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Solid Dispersions of Cefixime Using β-Cyclodextrin: Characterization and *in vitro* Evaluation

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***Abstract*—**Cefixime, a BCS class II drug, is insoluble in water but freely soluble in acetone and in alcohol. The aqueous solubility of cefixime in water is poor and exhibits exceptionally slow and intrinsic dissolution rate. In the present study, cefixime and β-Cyclodextrin (β-CD) solid dispersions were prepared with a view to study the effect and influence of β-CD on the solubility and dissolution rate of this poorly aqueous soluble drug. Phase solubility profile revealed that the solubility of cefixime was increased in the presence of β-CD and was classified as A_L-type. Effect of variable, such as drug:carrier ratio, was studied. Physical characterization of the solid dispersion was characterized by Fourier transform infrared spectroscopy (FT-IR) and Differential scanning calorimetry (DSC). These studies revealed that a distinct loss of drug crystallinity in the solid molecular dispersions is ostensibly accounting for enhancement of dissolution rate in distilled water. The drug release from the prepared solid dispersion exhibited a first order kinetics. Solid dispersions of cefixime showed a 6.77 times fold increase in dissolution rate over the pure drug.

***Keywords*—**Cefixime, β-Cyclodextrin, solid dispersions, kneading method, dissolution, release kinetics.

I. Introduction

POOR aqueous soluble drugs are generally associated with certain problems such as slow drug absorption which eventually leads to insufficient and variable bioavailability [1], [2]. Approximately 40% of the newly discovered drugs are reported to be poorly water soluble [3], [4]. Therefore, certain attempts have been made to enhance the drug solubility of these therapeutic agents to correlate well with enhancement of their bioavailability. Many techniques have been investigated by researchers to improve the solubility of poorly aqueous soluble drugs, among them solid dispersion technology was proven to be a successful technique. Numerous insoluble drugs have shown to improve their dissolution character upon conversion to solid dispersion. [5]. Solid dispersion technology is a well known process used to increase the dissolution kinetics and in turn alters the oral absorption of poorly water soluble drugs using water soluble inert carriers [6]. The usage of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drugs is gaining greater interest [7], [8]. CDs are used to increase the solubility of water insoluble drugs, through the formation of inclusion complexation [9]-[12]. Generally, the small drug molecules, and those compounds with the lowest water solubility showed a preferential increase in solubility as a function of CD concentration. Therefore, CD have been given much priority for their use in pharmaceutical preparations in order to increase the stability and bioavailability of poorly water soluble drugs [13]. The aqueous solubility of cefixime in water is poor and the oral bioavailability is 40-50% [14].

A. Objective

In the present investigation, an attempt was made for cefixime by inclusion complexation with β-CD to improve its pharmaceutical properties such as aqueous solubility, dissolution properties with a view of increasing its bioavailability and therapeutic efficacy.

II. Experimental Design

A. Preparation of Cefixime β-CD Solid Dispersion by Kneading Method [15]

A physical mixture of cefixime and β-CD (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8 and 1:9 w/w) was wetted with a mixture of methanol and water (1:1 v/v) thoroughly for 30 minutes in a glass mortar and pestle. The paste formed was dried under vacuum for 24 h, dried powder was scrapped, crushed, pulverized, passed through sieve no 100 (ASTM-100, 150 μm) and stored in desiccator for further studies.

B. Solid State Studies

Percent Yield

The percentage yield of the solid dispersion was calculated on the basis of dry weight and carrier with respect to the final weight of the inclusion complexes.

$$\%Yield = \frac{Finalweigh\ toftheprod\ uctx100}{Dryweighto\ fthedrugan\ dcarrier} \quad (1)$$

Average Particle Size

The solid dispersion of cefixime was dispersed in liquid paraffin and mounted on slides. A random of 200 particles were measured using a calibrated stage micrometer and eye piece micrometer, their average particle size were calculated.

Moisture Uptake Studies

The solid dispersion was dried in a dessicator under anhydrous calcium chloride for two days. A known quantity (200 mg) of each formulation (W_1) was placed on a watch glass and exposed to ambient atmospheric conditions (60±5%

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RH, 25±2 °C) and saturation humidity conditions (75±1% RH, 25±2 °C) for two days using a stability chamber (Thermolab, Mumbai, India). The solid dispersion are reweighed (W_2) and percentage moisture gained was calculated using

$$Percentage moisture absorbed = \frac{W2 - W1X100}{W2} \quad (2)$$

FTIR Spectroscopy

FTIR spectra were recorded for pure drug, solid dispersions of drug with carrier in KBr pellets using FTIR – 5300 (Shimadzu, Tokyo, Japan). The scanning range was 450 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

DSC

DSC analysis was performed for drug and drug in solid dispersions using DSC Q200, TA instruments, Mumbai, India. The samples (5 mg of cefixime or its equivalent) were heated in a sealed aluminium pans at a rate of 10 °C per/min in a temperature range of 30 to 300 °C under nitrogen flow of 40 ml/min. An empty aluminum pan was used as reference.

C. Liquid State Studies

Phase Solubility Study

An excess of cefixime (50 mg) was added to screw capped bottles containing various concentrations of β-CD solution (0.2, 0.4, 0.6, 0.8 and 1 $mM \times 10^4$). All bottles were closed with stopper and covered with cellophane membrane to avoid solvent loss. Bottles were shaken mechanically at 25±0.5 °C for 24 hours using rotary flask shaker. After 24 h of shaking to achieve equilibrium, 5 ml of aliquots were withdrawn, filtered (0.45 µm pore size) and analyzed spectrophotometrically for drug content at 288 nm using UV 1700 spectrophotometer (Shimadzu, Japan) (Fig. 1).

Estimation of Drug Content

The content of cefixime in the formulated solid dispersion was determined by UV spectrophotometer (Shimadzu, Japan). An accurately weighed quantity of solid dispersion (100 mg) was transferred into a beaker containing 0.8 ml of methanol and volume was made up to 10 ml with double distilled water and the absorbance was measured at 288 nm against blank.

Dissolution Rate Studies

The dissolution studies were carried out using USP (XXII) dissolution apparatus following paddle method, freshly prepared double distilled water (900 ml) was placed in the dissolution flask and allowed to attain a temperature of 37±0.5 °C. The solid dispersion containing a quantity equivalent to 50 mg of cefixime was filled in hard gelatin capsule (Size 2) and placed in the basket and immersed in the dissolution medium. The basket was rotated at 50 rpm for 1 h. 5 ml of the sample was withdrawn at different time intervals of 0, 15, 30, 45 and 60 min. After each withdrawal, the medium was replaced with equal amount of fresh buffer to maintain the sink conditions. The drug content was estimated by measuring the absorbance at 288 nm against blank. Data variations were analyzed statistically using one way analysis of variance (ANOVA) procedure and significance was tested at p values of 0.05.

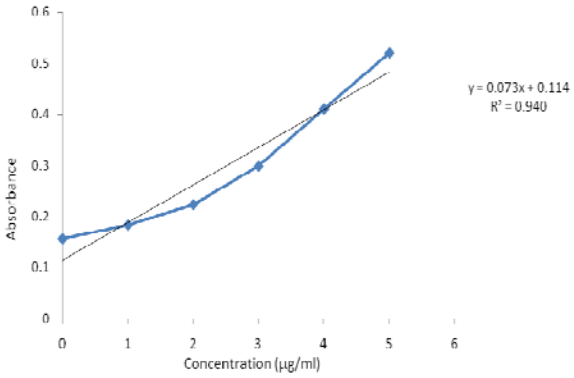


Fig. 1 Phase solubility study of cefixime

$$DE = \int_0^t ydtx100 / y100.t \quad (3)$$

Dissolution percentage (DP_{10}, DP_{30}), dissolution efficiency (DE_{10}, DE_{30}) and time for 50% (t_{50}) dissolution were calculated from dissolution data.

D. Release Kinetics

The *in vitro* dissolution profiles of all inclusion complexes of cefixime were subjected to different kinetic analysis to elucidate the drug release mechanism. The release data were fitted into zero order (4), first order (5), Higuchi matrix model (6) and Hixson-Crowell (7) to understand the kinetic modeling of drug release.

$$M_0 - M_t = K_0 t \quad (4)$$

$$ln (M_0/M_t) = K_1 t \quad (5)$$

$$M_t = K_H \sqrt{t} \quad (6)$$

$$(W_0)^{1/3} - (W_t)^{1/3} = K_{1/3} t \quad (7)$$

where, M_0 and M_t correspond to the drug amount taken at time equal to zero, dissolved at particular time, t. The terms M_0 and M_t refer to the weight of the drug taken initially and at time t, respectively. Various other terms viz, K_H, K_0, K_1 and $K_{1/3}$ refer to the release kinetic constants obtained from the linear curves of Higuchi model, zero order, first order and Hixson-Crowell cube root law respectively.

III. Results and Discussion

FTIR Study

Compatibility studies of cefixime with selected carrier β-CD were done by FTIR spectral matching approach. It was easily understood that there was no appearance and disappearance of peaks. The functional group (C=O) at 1737 cm^{-1} indicates that β-lactam absorbance band is present. OH at 3389 and 3238 cm^{-1} showed that hydroxyl groups are not

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involved in the reaction. Appearance of band at 1594 cm^{-1} (C=N) also exhibited the non-reactivity of both compounds. Ether functional group (C-O-C) bands at 1021 and 1157 cm^{-1} are present and provide more evidence for non-reactivity of both compounds. This indicates that the drug was compatible with the carrier. (Figs. 2, 3).

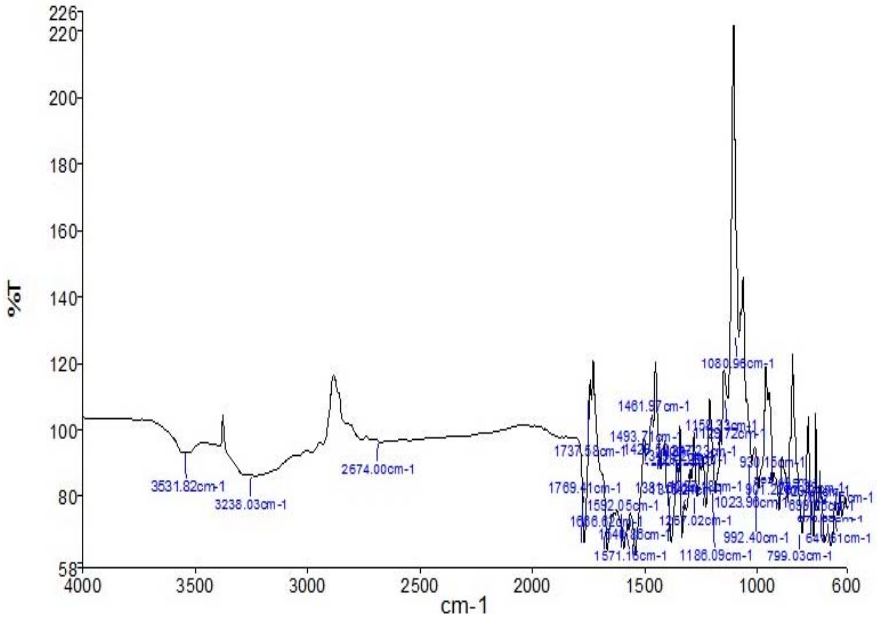


Fig. 2 FTIR spectra of cefixime

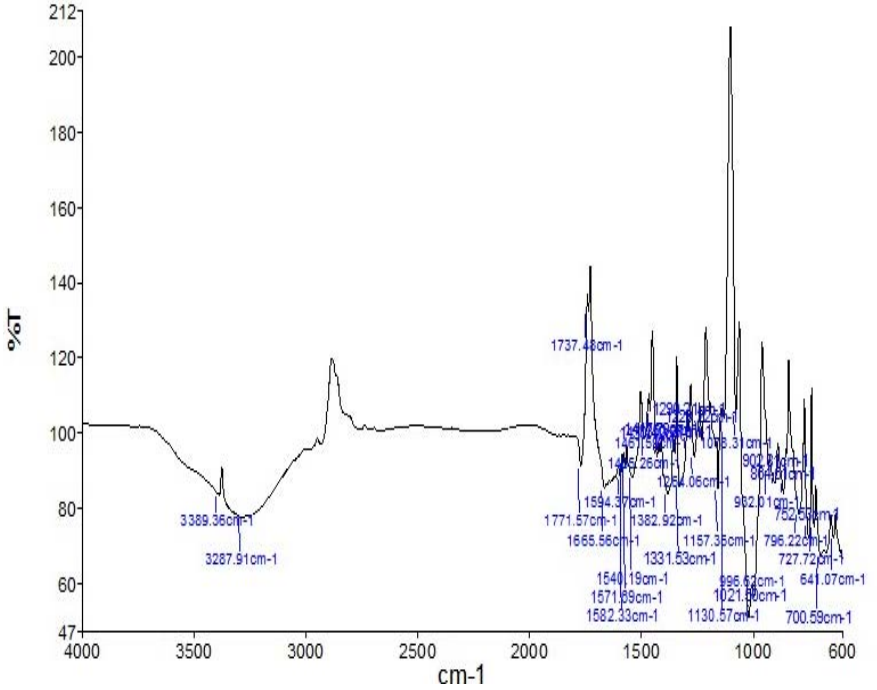


Fig. 3 FTIR Spectra of cefixime+β-cyclodextin

DSC Study

The DSC studies showed one endothermic peak at 129.21 °C and one exothermic peak at 223 °C corresponding to its melting point 218-225 °C. This revealed there was no major shifting of peak in the chemical complex. This could be due to higher concentration and uniform distribution of drug in the crust of carrier resulting in its complete miscibility. Moreover, these data also indicate that there seems to be no interaction between the components of binary systems. No significant difference in the DSC pattern of dispersions suggesting that the kneading process could not induce the interaction at molecular level and the solid dispersion formed as highly dispersed drug crystals in carrier. The thermograms were shown in Figs. 4, 5. The prepared solid dispersions were

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evaluated for average particle size, angle of repose, bulk density, moisture uptake, drug content and *in vitro* dissolution studies. The angle of repose values was ranged from 22 to 27^0 for kneading mixture. The formulations have shown good flow property. The bulk density values were ranged from 0.80 to 0.88 g/cc for kneading mixture. The compressibility values were ranged from 16-19% for kneading mixture, which was found to be ideal for the formulation of tablets. The moisture uptake values were 6-7% for kneading mixture which indicates that the powder was hygroscopic in nature. The drug content was ranged 96 to 98% for kneading method. The results are shown in Table I. The phase solubility diagram for the complex formation between cefixime and β-CD are presented in Fig. 2. The plot showed that the aqueous solubility of the drug increases linearity as a function of β-CD concentration.

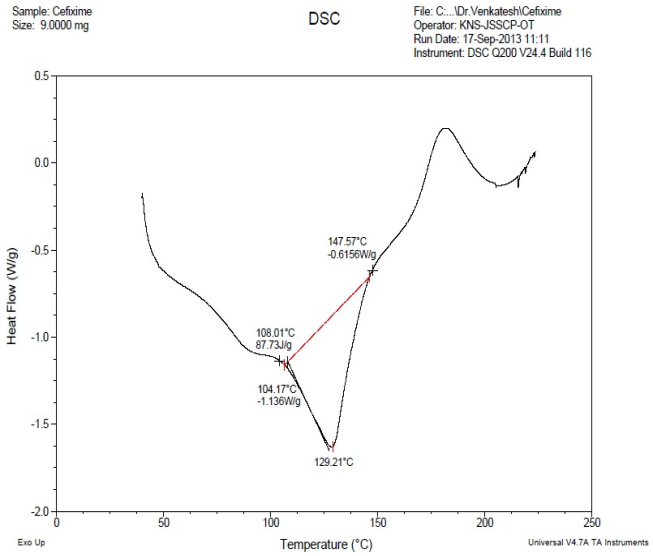


Fig. 4 DSC thermogram of cefixime

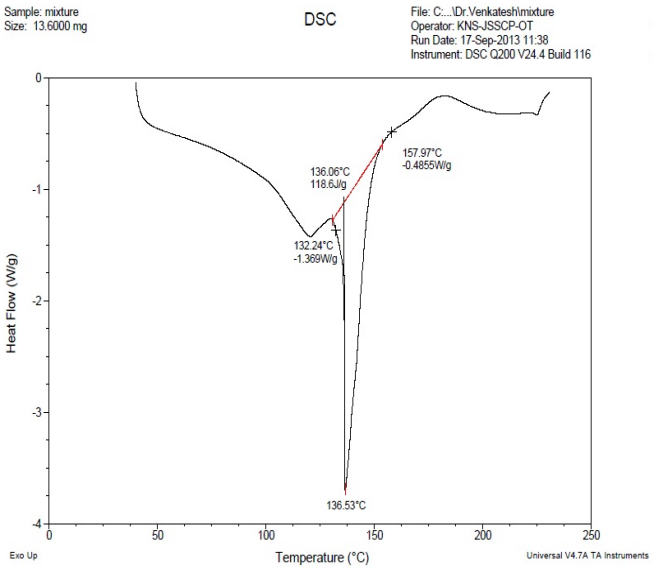


Fig. 5 DSC thermogram of cefixime+β-CD

TABLE I
EVALUATION OF SOLID DISPERSIONS OF CEFIXIME HYDROCHLORIDE

Parameters	Drug –Carrier Ratio (W/W)									
	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9	1:10
Yield (%)	95	97	94	95	95	97	95	95	96	94
Angle of Repose (^{0})	22	22	23	23	24	24	25	26	27	27
Bulk Density (g/cc)	0.80	0.82	0.82	0.86	0.86	0.88	0.82	0.84	0.85	0.81
Compressibility (%)	15	16	17	17	18	18	19	19	19	18
Moisture Uptake (%)	6	6	7	7	7	6	7	7	7	6
Drug Content (%)	96	97	96	97	98	98	98	98	98	99

IV. CONCLUSION

Phase solubility profile revealed that the presence of carrier increased the solubility and apparent stability constant of cefixime. The improvement in dissolution rate of cefixime from β-CD complexes is in agreement with the results of the solubility study. FT-IR and DSC studies showed no evidence of interaction between the drug and carrier. The SEM and XRD studies confirmed the amorphization of drug which offered an explanation for better dissolution rate of cefixime from solid dispersion. Solid dispersions of cefixime exhibited a preferential increase in dissolution over pure cefixime. The study shows that the dissolution rate of cefixime can be improved to a greater extent by solid dispersions technique employing an industrially feasible kneading method. The complexes prepared by the kneading method provided a dissolution rate of 95% in 30 minutes, which may be of particular interest for industrial scale preparation because of low cost and simple process involving less energy, time and equipment. It is concluded that the solid dispersion of cefixime increased the solubility and dissolution rate of drug, suggesting a possible enhancement of its oral bioavailability.

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