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ORIGINAL ARTICLE

# A comparative study of complexation methods for cefdinir-hydroxypropyl-β-cyclodextrin system

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**Abstract** The aim of this study was to investigate the effect of hydroxypropyl-β-cyclodextrin (HPβCD) on the solubility and dissolution rate of Cefdinir (CEF). The methods that were employed to prepare CEF–HPβCD complexes were Kneading (KN), Co-evaporation (CE), Spray drying (SD) and a novel approach of Microwave irradiation (MWI). The formation of inclusion complexes with HPβCD in the solid state, were characterized by Differential Scanning Calorimetry (DSC), Fourier Transformation Infrared spectroscopy (FTIR), Proton Nuclear Magnetic Resonance Spectroscopy (NMR), X Ray Diffraction (XRD) and Scanning Electron Microscopy (SEM) studies, and comparative studies on the in vitro dissolution of CEF were carried out. Phase solubility profile with HPβCD was classified as $A_L$ type, indicating the formation of 1:1 stoichiometric inclusion complexes. Characterization of binary systems by DSC, FTIR, NMR, XRD and SEM indicated that SD and MWI method resulted in formation of true complexes. Binary systems showed significant increase in dissolution rate as compared to plain drug. Amongst the various binary systems, MWI products were prepared in least time with better yield and highest dissolution rate.

**Keywords** Cefdinir · Hydroxypropyl-β-cyclodextrin · Inclusion complex · Dissolution rate · Microwave irradiation method

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## Introduction

Cefdinir (CEF), [6R-[6α, 7β (Z)]-7-[(2-amino-4-thaizolyl) (hydroxyimino) acetyl] amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0]-oct-2-ene-2-carboxylic acid, is a semi synthetic third generation oral cephalosporin, displaying antibacterial properties. It is used in the clinical practice for the treatment of acute chronic bronchitis, rhinosinusitis and pharyngitis [1]. CEF is a poorly water soluble drug with an aqueous solubility of 0.4 mg/mL. As poor solubility and in turn slower dissolution rate are detrimental in poor bioavailability of any drug, it can be confidently said that poor solubility of CEF leads to its low bioavailability of 21–26% [2].

One of the methods to increase solubility is to prepare inclusion complexes with cyclodextrins. Natural cyclodextrins (CDs) are cyclic oligosaccharides made up of glucose molecules linked by α-(l,4) bonds, α-, β-, and γ-cyclodextrins contain six, seven and eight glucose units, respectively, [3, 4]. Cyclodextrin inclusion complexes have been shown to improve the stability [5], solubility [6] and bioavailability [7] of many drugs. Recently, certain hydroxypropylated derivatives of CDs have been shown to display most of the useful properties of CDs without being toxic [8, 9]. HPβCD have gained importance, because of its suitable cavity size and greater hydrophilicity. There have been reports in improvement in the solubility and overall bioavailability of a number of drugs such as Glibenclamide [10], Vinpocetin [11], Lamotrigine [12] etc. by complexation with HPβCD.

There are various methods being used traditionally to prepare inclusion complexes (IC). These methods include co-evaporation (CE), kneading (KN), co-grinding (CG), spray drying (SD) and freeze drying (FD) [13]. All of these methods suffer from two major drawbacks as they are time

consuming and they involve the utilisation of large volume of organic solvent. Thus in order to bypass the disadvantages associated with traditional complexation techniques, novel methods like microwave irradiation (MWI) and complexation using supercritical fluid (SCF) technology have been explored. SCF technique makes use of specialised equipment and it is not feasible to be scaled up. On the other hand, MWI does not suffer from any of the above mentioned drawbacks [14, 15]. Microwaves have the ability to penetrate the substance. The molecules characterized by a dipolar moment are able to absorb microwave energy and convert it into heat [16]. This phenomenon occurs when the microwave frequency is close to the resonance frequency of the polar molecules. The efficient heating of materials by microwaves is dependent on the capacity of a specific material to absorb microwave energy. In fact with respect to conventional heating, i.e., conduction, convention or radiation with infrared light, microwaves irradiation offers several advantages such as: rapid volumetric heating, no overheating at the surface, addressable heating, energy-saving and low operating cost making microwaves a very attractive tool in organic chemistry [16, 17]. In addition the main advantage of not using organic solvents is the absence of any risk originating from residual solvents [18].

The use of MWI as a method for formation of inclusion complexes with HP$\beta$CD is not well explored and there are very few reports of the same. Microwave energy has been employed to change the crystalline state of a drug, instead of conventional heating. Moneghini et al. have reported the use of MWI for generation of Ibuprofen-HP$\beta$CD inclusion complex to improve is solubility [19]. Wen et al. have utilized MWI method for complexing CAR with $\beta$CD. Instrumental characterization and elemental analysis confirmed the complexation and highlighted the utilisation of MWI method for CD complexation [20].

Few researchers have tried to improve the aqueous solubility of CEF by CD complexation. Out of them, Aleem et al. have reported the formulation of IC of CEF with $\beta$CD and HP$\beta$CD by kneading technique, which showed improvement in the solubility of CEF [21]. The second study is being patented by Ren et al., which involves the complexation of CEF with $\beta$CD and its pharmaceutically acceptable derivatives such as HP$\beta$CD, sulphobutyl ether $\beta$CD and sulphobutyl ether HP$\beta$CD [22].

The main objective of the present study was to assess the feasibility and advantages offered by MWI method to prepare IC between CEF-HP$\beta$CD. To prove the superiority of MWI techniques, IC complexes were prepared by various other traditional techniques such as KN, CE and SD. The formation of inclusion complex was proven by Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) and X ray Diffractometry (XRD). Fourier Transform InfraRed spectroscopy (FTIR) and Nuclear Magnetic Resonance Spectroscopy (NMR) studies focused upon identifying the groups being encapsulated in the CD cavity. In order to prove the improvement in the solubility of drug prepared by MWI, aqueous solubility and dissolution rate were assessed and compared with that of plain CEF and CEF-HP$\beta$CD PM and IC made by other techniques.

## Experimental

### Materials

CEF was generously gifted by Alkem Research Lab. Ltd (India), HP$\beta$CD (MW-1380) was kindly provided by Wacker Fine Chemical Corporation (Germany). These chemicals were used as received without any further treatment. All solvents and reagents used were of analytical reagent grade purity. Double distilled water was used throughout the study.

### Phase-solubility studies

In order to determine the stochiometry of CEF-HP$\beta$CD complexation, phase solubility studies were carried out as per the method developed by Higuchi and Connors [23]. 10 mL of aqueous solutions of HP$\beta$CD ranging from 0 to 10 mM were taken in which an excess amount of drug (50 mg) was added The suspensions were then shaken at room temperature on a mechanical shaker for 48 h. After the attainment of equilibrium, the suspensions were filtered, duly diluted and the concentration of CEF was determined spectrophotometrically at 287 nm. The apparent stability constant Ks was calculated from the phase-solubility diagram according to the following equation.

$$Ks = \frac{\text{slope}}{So(1 - \text{slope})}$$

So is the solubility of CEF in absence of HP$\beta$CD.

### Preparation of binary systems

Binary systems of CEF-HP$\beta$CD were prepared in 1:1 M ratio by the following techniques.

#### *Kneading method (KN)*

To prepare binary system by KN method, preweighed quantities of CEF and HP$\beta$CD were taken in the mortar and triturated for 20 min. The resultant mixture was further kneaded with 66% ethanol for 45 min. The pasty mass obtained was kept overnight in a vacuum desicator for

drying. The dried product was finally sifted through sieve no 80 and collected.

*Co-evaporation method (CE)*

To prepare binary system by CE method, accurately weighed quantities of CEF and HP$\beta$CD were added to minimal volume of 66% ethanol and sonicated on a bath sonicator for 5 min in order to get a clear solution. This solution was then stirred on a magnetic stirrer at 60 °C. The pasty mass thus obtained was dried by storing overnight in a vacuum desicator, sifted through sieve no. 80 and collected.

*Spray drying method (SD)*

Accurately weighed quantities of CEF and HP$\beta$CD were dissolved in 100 mL of 66% ethanol. The resultant solution was dried using Spraymate LSD 48 apparatus. The spray dryer was operated at inlet temperature of 95 °C, outlet temperature of 55 °C, atomising pressure of 2 kg/cm$^2$ and a flow rate of 4 mL/min. This was done as per the method reported by Esclusa-Diaz et al. [10].

*Microwave irradiation method (MWI)*

Ethanol (66%) was added to a pre-triturated mixture of CEF and HP$\beta$CD. The resultant suspension was sonicated for 5 min to get a clear solution. The solution was further mirowaved at a power of 245 watts at 60 °C for a period of 90 s. In order to separate the uncomplexed CEF and HP$\beta$CD, ethanol was added to the microwaved product and then filtered. The residue was dried under vacuum and collected. The method was in accordance with the one utilized by Zhao et al. for the complexation of andrographolide with $\beta$CD [14].

For comparision purpose Physical Mixture (PM) was prepared.

CEF and HP$\beta$CD were sifted through sieve no. 80 and then mixed thoroughly to prepare PM.

Time required and yield obtained from various complexation methods

In order to determine the efficiency of complexation method, the total yield and the time required for preparation of binary systems was recorded.

*Assay of binary systems*

Binary systems equivalent to 50 mg of CEF were weighed and dissolved in 100 mL methanol with the aid of sonication. The concentration of CEF in binary systems was determined spectrophotometrically at 287 nm.

Characterization of CEF-HP$\beta$CD binary systems

*Differential scanning calorimetry*

DSC studies were carried out using a Mettler Toledo DSC 882e apparatus. Approximately 5 mg of sample was sealed in the aluminium sample pan and heated at the rate of 10 °C/min. The heating was carried out from room temperature to 300 °C, wherein dry nitrogen was used a purge gas.

*Fourier transformation infrared spectroscopy*

FTIR spectra of drug, CD's and all binary systems were recorded on Jasco-700 FT-IR spectrophotometer using KBr discs. The instrument was operated under dry air purge and the scans were collected at scanning speed of 2 mm/s with resolution of 4 cm$^{-1}$ over the region of 4000–400 cm$^{-1}$. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due to cyclodextrin and appearance of new peaks due to complex formation.

*Proton nuclear magnetic resonance ($^1$H NMR) spectroscopy*

H$^+$ spectra of CEF, HP$\beta$CD and MWI system were taken at 25 °C on a Variant Mercury Plus model operating at a proton frequency 400 MHz using a 5 mm sample tubes. DMSO [2.5 ppm from Tetramethylsilane (TMS)] was used as solvent. Chemical shifts were expressed in ppm downfield from the signal (0 ppm) of TMS. The magnetic field remained stable with the deuterium field lock, being confirmed by negligible change in the signal frequency before and after each experiment.

*X-ray diffraction spectroscopy*

Powder X-ray diffraction patterns were recorded using Phillips P Analytical X'Pert PRO powder X-ray diffractometer using Ni-filtered, CuK$\alpha$ radiation, a voltage of 40 kV and a current of 30 mA. The scanning rate employed was 1°/min and samples were analyzed between 2$\theta$ angles of over 5–45°. The powder diffraction patterns of CEF, HP$\beta$CD and MWI system were recorded.

*Scanning electron microscopy*

The surface morphology of drug, HP$\beta$CD and all binary systems of drug were examined by a scanning electron microscope (JSM-5510, JEOL, USA). The samples were fixed on a brass stub using double sided tape and made

electrically conductive by coating with a thin layer of gold by sputter coater Palaron E 5100. The photographs were taken at an electric voltage of 20 kV and a magnification of 500 and 3500.

*In vitro drug release study*

The in vitro drug release study was carried out using USP XXIII dissolution apparatus type-II (Paddle type). Binary systems equivalent to 125 mg of CEF were weighed accurately. The sample was then introduced into 900 mL of dissolution medium (phosphate buffer pH 6.8 or water). Aliquots were withdrawn at 10, 20, 30, 45, 60, 90, 120, 150 and 180 min, duly diluted and concentration of CEF was determined spectrophotometrically. For comparison purpose, dissolution study of plain drug (125 mg) was also carried out as per the above mentioned procedure.

## Results and discussion

Phase solubility studies

The phase-solubility plot of CEF- HP$\beta$CD (Fig. 1) showed that the aqueous solubility of CEF increased linearly with the concentration of HP$\beta$CD. As the slope of the plot was $0.4446 + 0.0017$, it could be concluded that the phase solubility profile was of $A_L$ type, indicating 1:1 stoichiometry. The stability constant of CEF-HP$\beta$CD system as reported by Aleem et al. [21] was 58.60 $M^{-1}$, whereas the stability constant deduced from the present experiment was $53.66 + 2.23$ $M^{-1}$.

Time required and yield obtained from various complexation methods

Table 1 gives the yield obtained and time required to prepare binary systems by various complexation techniques. From the results it could be inferred that, MWI took the shortest time for completion (6.5 min) and gave maximum yield

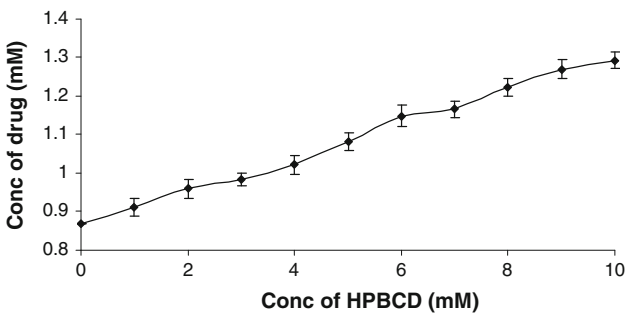


**Fig. 1** Phase solubility diagram

**Table 1** Time required and percentage yield from various methods of complexation

| Complexation method | Time required (min) | Percentage yield |
|---|---|---|
| Kneading | 65 | 56.95 |
| Co-evaporation | 95 | 58.36 |
| Spray drying | 25 | 50.32 |
| Microwave irradiation | 6.5 | 61.57 |

(61.57%) whereas the longest time for completion was taken by CE method (95 min) and SD method gave the least yield (50.32%) amongst all the techniques.

*Assay of binary systems*

The results of assay of each binary system are reported in Table 2. From the results of assay it was observed that drug content ranged from 97.42% (KN) to 99.88% (MWI).

Characterization of CEF-HP$\beta$CD binary systems

*Differential scanning calorimetry*

DSC thermograms of CEF, HP$\beta$CD and their binary systems are depicted in Fig. 2. From the figure it can be observed that thermogram of CEF (Fig. 2a) gave a sharp exothermic peak at 227.59 °C corresponding to its melting point. Thermogram of HP$\beta$CD showed a broad endothermic peak at 80.09 °C which indicated a loss of water molecule. The thermograms of the PM (Fig. 2c), KN (Fig. 2d) and CE (Fig. 2e) products showed two peaks, one corresponding to CEF with decreased intensities and other of HP$\beta$CD. This lead to the conclusion that the complexation was incomplete. On the other hand, thermograms of SD and MWI products showed a complete disappearance of exothermic CEF peak and the presence of slightly shifted peak of HP$\beta$CD. This proved that the products of SD and MWI were true inclusion complexes [24].

*Fourier transformation infrared spectroscopy*

Figure 3 gives the FTIR spectra of CEF, HP$\beta$CD and all binary systems. The FTIR spectrum of CEF (Fig. 3a)

**Table 2** Drug content in various binary systems

| Solid complexes | Amount of drug (mg) | % Drug content |
|---|---|---|
| Drug: HP$\beta$CD (PM) | 49.900 | 99.800 |
| Drug: HP$\beta$CD (KN) | 48.710 | 97.420 |
| Drug: HP$\beta$CD (CE) | 48.810 | 97.620 |
| Drug : HP$\beta$CD (SD) | 49.000 | 98.000 |
| Drug : HP$\beta$CD (MWI) | 49.940 | 99.880 |

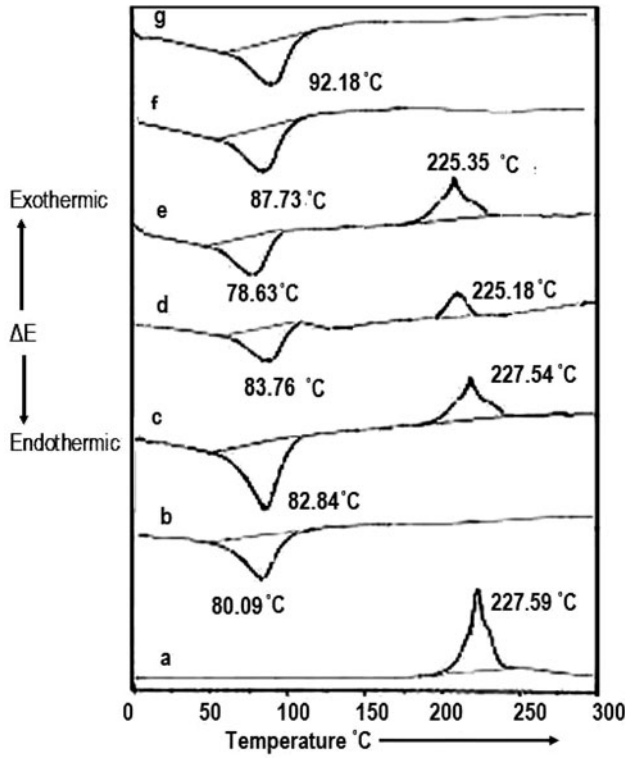


**Fig. 2** DSC thermograms of (*a*) CEF, (*b*) HP*β*CD, (*c*) PM, (*d*) KN, (*e*) CE, (*f*) SD and (*g*) MWI

showed principle absorption peaks at 3299.98 $cm^{-1}$(O–H stretching of hydroxyl group of COOH), 2968.24 $cm^{-1}$ (C–H stretch of the cyclic ring),1766.67 $cm^{-1}$ (C=O stretching of COOH group) 1683.74 $cm^{-1}$ (C=C stretching), 1623.95 $cm^{-1}$ (C=C stretching of aromatic ring), 1542.37 $cm^{-1}$ (N–H bending), 1428.64 $cm^{-1}$ (C–N stretching) and 657.68 $cm^{-1}$ (C–S stretching). The IR spectrum of HP*β*CD showed prominent peaks at 3384.84 $cm^{-1}$ (O–H stretching), 2929.67 $cm^{-1}$ (C–H stretching), 1652.89 $cm^{-1}$ (H–O–H bending). The FTIR spectrum of PM showed peaks corresponding to both parent compounds but three peaks of CEF, namely 3299.98, 2968.24 and 657.68 $cm^{-1}$ were slightly shifted showing some signs of interaction between CEF and HP*β*CD. Spectrums of KN, CE and SD compounds were similar to that of PM with an even more decrease in the peaks of CEF which were nonetheless present. This observation helped in concluding that the complex formation was not complete. In case of spectra of MWI product, the three peaks of CEF disappeared completely. These 3 peaks corresponded to the cephem ring with carboxyl functionality. This led to the conclusion that cephem ring along with COOH functional group gets entrapped in the CD cavity. This observation was in concurrence with those made by Aleem et al. [21].The results of FTIR spectroscopy echoes the result obtained from DSC indicating that true complex was formed only in case of MWI technique.

*Proton nuclear magnetic resonance spectroscopy*

NMR studies are carried out to study the modes of inclusion and stochiometries involved [25]. $^{1}H$ and $^{13}C$ NMR can be used for this purpose. In the present study, $^{1}H$ NMR spectroscopy was employed to elucidate the structure of CEF-HP*β*CD IC. Table 3 gives the chemical shift values of HP*β*CD in the free and complexed form.

The chemical shifts of HP*β*CD protons showed noteworthy, upfield changes of proton H-3 (0.033 ppm) and H-5 (0.014 ppm) which are located on the inner surface of the HP*β*CD cavity. These two later shifts clearly prove formation of inclusion complex and prove that the driving forces for the formation of the inclusion complex are hydrophobic interactions (Table 3).

In order to further confirm the inclusion complexation, 1H NMR spectroscopy data of CEF was evaluated. Figure 4 illustrates the structure of CEF along with assignment of protons. The difference in chemical shift values between CEF in the free and complexed state are shown in Table 4. The H-3–H-6 atoms representing the cephem ring with COOH functional group experienced a downfield shift attributable to diminished freedom of rotation caused by the penetration into the HP*β*CD cavity. It can thus be deduced that cephem ring along with COOH functionality entered the HP*β*CD cavity. This observation is in concurrence with that obtained from FTIR data.

*X-ray diffraction spectroscopy*

Powder X-ray diffraction analysis was employed in the characterization of crystalline structure. The analysis of a characteristic region in the diffraction pattern reflects the crystallinity of the sample. Complexation is confirmed when diffraction pattern of newly formed substance differs from the carrier. A reduction in, or even the disappearances of the characteristic maxima in the diffraction pattern of the guest molecule and CD together marked by appearance of new peaks in the diffraction pattern of the complex are the indications of formation of inclusion complexes.

The X ray diffractograms of drug, HP*β*CD and MWI complex were recorded and are depicted in Fig. 5 (Table 5).

The XRD pattern of CEF revealed many peaks that were intense and sharp. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of MWI binary system with those of reference. The relative degree of crystallinity (RDC) was determined according to the equation.

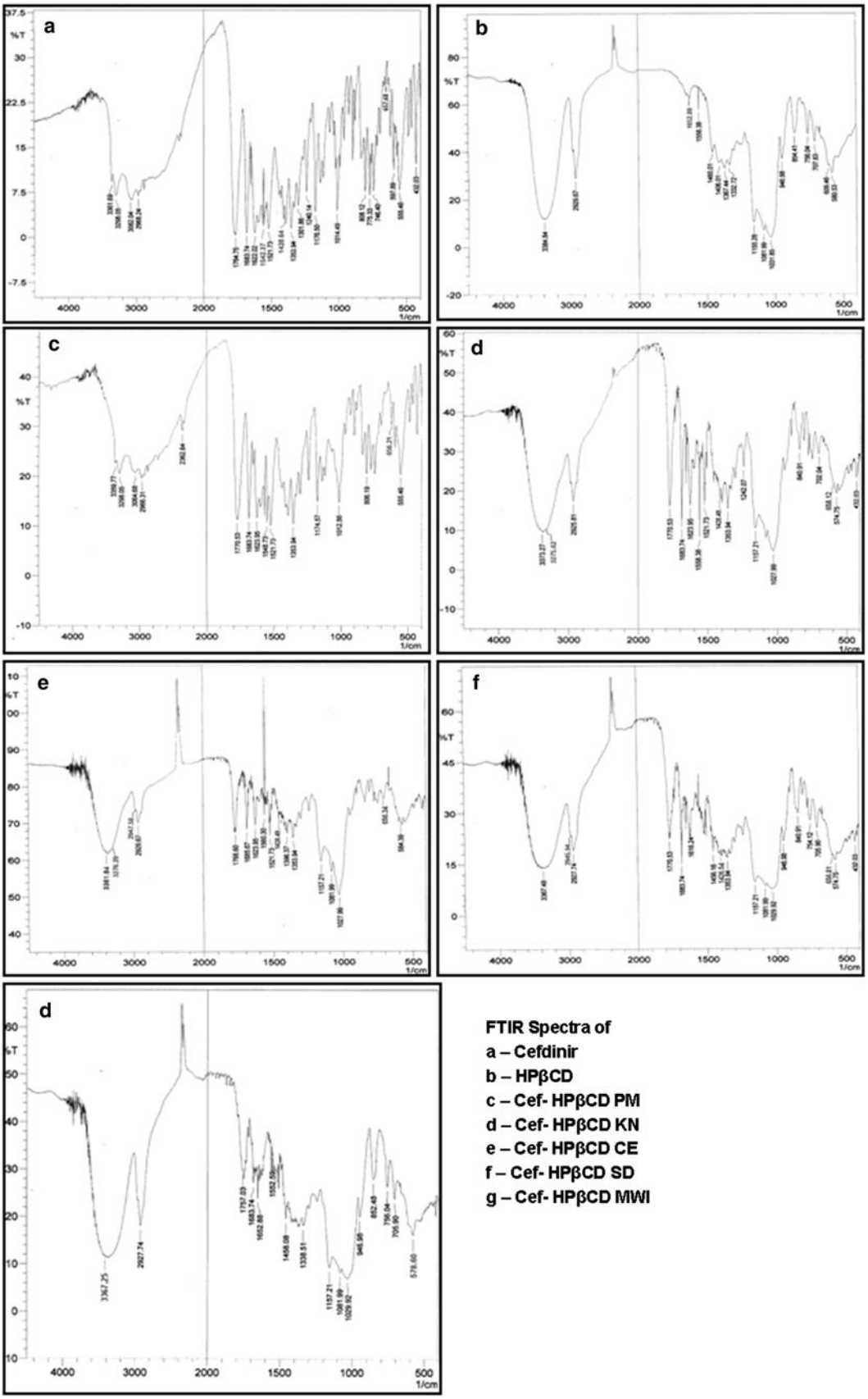


**Fig. 3** FTIR spectra of **a** CEF, **b** HP$\beta$CD, **c** PM, **d** KN, **e** CE, **f** SD and **g** MWI

**Table 3** Chemical shift values of HP$\beta$CD in free and complexed forms

| Proton no. | HP$\beta$CD ($\delta$0) | HP$\beta$CD-CEF ($\delta$) | $\Delta\delta$ ($\delta - \delta$0) |
|---|---|---|---|
| H 1 | 4.826 | 4.789 | −0.037 |
| H 3 | 3.603 | 3.570 | −0.033 |
| H 5 | 3.364 | 3.350 | −0.014 |
| H 6 | 3.557 | 3.549 | −0.008 |

Protons H 2 and H 4 are indistinguishable because of overlapping

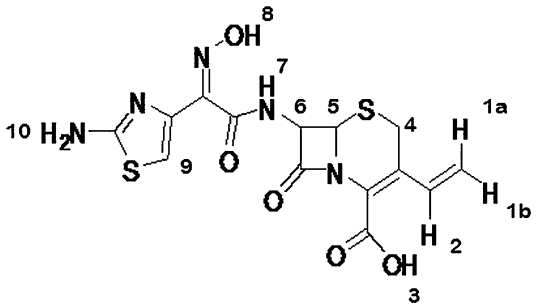


**Fig. 4** Structure of CEF along with assignment of protons

**Table 4** Chemical shift values of CEF in free and complexed forms with HP$\beta$CD

| Proton no. | CEF ($\delta$0) | HP$\beta$CD-CEF ($\delta$) | $\Delta\delta$ ($\delta - \delta$0) |
|---|---|---|---|
| H 3 | 12.564 | 12.603 | 0.039 |
| H 4 | 3.164 | 3.236 | 0.072 |
| H 5 | 5.172 | 5.268 | 0.096 |
| H 6 | 5.466 | 5.531 | 0.065 |

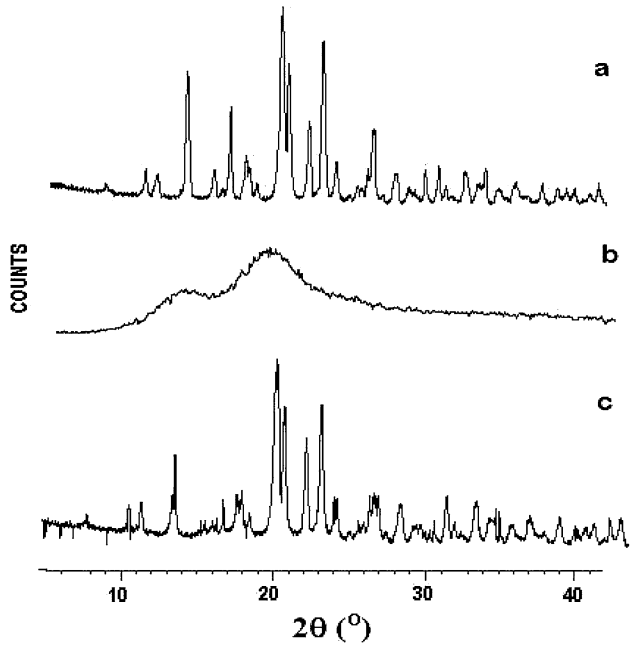


**Fig. 5** X Ray diffractograms of (*a*) CEF, (*b*) HP$\beta$CD and (*c*) MWI CEF-HP$\beta$CD complex

**Table 5** List of principal 2$\theta$ values, and relative intensities for drug, HP$\beta$CD and MWI complex

| Position 2$\theta$ | Intensity heights | | |
|---|---|---|---|
| | Drug | HP$\beta$CD | MWI complex |
| 21.75 | 3999.7 | 875 | 3021.3 |
| 22.71 | 2859 | 821 | 2352.3 |
| 24.703 | 3153 | 759 | 2614.3 |

$$RDC = \frac{\text{Isam}}{\text{Iref}}$$

where, *Isam* peak height of sample, *Iref* peak height of reference at same angleAs per the above equation, lesser the RDC value greater will be the amorphous nature of drug. The diffractograms of HP$\beta$CD did not show presence of sharp peaks as a result of its amorphous nature i.e.; absence of well defined crystal structure. The representative intensity peaks at 21.75, 22.71 and 24.703° were indicative of crystalline nature of Cefdinir. RDC values of MWI CEF HP$\beta$CD system were 0.755, 0.821 and 0.829 for 21.75, 22.71 and 24.703°, respectively.

The sharpness of peaks as well as the number of sharp peaks existing with plain drug was found to be significantly diminished in MWI complexes which may mainly be due to the existence of drug in a totally different form other than crystalline as a result of processing during the formulation of inclusion complexes. The significant decrease in peak intensity in MWI system clearly revealed that CEF has converted into amorphous state.

### *Scanning electron microscopy*

Figure 6 gives the SEM scans of CEF, HP$\beta$CD and its various binary systems. CEF showed an irregular crystal shape and HP$\beta$CD showed shrunken, spherical particles resembling a bowling ball [26]. In case of the PM, the particles of both CEF and HP$\beta$CD were clearly distinguishable from each other. This concludes that no interaction takes place between the two parent compounds in solid state. Products prepared by KN, CE and SD methods showed some agglomeration but they also showed the clear presence of the two parent compounds independently. In case of IC obtained from MWI the particles of the two parent compounds were indistinguishable. They appeared as agglomerates indicating the formation of new single solid phase.

### *Dissolution rate studies*

Figure 7 represents the dissolution curve of CEF and CEF-HP$\beta$CD binary systems in water and Fig. 8 depicts them in pH 6.8 phosphate buffer at 37 ± 0.5 °C. From these results

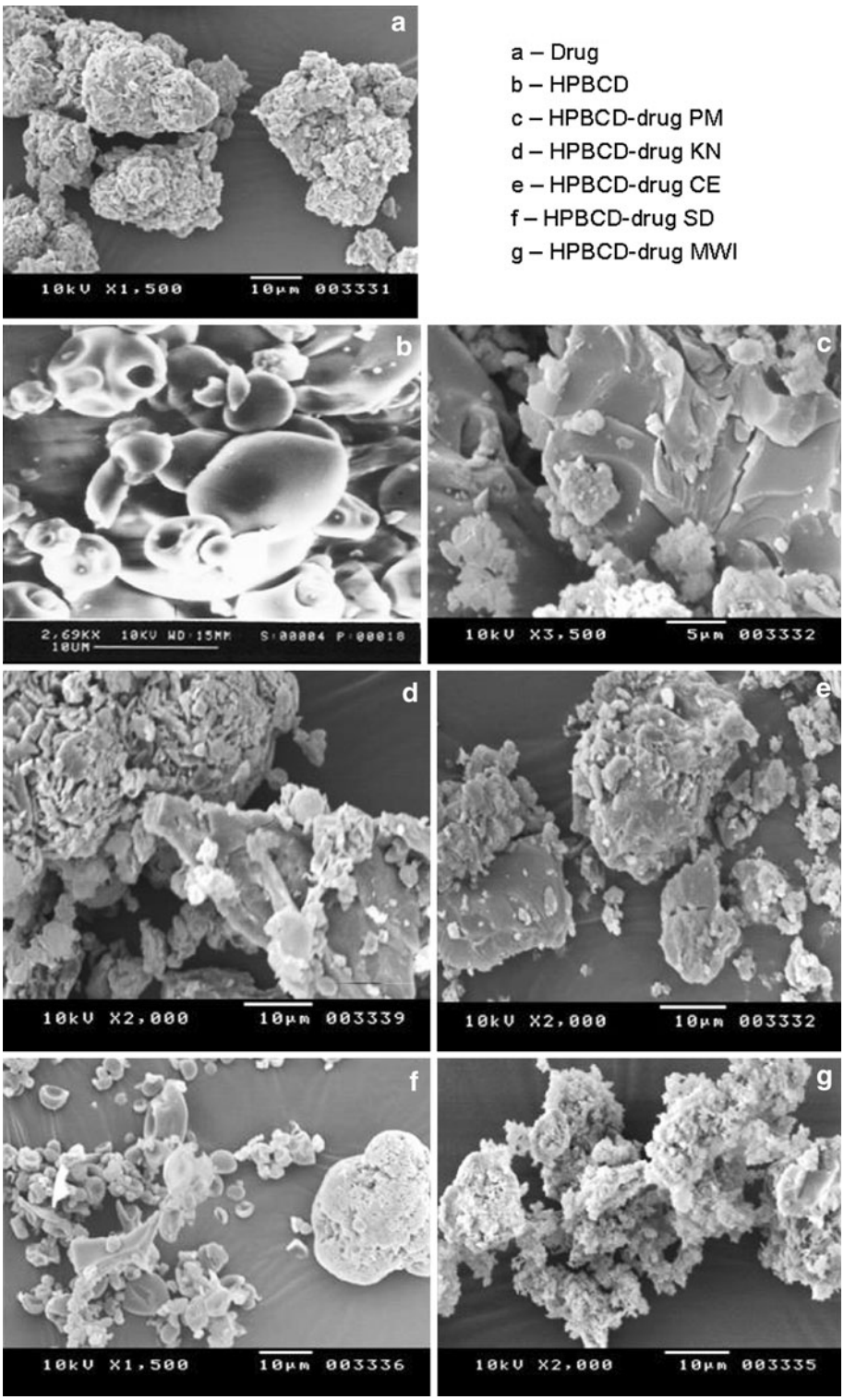


**Fig. 6** SEM scans of **a** CEF, **b** HP$\beta$CD, **c** PM, **d** KN, **e** CE, **f** SD and **g** MWI

it was observed that the release of CEF was not much improved by combining it physically with HP$\beta$CD. But the drug release from binary mixtures prepared by various methods like CE, KN, SD and MWI were high as compared to the PM and CEF alone. Binary systems prepared by CE, KN and SD methods released about 90% drug in 120, 90 and 60 min, respectively as compared to 180 min required for complete dissolution of plain drug. Esclusa-Dias et al., have studied the complexation of ketoconazole with HP$\beta$CD and they too have come to the conclusion that the dissolution of complexes with HP$\beta$CD prepared by spray drying techniques showed a faster rate of drug

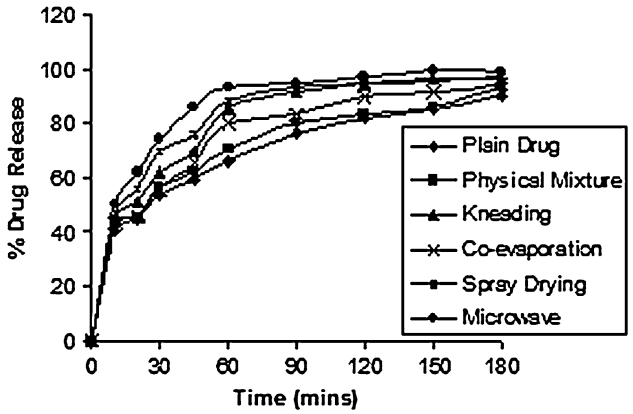


**Fig. 7** Dissolution profile of CEF–HP$\beta$CD binary systems in water (*filled diamond*) CEF; (*larged filled square*) PM; (*filled triangle*) KN; (*cross*) CE; (*small filled square*) SD and (*filled circle*) MWI

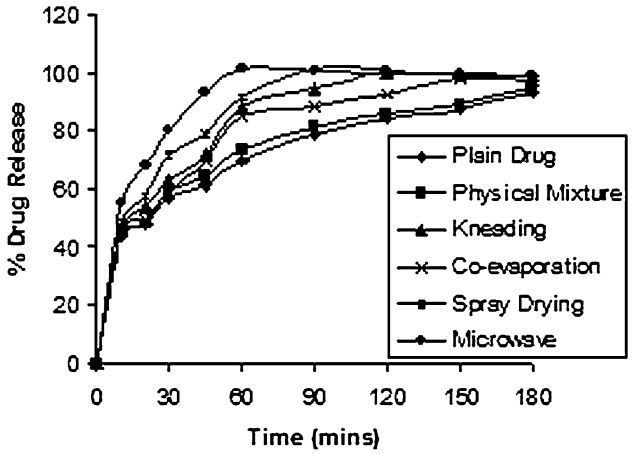


**Fig. 8** Dissolution profile of CEF–HP$\beta$CD binary systems in phosphate buffer pH 6.8 (*filled diamond*) CEF; (*large filled square*) PM; (*filled triangle*) KN; (*cross*) CE; (*small filled square*) SD and (*filled circle*) MWI

release as compared to those systems made by kneading method [27]. Inclusion complexes prepared by MWI method showed complete release of CEF within 60 min, thereby proving the efficiency of MWI method in improving the solubility and dissolution efficiency of CEF. A similar observation has been made in case of CEF-$\beta$CD complexation [28].

## Conclusion

From the experiments performed, it could be concluded that IC of CEF-HP$\beta$CD could be formed in 1:1 stoichiometry. Though various methods were tried to prepare the IC, only the products obtained from SD and MWI techniques were true IC as it could be proved by the results of DSC, SEM and XRD. NMR and FTIR studies revealed that the region of CEF being encapsulated in the hydrophobic cavity of HP$\beta$CD was the cephem ring with carboxyl functionality. The in vitro drug release lead to the conclusion that the dissolution rate of CEF from MWI technique was significantly higher than that of plain CEF, PM and other binary systems. MWI method prepared the complex within a short period of time and gave good yield. Thus it can be concluded that MWI method used for preparation of CEF-HP$\beta$CD complexes can be an efficient method giving better yield with higher dissolution rate.

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## References

1. Cabri, W., Ghetti, P., Alpegiani, M., Pozzi, Giovanni., Justo-Erbez, A., Perez-Martinez, J.I., Villalon-Rubio, R., Monedero-Perales, M.C., Munoz-Rubio, A.: Cefdinir: a comparative e study of anhydrous vs monohydrate form Microstructure and tableting behaviour. Eur. J. Pharm. Biopharm **64**, 212–221 (2006). doi: 10.1016/j.ejpb.2006.05.007
2. Inamoto, Y., Chiba, T., Kamimura, T., Takaya, T.: FK 482, a new orally active cephalosporin synthesis and biological properties. J. Antibiot. **41**, 828–830 (1988)
3. Szejtli, J.: Cyclodextrin Technology, pp. 1–78. Kluwer Academic Publishers, Dordrecht (1988)
4. Duchene, D., Wouessidjewe, D.: Pharmaceutical uses of cyclodextrins and derivatives. Drug Dev. Ind. Pharm. **16**(17), 2487–2499 (1990)
5. Loftsson, T., Bjornsdottir, S., Palsdottir, G., Bodor, N.: Cyclodextrins. The effects of 2-hydroxypropyl-$\beta$-cyclodextrin on the solubility and stability of chlorambucil and melphalan in a aqueous solution. Int. J. Pharm **57**, 63–72 (1989)
6. Bekers, O., Beijnen, J.M., Kempers, Y.A.G., Bult, A., Underberg, J.M.: Eeeects of cyclodextrins on N-trifluoroacetyl-doxorubicin-14-valerate (AD-32) stability and solubility in aqueous media. Int. J. Pharm **68**, 271–276 (1991)
7. Vila-Jato, J.L., Blanco, J., Torres, J.J.: Biopharmaceutical aspects of the tolbutamide-$\beta$-cyclodextrin inclusion compound. II Farmaco Edizione Pratica **643**(2), 37–45 (1988)
8. Le Bas, D., Rysanek, N.: Structural aspects of cyclodextrins. In: Duchene, D. (ed.) Cyclodextrins and Their Industrial Uses, pp. 105–125. Editions de SAnte, Paris (1987)
9. Loftsson, T., Brewster, M.E., Derendorf, H., Bodor, N.: 2-Hydroxypropyl-$\beta$-cyclodextrin. Properties and usage in pharmaceutical formulations. Pharm. Ztg. Wiss. **136**(1–4), 5–10 (1991)
10. Esclusa-Diaz, M.T., Torres-Labandeira, J.J., Kata, M., Vila-Jato, J.L.: Inclusion complexation of glibenclamide with 2-hydroxypropyl- $\beta$-cyclodextrin in solution and in solid state. Eur. J. Pharm. Biopharm. **1**, 291–296 (1994)
11. Ribeiro, L., Carvalho, R.A., Ferreira, D.C., Veiga, F.J.B.: Multicomponent complex formation between vinpocetine, cyclodextrins, tartaric acid and water soluble polymers monitored by NMR and solubility studies. Eur. J. Pharm. Sci. **24**, 1–13 (2005)
12. Parmar, K.R., Patel, K.A., Shah, S.R., Sheth, N.R.: Inclusion complexes of lamotrigine and hydroxypropyl-$\beta$-cyclodextrin:

solid state characterization and dissolution studies. J. Incl. Phenom. Macrocycl. Chem. **65**, 263–268 (2009)
13. Szente, L., Atwood, J.L., Davies, J.E.D., MacNicol, D.D., Vogtle, F.: Comprehensive Supramolecular Chemistry, vol. 3, p. 243. Elsevier Science Ltd., Oxford (1996)
14. Zhao, D.Y., Yang, S.G., Hu, M., Ma, X.Y.: Structural study of inclusion complex of andrographolide with $\beta$-cyclodextrin prepared under microwave irradiation. Chin. Chem. Lett. **14**, 155–158 (2003)
15. Zhao, D., Liao, K., Ma, X., Yan, N.: Study of supramolecular inclusion of $\beta$-cyclodextrin with andrographolide. J. Incl. Phenom. Macrocycl. Chem. **43**, 259–264 (2002)
16. Kappe, C.O.: Controlled microwave heating in modern organic synthesis. Angew. Chem. Int. Ed. **43**, 6250–6284 (2004)
17. Zhou, J., Shi, C., Mei, B., Yuan, R., Fu, Z.: Research on the technology and the mechanical properties of the microwave processing of polymer. J. Mater. Process. Tech. **137**, 156–158 (2003)
18. Passerini, N., Albertini, B., González-Rodríguez, M.L., Cavallari, C., Rodriguez, L.: Preparation and characterisation of ibuprofen–poloxamer 188 granules obtained by melt granulation. Eur. J. Pharm. Biopharm. **15**, 71–78 (2002)
19. Moneghini, M., Bellich, B., Baxa, P., Princivalle, F.: Microwave generated solid dispersions containing Ibufrofen. Int. J. Pharm. **361**, 125–130 (2008)
20. Wen, X., Tan, F., Jing, Z., Liu, Z.: Preparation and study the 1:2 inclusion complex of carvedilol with $\beta$-cyclodextrin. J. Pharm. Biomed. Anal. **34**(3), 517–523 (2004)
21. Aleem, O., Kuchekar, B., Pore, Y., Late, S.: Effect of $\beta$-cyclodextrin and hydroxypropyl $\beta$-cyclodextrin complexation on physicochemical properties and antimicrobial activity of Cefdinir. J. Pharm. Biomed. Anal. **47**, 535–540 (2008). doi:10.1016/jpba.2008.02.006
22. Ren, Y., Gao, J., Han, B., Ma, X.: Medical composition containing cyclodextrin inclusion compound of cefdinir and its preparation method. PCT Int. Appl. PCT/CN2008/000514 (2008)
23. Higuchi, T., Connors, K.A.: Phase-solubility techniques. Adv. Anal. Chem. Instrum. **4**, 117–212 (1965)
24. Bodmeier, R., Chen, H.: Preparation of biodegradable poly (±) lactide microparticles using a spray-drying technique. J. Pharm. Pharma¢ol **40**, 754–757 (1988)
25. Benesi, H., Hildebrand, J.: A spectrophotometric investigation of the interaction of iodine with aromatic hydrocarbon. J. Am. Chem. Soc. **71**, 2701–2705 (1949)
26. Spulber, M., Pinteala, M., Harbagiu, V., Simionescu, B.C.: Inclusion complexes of Sulconazole with b-cyclodextrin and hydroxypropyl $\beta$-cyclodextrin: characterization in aqueous solution and in solid state. J. Incl. Phenom. Macrocycl. Chem. **61**, 41–51 (2008)
27. Esclusa-Diaz, M.T., Guimaraens-Mfndez, M., Pfrez-Marcos, M.B., Vila-Jato, J.L., Torres-Labandeira, J.J.: Characterization and in vitro dissolution behaviour of ketoconazole/$\beta$- and 2-hydroxypropyl-$\beta$-cyclodextrin inclusion compounds. Int. J. Pharm. **143**, 203–210 (1996)
28. Vij, M., Garse, H., Dand, N., Kadam, V., Hirlekar, R.: Effect of preparation method on complexation of Cefdinir with $\beta$-cyclodextrin. J. Inc. Phenom. Macrocycl. Chem. (2009). doi:10.1007/s10847-009-9666-y