

Solubility measurements were performed according to the method of Higuchi and Connors (1965). An excess amount of solid dispersion was added in 10ml distilled water taken in test tubes. The samples were sonicated for 1 hr at room temperature. Thereafter, the capped test tubes were shaken at 25 or 45±0.1°C for 24 hrs in rotary flask shaker. Subsequently, the suspensions were filtered through Whatman filter paper no. 41, and the filtered solutions were analyzed spectrophotometrically at 288 nm [7].

2.2.3. Dissolution studies

Dissolution studies were performed using USP eight station dissolution test apparatus (Lab India) employing USP type I apparatus. Dissolution study was carried out in a 900 ml of pH 7.2 buffer at 37 ± 0.5 °C at 100 rpm. Five ml samples were withdrawn at time intervals of 5, 10, 15, 20,

25, 30, 35, 40, 45 and 60 min. the volume of dissolution medium was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5ml of fresh pH 7.2 phosphate buffer. The concentrations of drug in samples were determined by measuring absorbance at 288 nm. Cumulative percent drug released was determined at each time interval. Pure CFX was used as control [7].

2.2.4. Powder XRD

Samples were evaluated by using a Philips Analytic X-Ray—PW3710 (Holland) diffractometer with tube anode Cu over the interval 5–80°/2θ. The operation data were as follows: generator tension (voltage) 40 kV, generator current 30mA and scanning speed 2°/min. X-ray powder diffractometry (XRD) were used to characterize the solid-state properties of CFX [8].

2.2.5. FTIR spectroscopy

Infrared spectra were obtained using a Jasco 5300 FTIR spectrometer using KBr disks. The samples were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4600 to 400cm−1 [9].

3. Results and discussion

3.1. Fourier transformation-infrared spectroscopy

In order to further study the possibility of an interaction of CFX with PVP K-30 in the solid state. (Figure 1)illustrates the FTIR spectra of CFX, PVP K-30, PM and CFX–PVP K-30 system (1:3) A3. IR spectrum of CFX (a) is characterized by principal absorption peaks at 3365 cm−1 (N-H stretch), 2923 cm−1 (C-H), 1770 cm−1 (C=O stretching acid/ester), 1668 cm−1 (C=O stretching amide), 1592 cm−1 (C=N stretching), 1382 cm−1 (N-O stretching).

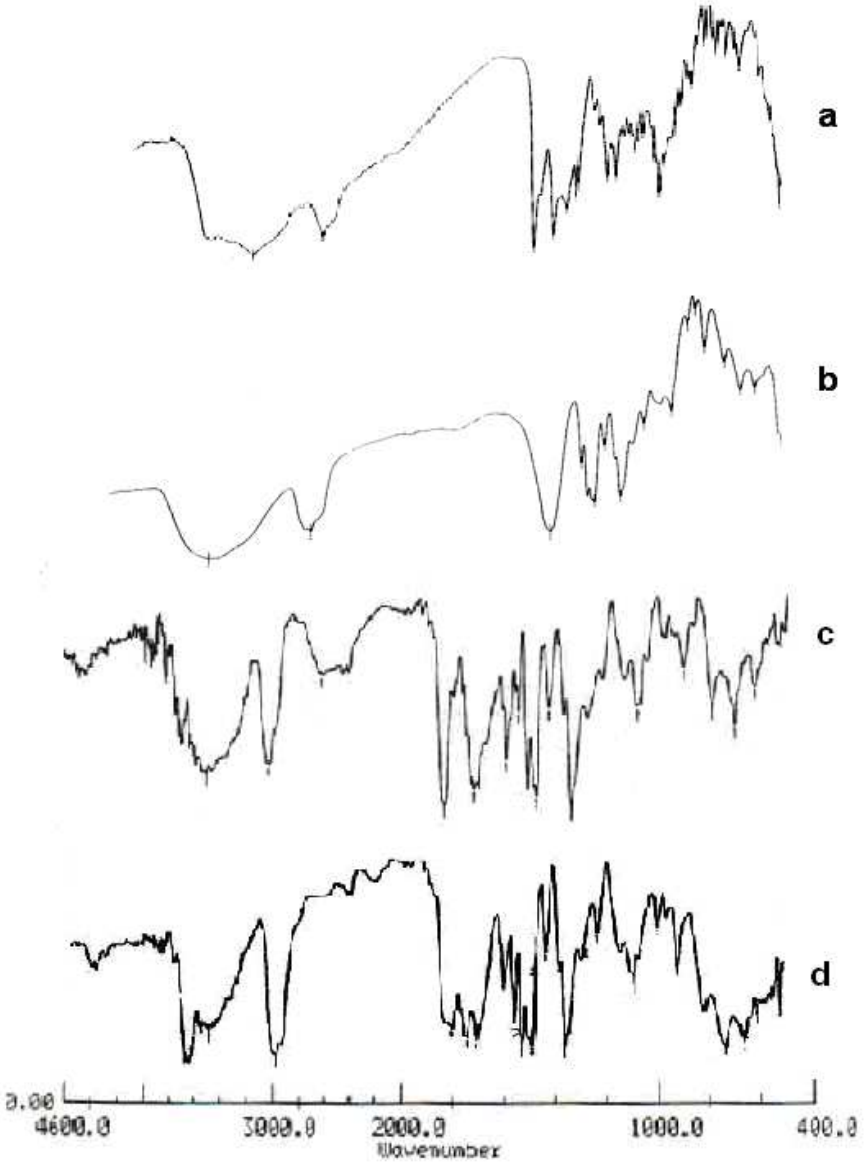


Fig. 1: FTIR spectra of CFX–PVP K-30 systems: (a) CFX; (b) PVP K-30; (c) Physical mixture and (d) Binary system

The IR spectrum of PM (c) shows peaks of both CFX and PVP K-30 with decrease in the peak intensity. However some peaks of CFX at 3423, 2947, 1780, 1668 and at 1288 cm−1 were disappeared indicating strong physical interaction of CFX with PVP K-30. In the IR spectra of binary system A3 (d) the peaks of CFX at 3454, 2926, 1749, 1684 and at 1288 cm−1 completely disappeared indicating that cephem ring with carboxylic functional group of guest had been

entrapped in the hydrophobic cavity of host molecule. The peak of OH group of PVP K-30 at 3457 cm−1 was shifted towards lower frequency 3423cm−1 due to intermolecular hydrogen bonding with CFX. The peak at 1665 cm−1 in IR spectra of PVP K-30 due to water of crystallization, also disappeared in both PM and binary system. These changes occurred in IR spectra of binary system indicated formation of complex in solid state [10].

3.2. X-ray powder diffractometry

The solid dispersions of CFX were studied by following XRD (Fig 2). The XRD pattern of CFX showed peaks that were intense and sharp, indicating its crystalline nature. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference. PVP being amorphous did not show any peaks. The powder diffraction patterns (PDP) of pure CFX showed characteristic high-intensity diffraction peak between 9.05˚2θ to 26.45 ˚2θ that matched the known PDP of CFX. The pdp of the formulation did not show peaks corresponding to CFX thus indicating that formulation was in amorphous form [11].

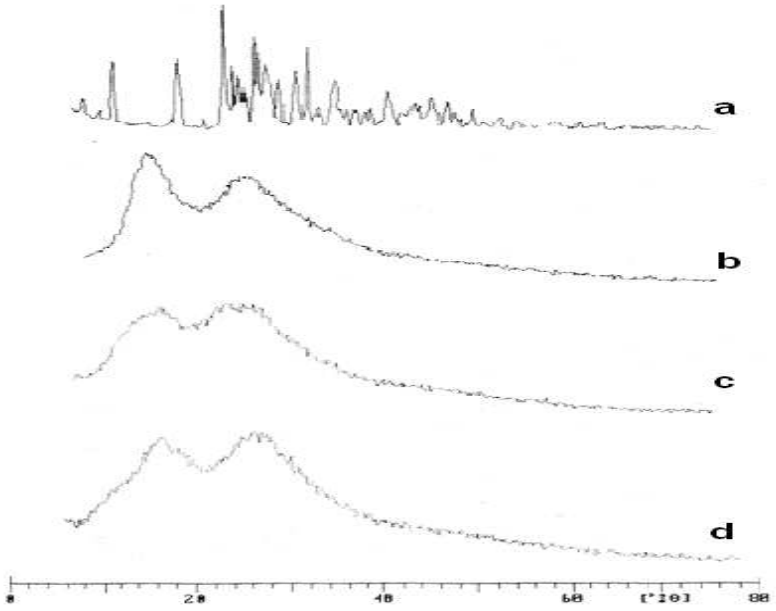


Fig. 2: XRD patterns of CFX-PVP K30 system: (a) CFX; (b) PVP K-30; (c) Physical mixture and (d) Binary system

3.3. SEM

The microphotographs of pure CFX (a) and CFX:PVP K-30 (1:3) (b) are shown in Fig. 3. Pure drug consisted of some crystals shows rectangular shape. CFX with PVP K-30 (1:3) on the other hand looked like a loose aggregate and are in irregular shape, indicating presence of amorphous form. Therefore, it is possible that the reduced particle size, increased surface area and the close contact between the hydrophilic carrier and the drug may be responsible for the enhanced drug solubility and dissolution rate observed for the solid dispersion [12].

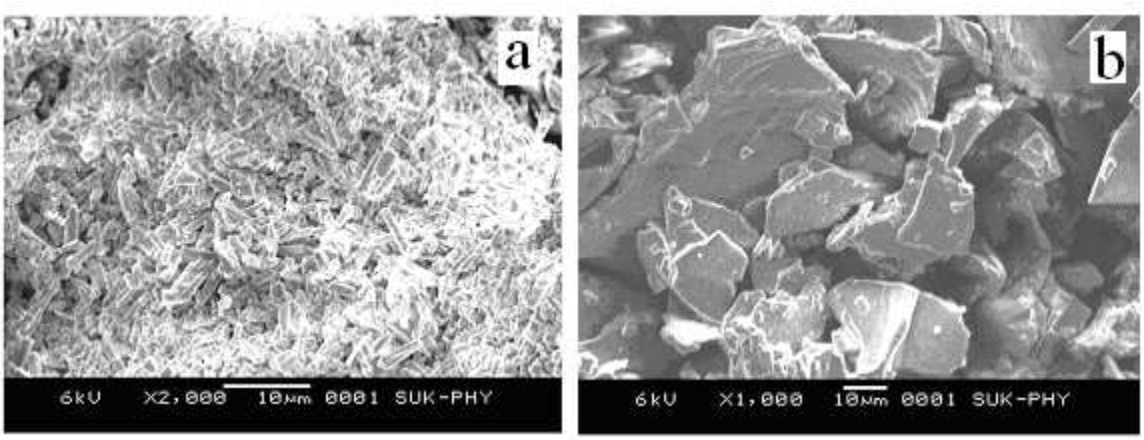


Fig. 3 Scanning electron microphotographs of pure (a) CFX and (b) Binary system

3.4. Saturation solubility studies

All the binary systems of CFX showed enhancement in the aqueous solubility as compared to pure drug alone (Table 3). The 1:3 ratio of CFX with PVP K-30 showed higher solubility than all other ratios of CFX. The enhancement in the solubility of complex is mainly attributed to the formation of stable amorphous system of CFX with PVP K-30. These sample solutions were analyzed using Shimadzu-1700 UV/VIS Spectrophotometer at 288nm [14].

Table 3: Saturation Solubility Study of the formulations

Systems	Saturation solubility (µg/ml)*
Pure drug	0.273 ± 0.04
A1	0.336 ± 0.06
A2	0.433 ± 0.03
A3	0.521 ± 0.07

* Indicates mean of three experiments; A1: Binary system (CFX:PVP K-30) (1:1); A2: Binary system (CFX:PVP K-30) (1:2); A3: Binary system (CFX:PVP K-30) (1:3)

3.5. Dissolution rate studies

All solid dispersions prepared by freeze drying method showed faster dissolution as compared to pure drug alone (Table 4). Dissolution rate of pure CFX is less because of hydrophobic nature of drug. The rapid dissolution of CFX from solid dispersion may be attributed to molecular and colloidal dispersion of drug in hydrophilic carrier matrix.

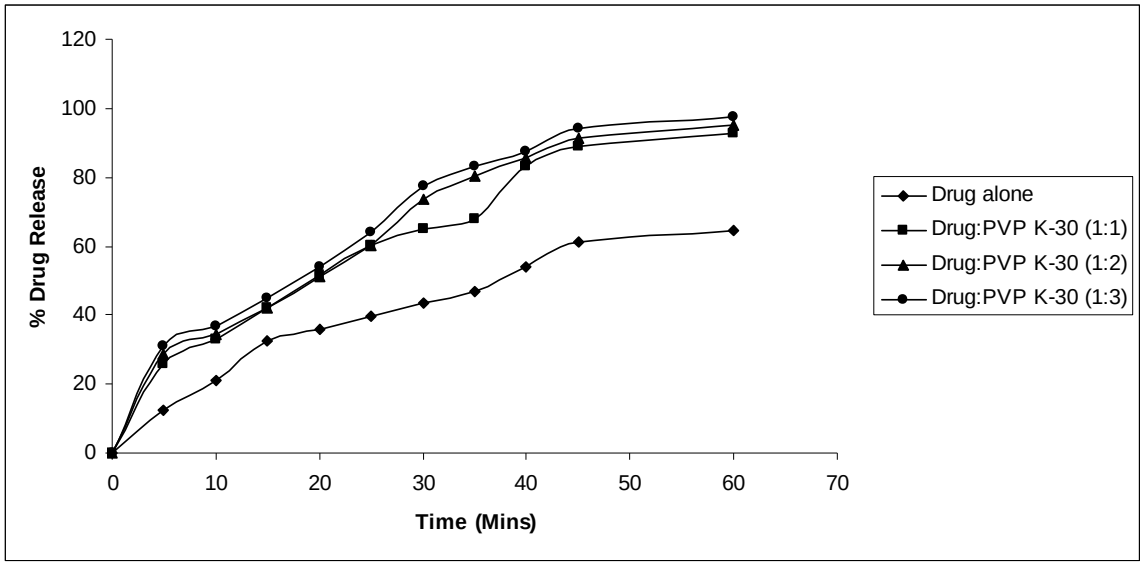
Table 4: % drug release in different binary systems

Time	Cumulative % Drug Release*			
	Drug	A1	A2	A3
5	12.36 ± 2.3	25.69 ± 2.6	28.49 ± 1.6	31.23 ± 2.4
10	21.05 ± 3.4	32.91 ± 3.1	34.21 ± 3.2	36.95 ± 2.1
15	32.43 ± 1.6	42.15 ± 2.7	41.94 ± 4.2	44.93 ± 3.2
20	35.73 ± 3.8	51.75 ± 0.7	51.35 ± 2.7	53.95 ± 2.8
25	39.79 ± 0.6	60.17 ± 2.2	60.25 ± 3.5	64.05 ± 1.5
30	43.45 ± 0.9	65.16 ± 2.9	73.62 ± 0.8	77.63 ± 1.1
35	47.07 ± 2.6	67.89 ± 4.4	80.19 ± 1.2	83.24 ± 2.2
40	54.26 ± 2.5	83.13 ± 3.2	85.57 ± 1.8	87.61 ± 3.6
45	61.14 ± 3.3	88.88 ± 3.6	91.17 ± 2.1	94.24 ± 2.3
60	64.30 ± 1.6	92.94 ± 2.7	95.23 ± 3.2	97.44 ± 4.3

*Indicates mean of three experiments; A1: Binary system (1:1); A2: Binary system (1:2); A3: Binary system (1:3)

The drug:carrier ratio (1:3) showed faster dissolution as compared to 1:1 and 1:2 ratio in solid dispersions (Fig. 4). This may be due to increased proportion of water soluble carriers in solid dispersions. As soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution [17].

Fig. 4: Binary system dissolution profile



From above observations, it was concluded that CFX:PVP K-30 (Binary system) ratio 1:3 showed fastest dissolution as compared to other solid dispersion. The dissolution rate increase for binary system was due to greater hydrophilicity, higher wetting effect, mechanical treatment, which increased the contact between the drug and the carrier and ability to form stable complex [18].

3.6. Antimicrobial studies

The antimicrobial activity of all binary systems of CFX with PVP K-30 against Gram-positive (S. aureus) and Gram-negative (E. coli) species was checked by cup-plate method and compared with the pure CFX. The results are summarized in Table 5. These studies revealed that all binary systems of CFX have shown greater antimicrobial activity than CFX alone [19].

Table 5: Antimicrobial activity of pure CFX and Binary system

System	Zone size (mm)*			
	E-Coli	**Standard Deviation (S.D.)**	**Staphylococcus aureus**	**Standard Deviation (S.D.)**
Pure Drug	21.65	0.3815	21.16	0.3971
A3	24.46	0.4636	24.48	0.6436

* Indicates mean of three experiments; S.D.: standard deviation; A3: Binary system (1:3)

4. Conclusions

Solid dispersions of CFX with PVP K30 gave higher intrinsic dissolution rates. CFX in the solid dispersions was present in amorphous form and was found to interact with PVP K-30 suggesting greater stability for the drug. In present study, initial characterization confirmed the presence of amorphous form of CFX in all samples obtained by technique of freeze drying. Further, it is found that carrier can also improve the antimicrobial activity of CFX in vitro by increasing its release rate.

Acknowledgements

The authors are thankful to Emcure Pvt. Ltd. (Pune, India) for providing gift sample of cefixime. Authors are very much thankful to Principal, Govt. College of Pharmacy, Karad, Maharashtra, India for providing laboratory facilities and constant encouragement.

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