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PREPARATION AND EVALUATION OF FAST DISSOLVING DOSAGE FORMS OF CEFUROXIME AXETIL

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ABSTRACT

In the present work, three different approaches are employed to prepare fast dissolving forms of cefuroxime. Cefuroxime axetil (CA) and beta cyclodextrin complex is prepared by kneading method and it is found that the complex is formed in 1 : 1 molar ratio as evidenced by the phase solubility studies. Compared to the pure drug, the complex exhibited faster dissolution of the drug. Solid dispersion of the drug with polyglycolized lipid - gelucire (50/13) also significantly enhanced dissolution but the product is found to be not free flowing and is found to be unhandable. So a modified approach of depositing the drug and gelucire dispersion on microcrystalline cellulose is employed, which not only showed good free flowing property (suitable for conversion to a tablet dosage form) but also gave higher dissolution than the drug and gelucire dispersion. A solid dispersion of drug in hydroxypropyl cellulose (HPC) is prepared, which exhibited highest dissolution rate compared to the other two approaches. The CA - HPC dispersion is converted into tablet dosage forms by direct compression employing MCC or Prosolv (silicified MCC) and a combination of excipients. The formulation prepared with Prosolv gave tablets of better pharmaceutical characteristics than those prepared with MCC.

Key words: Cefuroxime, Fast dissolving tablets, Direct compression, Gelucire, Prosolv.

INTRODUCTION

Cefuroxime axetil is used orally for the treatment of patients with mild-to-moderate infections, caused by susceptible strains of microorganisms. One of the major problems of this drug is its very poor solubility in biological fluids, which results in poor bioavailability after oral administration. It shows erratic dissolution problems in the gastric and intestinal fluids, due to its poor water solubility. The rate of absorption and/or extent of bioavailability for such insoluble drugs is controlled by the rate of dissolution in the gastrointestinal fluids[1]. The peak plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) depend on the extent and rate of dissolution of the drug, respectively. The effort to improve the dissolution

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and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development. Several methods have been introduced to overcome this problem, such as, solid dispersions, complexation, Zydis technology, and the use of hydrophilic carriers.

Solid dispersion, which was introduced in the early 1970s[2], refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[2]. The solid dispersion technique has been used for a wide variety of poorly soluble drugs such as nimesulide[3], ketoprofen[4], tenoxicam[5], nifedipine[6]. Various hydrophilic carriers, such as polyethylene glycols[7], polyvinylpyrrolidone[8], hydroxypropyl methylcellulose[9], and urea[10], have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.

There are some reports on the formulation of cefuroxime solid oral dosage forms by employing solid dispersions with urea[11], Spray drying obtain a solid dispersion of cefuroxime with Gelucire 50/13[12], preparation of amorphous cefuroxime axetil nano particles by sono precipitation for enhancement of bioavailability[13].

In the present work, different approaches are employed to prepare fast dissolving dosage forms of cefuroxime by employing complexation with beta cyclodextrin, solid dispersion in hydroxypropyl cellulose and a solid dispersion in gelucire (50/13)-microcrystalline cellulose.

EXPERIMENTAL

Materials and methods

Cefuroxime axetil (CA) was procured as a gift sample from Genova Life Sciences, Bangalore, hydroxy propyl cellulose, beta cyclodextrin are obtained from Colorcon Asia (Goa, India) Gelucire (50/13) and Prosolv were obtained as a gift sample from Orchid Laboratories, Chennai. All other excipients are obtained from s.d. fine Chemicals, Mumbai. All other chemicals and solvents are of analytical grade.

Preparation of cefuroxime-beta cyclodextrin inclusion complex

Phase solubility analysis for cefuroxime

Phase solubility studies were performed according to the method of Higuchi and Connors[14] to determine the stoichiometric proportions of cefuroxime with β-cyclodextrin in the cyclodextrin complexes that will be prepared. The data was used to determine the stability constant of the complexes.

A stock solution of 0.01 M β-cyclodextrin was prepared using distilled water. These stock solutions were diluted with distilled water to give solutions in the range of 0.001 to 0.01 moles per liter of β-cyclodextrin. Excess amounts of drug were added to an aqueous solution containing various concentrations of cyclodextrin, and shaken at 25 ± 0.5°C. At equilibrium after 2 days, the supernatant was filtered (0.45 mm pore size) and spectrophotometrically assayed for drug content. No changes in λ_{max} of the drug were found after complexation with cyclodextrin, hence absorbance of the resultant solutions were recorded at 278 nm, which was the λ_{max} of the drug. From the slope and intercept value (S_0) of the phase solubility curve, the stability constant (K_S) was determined.

$$K_S = \text{Slope} / [S_0 (1 - \text{Slope})]$$

The solubility of Cefuroxime with different concentrations of beta cyclodextrin is given in Table 1 and the phase solubility diagram is shown in Fig. 1.

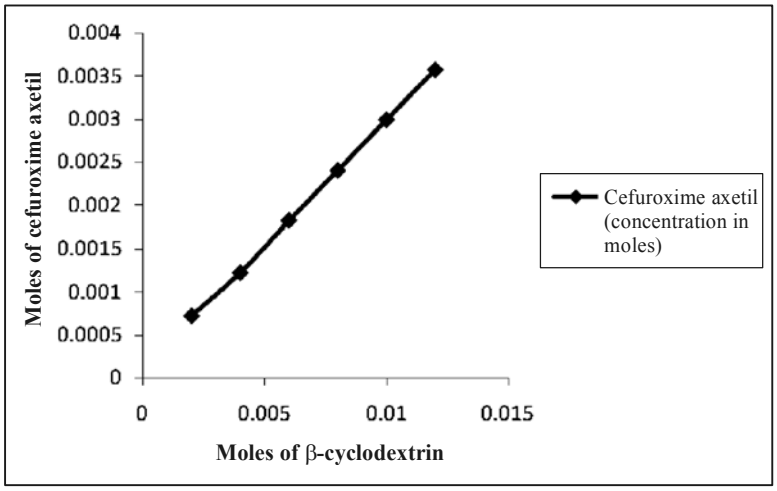

Fig. 1: Phase Solubility curves of Cefuroxime Axetil – β Cyclodextrin system

Table 1: Phase solubility data of Cefuroxime Axetil – β Cyclodextrin system

β -CD (concentration in moles/L)	Cefuroxime axetil (concentration in moles/L)
0.002	0.00072
0.004	0.00122
0.006	0.00182

Cont…

β-CD (concentration in moles/L)	Cefuroxime axetil (concentration in moles/L)
0.008	0.00240
0.010	0.00299
0.012	0.00357

Preparation by kneading method

The required quantities of the drug (cefuroxime axetil) and β-cyclodextrin were weighed accurately in a molar ratio of 1 : 1. A homogenous paste of cyclodextrin was prepared in a mortar by adding water: methanol mixture (1 : 1) in small quantities. Cefuroxime axetil powder was then added to this paste in portions, with continuous kneading, for three hours. An appropriate quantity of water: methanol mixture (1 : 1) was added further to maintain suitable consistency of the paste. This paste was dried in a hot air oven at $45^{o} – 50^{o}$C for 24 hrs. The dried complexes were then powdered and passed through sieve No. 100 and stored in airtight containers till further use.

Preparation of Cefuroxime - Gelucire dispersion

The drug and the Gelucire (Ge) solid dispersions were prepared in 1 : 1 ratio. The drug is first dissolved in methanol and latter gelucire is also dissolved in it to get a clear solution. Then methanol is evaporated under reduced pressure (8 in Hg Abs) at 30^{o}C. The resulting solid powder was placed in a vacuum drier for 24 hours to remove the residual solvent, if any and then stored in a desiccated environment until further study.

As the dispersion prepared in gelucire as such is found to be not free flowing a modified solvent deposited system is prepared as given below.

To the methanolic solution of CA and Gelucire, microcrystalline cellulose is added (CA : Ge : MCC – 7 : 3 : 5). The solvent methanol is removed by evaporation and the mass obtained is powdered and passed through mesh no. 100 and stored in a dessiccator till further study.

Preparation of Cefuroxime - Hydroxypropyl cellulose dispersion

The drug and the hydroxypropyl cellulose (HPC) solid dispersions were prepared in 1 : 1 ratio. The drug is first dissolved in methanol and latter hydroxypropyl cellulose is also dissolved in it to get a clear solution. Then methanol is evaporated under reduced pressure (8 in Hg Abs) at 30^{o}C. The resulting solid powder was placed in a vacuum drier for 24 hours

to remove the residual solvent, if any and then stored in a desiccated environment until further study.

Estimation of Cefuroxime

Cefuroxime content in the various solid dispersion prepared is estimated by UV-spectrophotometric method. Cefuroxime from accurately weighed samples was extracted into methanol and the extracts were suitably diluted with 0.07 N HCl and assayed for cefuroxime by measuring the absorbance at 278 nm using 0.07 N HCl as blank. The method obeyed Beer's law in the concentration range of 5-25 µg/ mL. The drug contents of various products prepared are given in Table 2.

Table 2: Drug contents of various dispersions or complex of Cefuroxime axetil prepared

S. No.	Product	Drug content %	Standard deviation	Co-effiecent of variation %
1	CA : β-CD (1 : 1)	48.23	0.2049	0.88278
2	CA : HPC (1 : 1)	49.80	0.01211	0.1839
3	CA : GE : MCC (7 : 3 : 5)	46.40	0.0150	0.0040

Dissolution rate studies

The dissolution rate of cefuroxime in pure form and from various solid dispersions and complex was studied using USP dissolution rate test apparatus employing a paddle stirrer. In 900 mL of dissolution medium (0.07 N HCl), a sample of the product equivalent to 125 mg of cefuroxime is added. The temperature is maintained at 37^{o}C and a speed of 50 rpm was employed to stir the paddle. A 5 mL aliquot of dissolution medium was withdrawn at various intervals of time and immediately filtered through Whatman No. 1 filter paper, the same volume of fresh dissolution medium was replaced into dissolution vessel. And the concentration of Cefuroxime axetil in the withdrawn samples was determined spectrophotometrically by measuring the absorbance at 278 nm.

Formulation of fast dissolving tablets

The fast dissolving tablets of cefuroxime were prepared employing Cefuroxime-Hydroxypropyl cellulose dispersion. The tablets were prepared by direct compression method using Microcrystalline Cellulose or Prosolv as the directly compressible vehicles. Two different superdisintegrants Crosscarmellose or Sodium starch glycolate were employed. The details of the formulation are given in Table 3.

Table 3: Formulation of CA-HPC dispersion into tablets

Ingredients (mg/tab)	F-1	F-2	F-3	F-4	F-5
CA-HPC (dispersion equivalent to 125 mg of CA)	250	250	250	250	250
Microcrystalline cellulose	160	160	-	-	-
Prosolv	-	-	160	160	140
Croscarmellose	20	-	20	-	20
Sodium starch glycolate	-	20	-	20	20
Talc	10	10	10	10	10
Magnesium stearate	10	10	10	10	10

X - Ray diffraction study

X ray powder diffraction patterns of the various products were obtained using an X - ray powder diffractometer PANalytical X'pert PRO. The diffractograms were run at 2 theta and oscillated between 10-90^{o}, employing Ni filtered Cu K_{α} radiation.

IR studies

All the prepared solid dispersions were subjected to FTIR spectroscopic studies to determine drug-carrier interaction. The FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks, using a Fourier Transform IR spectrophotometer (BRUKER ALPHA). The samples were prepared in KBr disks by means of a hydrostatic press and the samples were kept in the IR path. The scanning range was 400 to 4000 cm^{-1} and the resolution was 2 cm^{-1}. The sample spectra were analyzed using OPUS software.

RESULTS AND DISCUSSION

Preparation of Cefuroxime-β cyclodextrin complex

Phase solubility analysis

The phase solubility profile (shown in Fig. 1 and given in Table 1) indicated that the solubility of CA has increased in the presence of β-CD. The phase solubility curve indicated a linear increase in solubility of CA as a function of β-CD concentration, demonstrating A_L-type phase solubility curve. The possible stoichiometry of the complex assessed was 1 : 1

as the slope of this solubility diagram was all less than 1. The stability constant calculated for the complex is found to be 3037 M^{-1}. It is reported that cyclodextrin-drug complexes with the values of Ks in the range of 200 to 5,000 M^{-1} show improved stability and dissolution properties.

Characterization of the complex and the dispersions

The inclusion complex prepared by using kneading method was found to be white and free-flowing powder.

The dispersion of CA in Gelucire alone in 1 : 1 ratio is found to be not handable and as such a solvent deposited system of the dispersion on microcrystalline cellulose was prepared and it is found to be free flowing. Similarly the dispersion in hydroxypropyl cellulose is also found to be free flowing. The drug content values in various products prepared are given in Table 2. Low s.d. values in the percent drug content ensured uniformity of drug content in the various prepared products.

The dissolution of CA from the cyclodextrin complex and from the 2 solid dispersions is found to be higher that that of pure CA. The dissolution rate constant values are given in Table 4 and the dissolution profiles are shown in Fig. 2. With complexation in beta cyclodextrin and dispersion in Gelucire and in HPC, there was 9.3, 5.3 and 11.65 fold raise in the dissolution rate respectively. It was observed that at the proportion that gelucire was employed the resulting product is not free flowing as such and not very conducive for subsequent conversion to a suitable solid dosage form. So the dispersion in Gelucire is deposited on microcrystalline cellulose which not only resulted in a very free flowing powder but also the dissolution rate is enhanced as evidenced by the higher K_1 value. Of the various products prepared the CA - HPC dispersion gave the highest dissolution (dissolution efficiency 70.37% and T_{50} of 10 minutes).

Table 4: Dissolution parameters of fast dissolving dispersions/complexes of CA

Product	Percent dissolved		D.E $_{30}$	T_{50} (in min.)	K_1 (min^{-1})
	PD-15	PD-45			
CA (Pure drug)	8.11	19.15	9.259	∞	0.005158
CA- : β.CD	61.28	86.25	55.55	13	0.04816
CA : Gel : MCC	35.72	68.45	33.33	28	0.02708
CA : HPC	81.25	98.55	70.37	10	0.06010

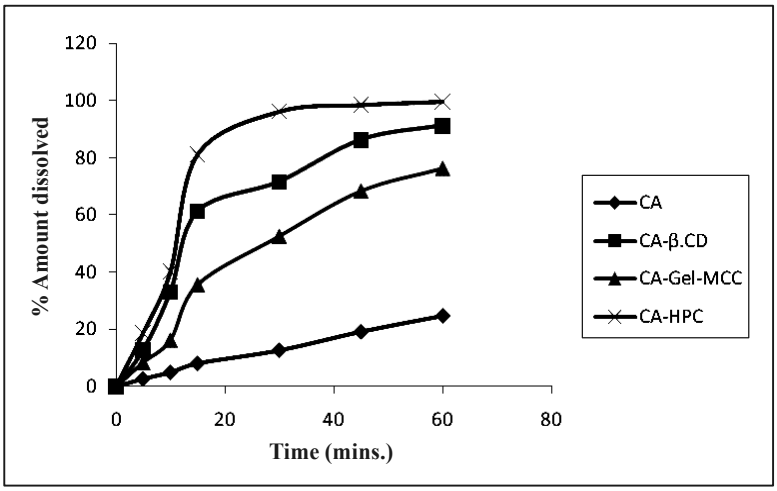

Fig. 2: Dissolution profiles of various dispersions and complex of Cefuroxime axetil

Evaluation of increased dissolution

Solubility XRD study

To evaluate the mechanism involved in the increased dissolution rate of cefuroxime axetil from the solid dispersions or the complex prepared, solubility and XRD studies were performed.

The solubility of CA was found to be 62, 187, 112 and 247 µg/mL in distilled water (pH 6.8) and in distilled water containing 1% beta cyclodextrin or Gelucire or HPC, respectively. Thus the solubility of CA was found to be enhanced in the presence of the 3 carriers, particularly with HPC.

Diffractograms of the different products obtained are shown in Fig. 3 and 3A. X - Ray diffractograms of CA exhibited characteristic crystalline diffraction pattern whereas in the case of the solid dispersions in the 3 carriers the sharp diffraction peaks of CA have disappeared. Absence of diffraction peaks indicates that the drug CA is essentially in amorphous form in the complex or the solid dispersion. Thus HPC or Gelucire are inhibiting the crystallization of CA during the preparation of the dispersions.

Hence the fast and rapid dissolution of CA is due to the following reasons –

(a) The existence of CA in amorphous form in the dispersions and since the amorphous form is a high energy form - it produces faster dissolution and

(b) The enhancing effect of beta cyclodextrin or Gelucire or HPC on the solubility of CA.

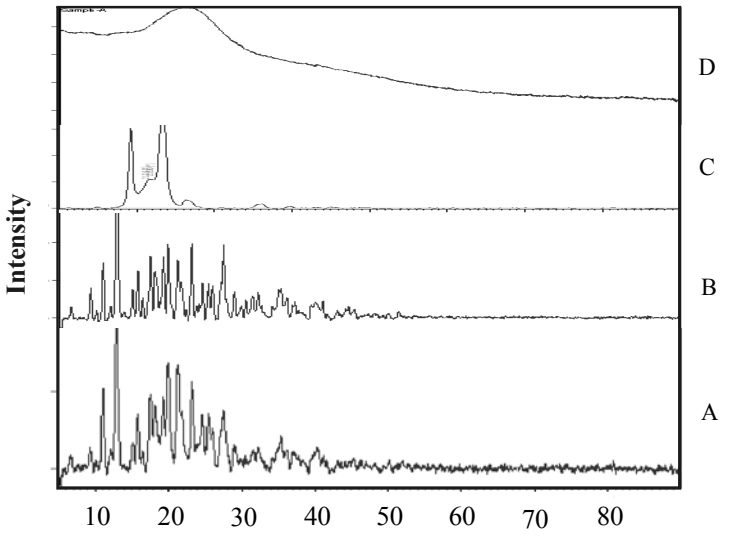

Fig. 3: XRD Spectra of (A) Cefuroxime Axetil (B) Beta Cyclodextrin (C) Gelucire (D) Hydroxy propyl cellulose

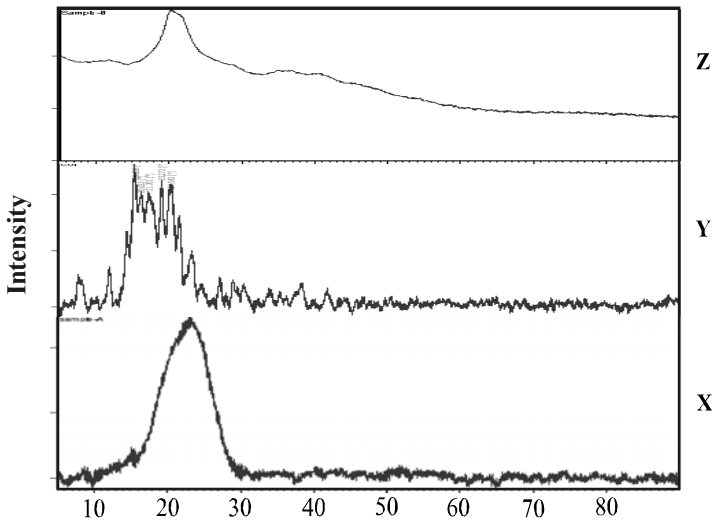

Fig. 3A: XRD Spectra of various products: (X) Cefuroxime Axetil-Beta Cyclodextrin complex (Y) Cefuroxime Axetil- Gelucire dispersion and (Z) Cefuroxime Axetil –Hydroxypropyl cellulose dispersion

In addition, other factors such as likely reduction in particle size, absence of aggregation and agglomeration between drug particles and good wettability and dispersibility of CA in the 3 carriers might also have contributed to the increased dissolution rate of CA.

Drug and polymer interaction studies by FT-IR

FT-IR spectra of cefuroxime axetil and the various products are shown in Fig. 4. The IR spectrum of cefuroxime axetil pure drug exhibits bands in the region of 3469.2, 1677.68, 1390, 943, 1071.34 cm^{-1}, due to the presence of NH-Amide, C=O, C-N, C-C and C-S linkage, respectively. These bands are also present in the spectra of drug loaded in various polymers. The absence of any significant change in the IR spectral pattern in the various products indicated the absence of any interaction between the drug and the polymers. So the findings of the IR spectral investigations indicate that there is no significant interaction between the drug and the polymers employed in the present study.

Formulation of CA-HPC dispersion into tablet

The details of various formulations are shown in Table 3. The characteristics of different tablets prepared are given in Table 5. It was observed that all the tablets were found to be having satisfactory characteristics of hardness, friability and weight variation. However in between MCC and Prosolv, the tablets prepared employing Prosolv are found to be giving tablets with better characteristics. Prosolv which is a silicified MCC (SMCC) is reported to posses the following properties-high compactibility, enhanced lubrication efficiency, improved blending and good intrinsic flow.

Table 5: Hardness, friability, disintegration time and weight variation of CA tablet formulations

Formulation	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration time (in min-sec)	Weight variation (maximum % deviation)	T_{50} (in min.)	K_1 (min^{-1})
F-1	5.5	0.64	6-45	3.5	12	0.03859
F-2	5.75	0.78	6-15	2.5	13	0.04444
F-3	6.25	0.57	3-45	1.25	13	0.05116
F-4	6.00	0.50	3-27	1.45	12	0.05609
F-5	6.00	0.47	1-35	1.05	9	0.06010

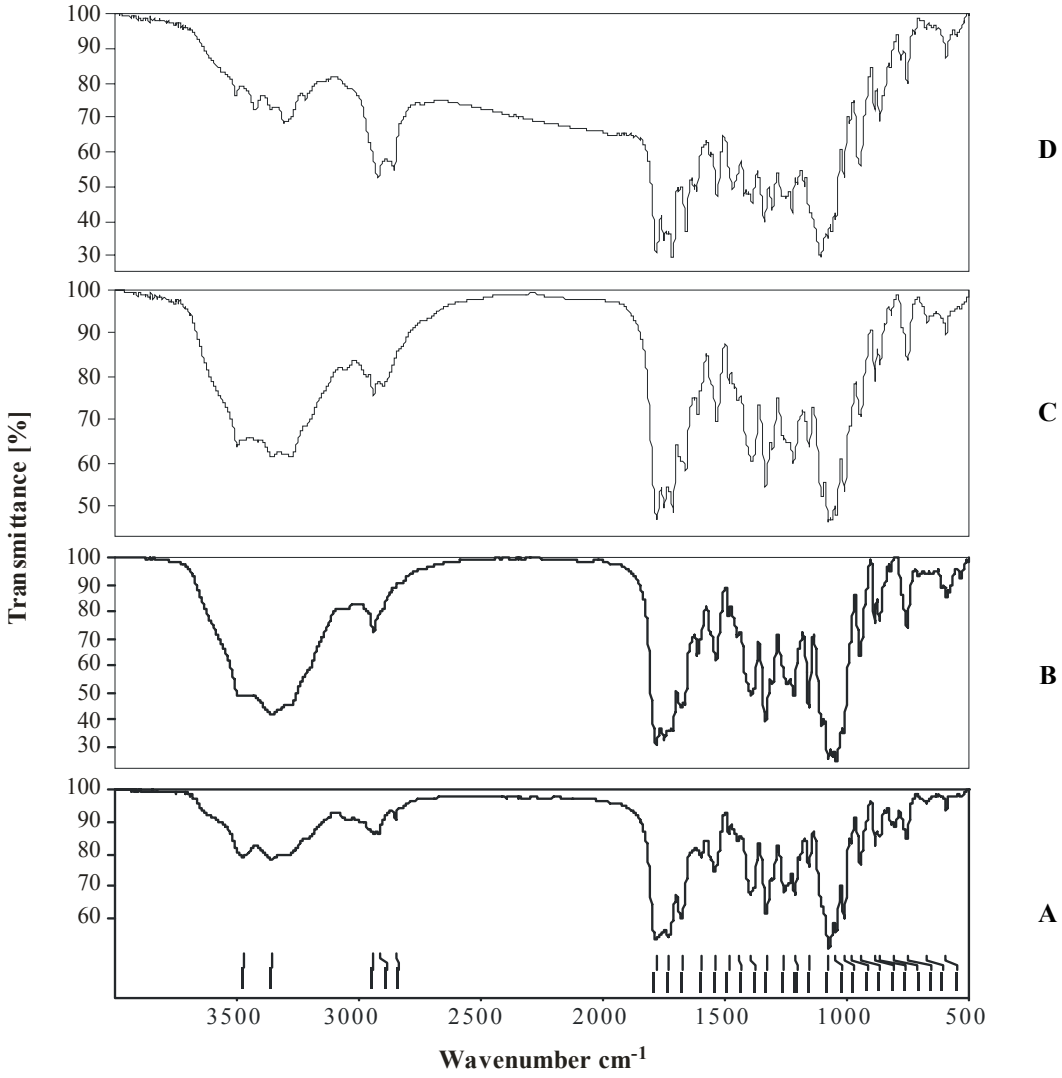

Fig. 4: IR Spectra of (A) Cefuroxime axetil (B) Cefuroxime axetil - Beta cyclodextrin complex (C) Cefuroxime axetil - Gelucire dispersion and (D) Cefuroxime axetil - Hydroxypropyl cellulose dispersion.

SMCC shows higher bulk density than common types of MCC. Tabletting studies[15,16] have shown that SMCC has enhanced compactibility and reduced lubricant sensitivity. Products formulated with SMCC showed[17] faster dissolution than the products formulated with modified starches (pregelatinised starch etc). In the present investigation also, it was observed that tablets of CA - HPC dispersion prepared with Prosolv (SMCC)

gave tablets of good hardness, low friability and also rapid disintegration and dissolution. Of all the formulations, F5 showed the highest dissolution rate of 0.0601 min^{-1} and a T_{50} of 9 minutes.

CONCLUSION

From the findings of the present investigations, the following conclusions can be drawn.

(i) Cefuroxime axetil and beta cyclodextrin inclusion complex could be prepared in 1 : 1 molar ratio.

(ii) The cefuroxime axetil and gelucire solid dispersion prepared was found to be not free flowing and unhandable and a cefuroxime axetil - gelucire - MCC solvent deposited system is found to be more free flowing.

(iii) The dissolution rate of the drug cefuroxime is found to be highest from the CA - HPC dispersions prepared.

(iv) The drug when present in the polymers - is in reduced crystalline state, which is contributing to the higher dissolution rate of the drug.

(v) There is no interaction between the drug and the polymers employed in the present study as evidenced by the IR Spectra.

(vi) Tablets of CA-HPC dispersion could be prepared by direct compression employing MCC or SMCC (Prosolv).

(vii) Tablets prepared with Prosolv gave tablets of better pharmaceutical characteristics than those prepared with MCC.

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