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Research Article

EFFECT OF HYDROPHILIC POLYMERS ON CEFIXIME COMPLEXATION WITH β-CYCLODEXTRIN

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INTRODUCTION

With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates have risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.[1] The solubility behavior of a drug is a key determinant of its dissolution and consequently its oral bioavailability.[2] Various formulation techniques are applied to compensate for their insolubility and consequent slow dissolution rate. These include formulation of the amorphous solid form, nanoparticles, microemulsions, solid dispersions; melt extrusion, salt formation and formation of water-soluble complexes.[3,4]Among the different methods proposed to overcome this problem, the molecular encapsulation of the drugs by cyclodextrins is probably the most widely used method.[5,6]

Unfortunately, the complexation efficiency of cyclodextrins is low and consequently large amounts of CDs are needed to solubilize small amounts of water-insoluble compounds. For a variety of reasons including cost, production capability and toxicology, the amount of cyclodextrin incorporated into a drug formulation is limited.[7,8]It is therefore important to develop methods, which can be applied in order to enhance the efficiency of drug-cyclodextrin complexation. On this subject, earlier papers have reported the positive effect of addition of small amounts of a suitable water-soluble polymer to a drug-CD system in improving both the complexing and solubilizing efficiencies of the CDs.[9-16]This might be a useful strategy to reduce the dose of drug and the amount of cyclodextrin needed in pharmaceutical dosage forms.[17]

Cefixime is a semisynthetic, orally active third generation cephalosporin. It is currently being used in treatment of a variety of respiratory tract infections (e.g. acute bronchitis, pharyngitis and tonsillitis), otitis media, uncomplicated urinary tract infections and gonorrhea caused by β-lactamase-producing bacterial strains. It is poorly soluble in water, which is one of the reason for its low oral bioavailability (40-50%).[18,19]

Consequently, the rationale of the present study was to investigate the effect of hydrophilic polymers PVP and HPMC on cefixime complexation with β-cyclodextrin and thus to study combined effect of hydrophilic polymers and cyclodextrin on the solubility and dissolution rate of Cefixime.

MATERIALS AND METHODS

Materials

Cefixime trihydrate was kindly provided by Okasa Pharma Pvt. Ltd (Satara, India). β-cyclodextrin was obtained from S.A Chemicals (Mumbai, India). PVP K-30 and HPMC K4 were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). All the reagents and solvents used were of analytical grade.

Methods

Phase Solubility Studies

Phase solubility studies were performed for both binary and ternary systems at room temperature according to the method of Higuchi and Connors.[20] An excess amount of cefixime was weighed in stoppered glass tubes to which 10 ml aqueous solutions containing increasing concentrations of β-CD (0-0.3M) with or without a fixed amount of polymer i.e. PVP (0.25%w/v) and HPMC (0.1%w/v) were added. Those polymer concentrations were selected on the basis of preliminary studies carried out between cefixime and PVP or HPMC as no further improvement in solubility values of cefixime was achieved by increasing polymer concentrations.The suspensions were equilibrated at room temperature by mechanical stirring for 48. Aliquotes were drawn and filtered through Whatman filter paper (No.40). The filtered samples were suitably diluted and assayed for cefixime content by UV spectrophotometry against blanks prepared in the same concentration of β-CD, β-CD-PVP and β-CD-HPMC.

The phase solubility diagram (Figure 1) was constructed by plotting the dissolved cefixime concentration against the respective concentration of cyclodextrin. The binding constants for both binary and ternary systems (Kc) were calculated from the phase solubility diagram using its slope and intercept values.

Preparation of Binary and Ternary Systems

Physical Binary and Ternary Mixtures (PM)

Equimolar mixtures were prepared by homogeneously blending exactly weighed amounts of previously sieved cefixime and β-CD by geometric dilution method until homogeneous mixture is obtained. For ternary PMs 15 %(w/w) of PVP K-30 and 6 % (w/w) of HPMC were added.

Lyophilized (Lph) Binary and Ternary Products

For binary product, equimolar amounts of β-CD and cefixime were dissolved in water and methanol respectively. The two solutions were sonicated for 15 min. and mixed for 2 hrs at 50^{0}C.The resultant clear solution was taken in a beaker and freezed at -22^{0}C in a deep freezer. Then the beaker was kept in lyophilizer (Khera Instruments). The temperature was set and maintained at -40^{0}C for 12 hrs until sample was completely dry. Vacuum upto 0.01mpa was kept throughout the freeze-drying processes. For ternary products, equimolar amounts of β-CD and cefixime were dissolved in 0.25% w/v of PVP solution or 0.1% w/v of a HPMC solution and in methanol respectively. The resultant solution was mixed and sonicated for 15 min. After an equilibrium period of 24 hrs at room temperature, the clear solution was frozen and then freeze dried as above.

All the dried products were sieved and fractions smaller than 100 µm were used for further study.

Differential Scanning Calorimetry (DSC)

DSC curves of the pure drug, binary and ternary systems were recorded on a TA instrument model SDT-2960, USA. An empty aluminum pan was used as a reference. DSC measurements were performed at a heating rate of 10ºC/min from 25 to 250ºC using aluminum sealed pan. The sample size was 5-10 mg for each measurement. During the measurement, the sample cell was purged with nitrogen gas.

X-ray Diffractometry (XRD)

Powder X-ray diffraction patterns of pure drug, CD, polymers, binary and ternary systems were recorded on an automated Philips X'Pert

diffractometer system. The samples were irradiated with mono-chromatized CuKα radiation and analyzed between 2-80º 2θ. The diffraction patterns were collected with voltage of 30kV and current of 30mA respectively. The scanning rate was 2^0 min^{-1}.

Fourier Transform Infrared Spectroscopy (FTIR)

A Jasco FTIR spectrophotometer (Jasco FTIR- 401, Japan) was used for infrared analysis of samples. About 1-2 mg of sample was mixed with dry potassium bromide and the samples were examined at transmission mode over wave number range 4000 to 400cm^{-1}.

In-Vitro Drug Release Study[21]

The release rate studies of cefixime, alone and from binary and ternary systems (complex and physical mixtures) were performed using USP XXI type II apparatus (paddle method, 100rpm). Samples equivalent to 100 mg of drug were added to 900 ml of dissolution medium (phosphate buffer pH 7.2) and temperature of dissolution medium was maintained at 37±0.5^{0}C. Sample (5 ml) was withdrawn at regular intervals maintaining sink condition and filtered through Whatman filter paper no.40. The sample was suitably diluted and the absorbance of the resultant solution was measured at 288 nm. The percent drug released from the complex was determined. The dissolution pattern of binary system was compared with that of the pure drug and physical mixture while dissolution pattern of ternary system was compared with pure drug, physical mixture as well as binary system.

RESULTS AND DISCUSSION

Phsae-Solubility Studies

The phase solubility diagram obtained with β-CD in presence or absence of water soluble polymers (PVP and HPMC) is shown in Fig.1. It displayed A_L type equilibrium phase solubility diagram for both binary and ternary systems showing that solubility of cefixime increases linearly as a function of CD concentration and that soluble complexes were formed without occurrence of precipitation in the range of CD concentration used. As the slope value for binary system in this diagram was less than 1, it was possible to assess 1:1 stoichometry and calculate stability constant of binary drug-β-CD complex using equation of Higuchi and Connors. The stability constant (Kc) values of binary and ternary systems and drug solubility ratio values in solutions of different composition are shown in table 1.The addition of water soluble polymers to the CD solution did not change the type of phase-solubility diagram obtained for binary system but resulted in increase in stability constants (Kc). Apparent stability constants of cefixime with binary and ternary systems under study increased in the order of

D-β-CD-HPMC > D-β-CD-PVP > D-β-CD

Increase in stability constants of ternary systems as compared to binary indicates increase in complexation efficiency of cyclodextrin and thus solubility of cefixime.

System	Binding const. Kc	K_{TS}/K_{BS}	Solubility ratio (S_{CD+pol}/S_{CD})
CFX-β-CD	138.88	-	-
CFX –β-CD-PVP	305.16	2.19	1.68
CFX –β-CD-HPMC	460.0	3.31	2.02

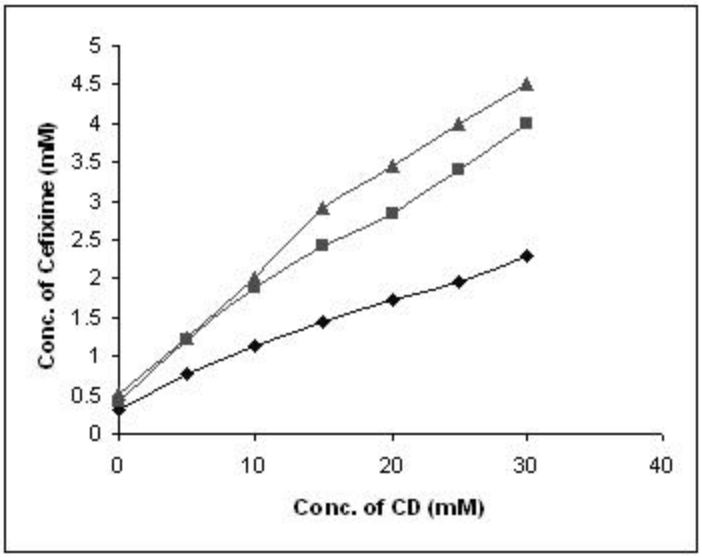

Fig. 1: Phase solubility diagram in aqueous solutions of β-CD without water soluble polymers (♦) and with 0.25 %w/v PVP (■) or 0.1%w/v HPMC (▲).

Differential Scanning Calorimetry (DSC)

DSC thermograms of pure drug and corresponding binary and ternary systems are shown in Fig.2. The thermal curve of pure cefixime was typical of crystalline substance with a endothermic peak at 218.91^{0}C corresponding to the melting point of the drug. DSC curve of binary and ternary system did not show significant differences. DSC curves of lyophilized products exhibited the complete disappearance of the endothermic melting peak of cefixime. The disappearance of an endothermic peak may be a strong indication of the formation of amorphous entities. These results suggest that LPh system can be considered to form the true complexes.

X-ray Diffractometry (XRD)

The X-ray diffraction patterns of drug, β-CD, PVP, HPMC, binary and ternary systems are shown in Fig.3. X-ray diffraction pattern for pure drug indicated crystalline form of cefixime with sharp peak between 9.05°2θ to 26.45 °2θ, a characteristic of cefixime. Comparing the diffraction patterns of pure components with those of binary and ternary systems, it was observed that there were no marked

dissimilarities between the diffraction patterns of the binary and ternary PMs, being all of them the superpositions of pure components. Furthermore, for binary and ternary LPh products the obtained patterns were diffused indicating the amorphous state reached by lyophilization technique.

The relative degree of crystallinity (RDC) was calculated by dividing highest intensity peak of sample by peak intensity of the reference at the same angle. [RDC= I sample / I reference]. RDC values were found to be 0.092, 0.064, 0.045 for D-β-CD binary, D-β- PVP and D-β-CD-HPMC ternary systems respectively.

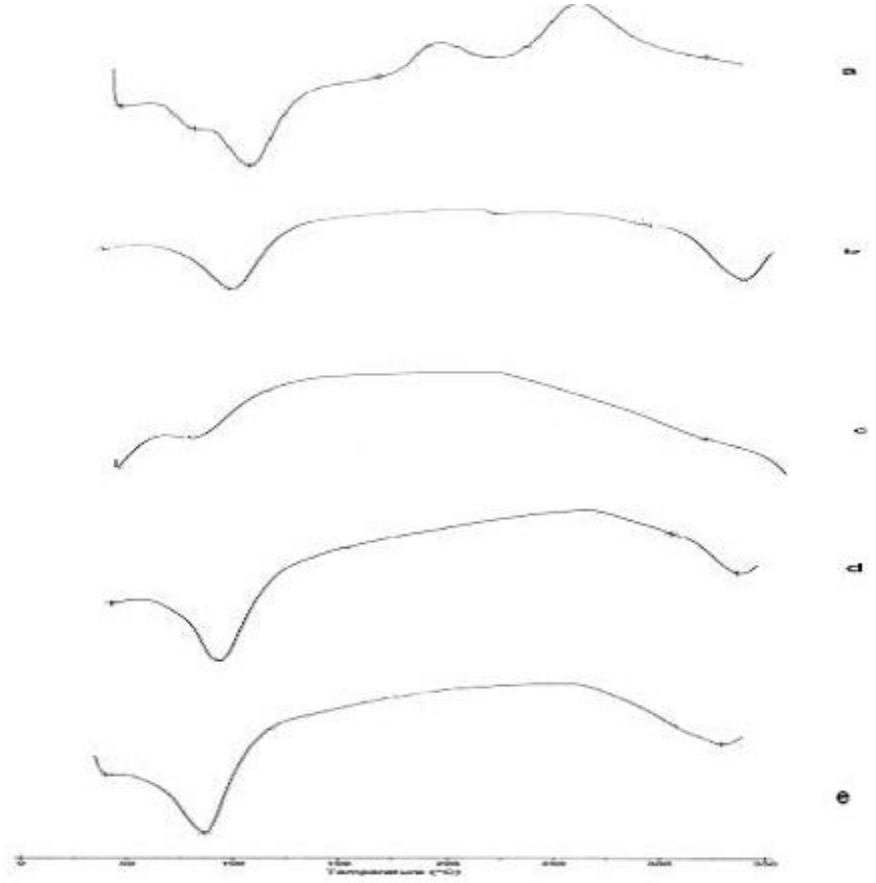

Fig. 2: DSC thermograms of a) CFX b) β-CD c) HPMC d) CFX- β-CD complex e) CFX- β-CD-HPMC complex(Lyophilized)

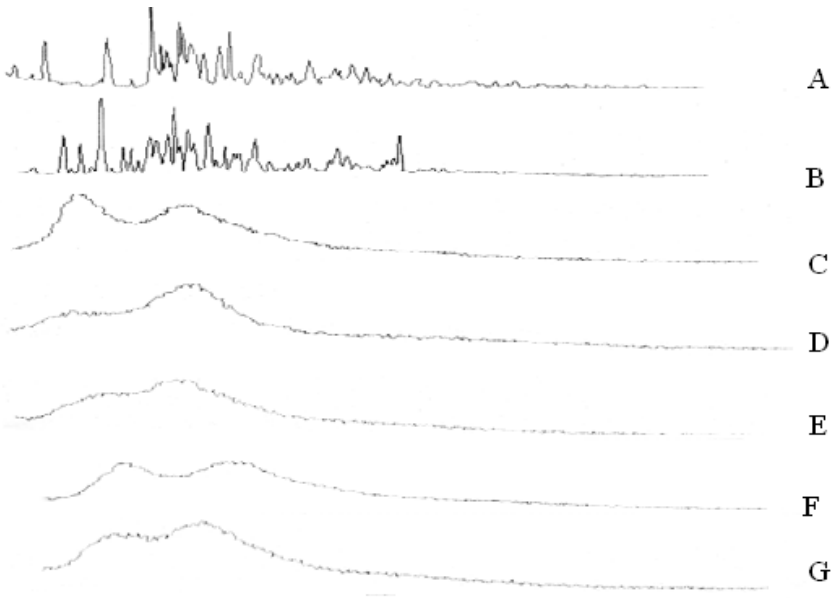

Fig. 3 : X-ray diffraction patterns of (A) CFX B) β-CD C) PVP D) HPMC E) CFX- β-CD (Lyophilized complex) F) CFX- β-CD- PVP (Lyophilized complex) G) CFX- β-CD-HPMC (Lyophilized complex).

Fourier Transform Infrared Spectroscopy (FTIR)

Principle peaks of cefixime in its IR spectra (Fig.5) were observed at 3365.61cm^{-1}, 2923.56 cm^{-1}1770.33 cm^{-1}, 1668.12cm^{-1}, 1592.91cm^{-1}, and 1382.17cm^{-1} which were used in the analysis of solid-state interaction between components. No significant changes in principle peaks of drug were observed for binary and ternary physical mixtures (PMs). This indicates that no interaction between drug and CD or polymers produced by simple mixing. The FT-TR spectra of both binary &ternary complexes exhibited some significant differences (shifts, broadening and attenuation) in the characteristic bands revealing a modification of the drug environment. N-H stretching band at 3365.61cm^{-1} and C-H stretching band at 2923.56 cm^{-1}were highly diminished, broader and shifted to higher frequencies in all spectral patterns LPh binary and ternary products. Absorption bands at 1770.33 cm^{-1} and1668.12 cm^{-1} are attributed to stretching vibration of the carbonyl group in carboxylic acid / ester and stretching vibration of the amide carbonyl. In case of carboxylic acid C=O stretch (1770.33 cm^{-1}) no change in peak position was observed in case of both binary and ternary systems which suggests that carbonyl group remains free. While slight shifting of absorption band for the carbonyl group of the amide to a lower frequency suggested that it is almost likely encapsulated by CD to form complex. Peak due to aromatic C=N stretch at 1592.91cm^{-1} and due to N-O stretch at 1382.71 cm^{-1} disappear in all binary and ternary systems.

From these results, the existence of strong interactions between cefixime, β-CD and water soluble polymers (PVP and HPMC) were confirmed since the spectral changes can be explained by the dissociation of the intermolecular hydrogen bonds of drug through inclusion complexation and also drug dispersion as a consequence of the interaction with β-CD and polymers which could result in better inclusion of drug into hydrophobic cavity of the CD.

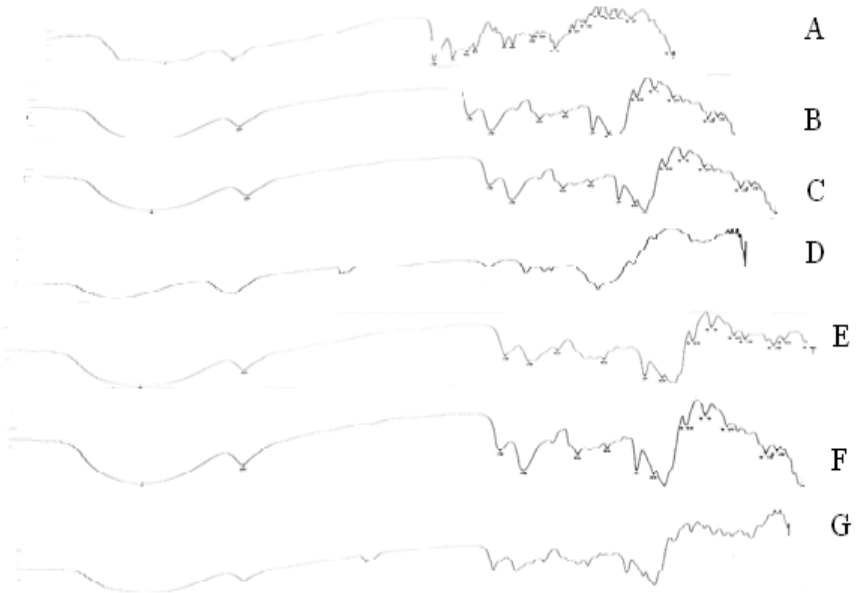

Fig. 4: FTIR Spectra of (A) CFX B) β-CD C) PVP D) HPMC E) CFX- β-CD (Lyophilized complex) F) CFX- β-CD- PVP (Lyophilized complex) G) CFX- β-CD-HPMC (Lyophilized complex).

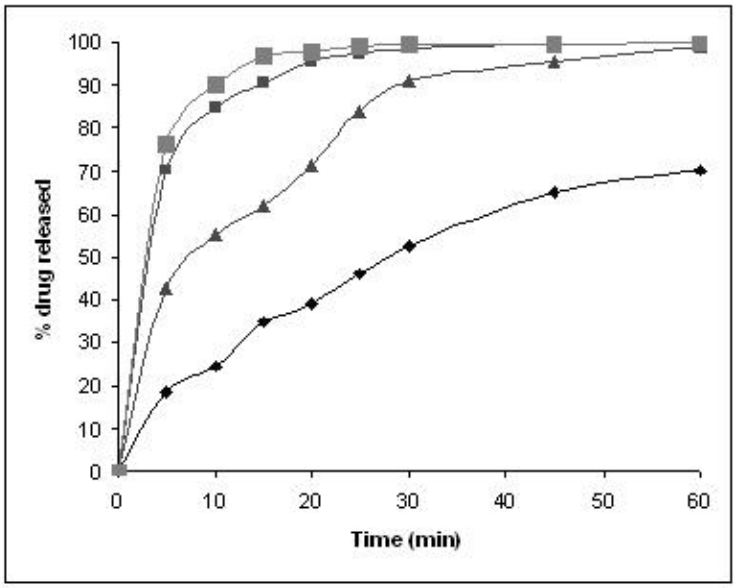

Fig. 5: Dissolution profiles of Cefixime (CFX) (♦), CFX-β-CD (▲), CFX-β-CD-PVP (▀) and CFX-β-CD-HPMC (■) complexes

In-Vitro Drug Release Study

The dissolution curves of cefixime from binary and ternary systems are presented in Fig.5, which exhibits better dissolution properties than pure drug alone. A marked increase in dissolution rate of drug was evident in binary and ternary systems and can be attributed to both improvement in drug wettability and formation of readily soluble complexes in the dissolution medium. The increase in dissolution rate was found to be higher for the ternary systems than respective binary compositions. D-β-CD-HPMC ternary system was found to exhibit faster dissolution profile as compared to other systems. The increase in the dissolution rate of drug in case of ternary systems as compared to binary system might be due to enhancement of complexation efficiency and solubilizing effect of β-CD in the presence of water soluble polymers.

CONCLUSION

Combined use of cyclodextrin and hydrophilic polymers greatly improved drug solubility and dissolution rate because of enhanced complexation efficiency of cyclodextrin. Thus the association of hydrophilic polymers to drug-CD systems would offer a promising drug delivery system having the great advantage of reducing dose of the drug and the amount of cyclodextrin needed.

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