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ORIGINAL ARTICLE

Effect of preparation method on complexation of Cefdinir with β-cyclodextrin

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Abstract The inclusion behaviour of β-cyclodextrin (βCD) was studied toward Cefdinir (CEF) in order to enhance the solubility and dissolution rate, following cyclodextrin complexation. Drug cyclodextrin solid systems were prepared by conventional methods of kneading (KN), co-evaporation (CE), spray drying (SD) and with a novel approach of microwave irradiation (MWI). The formation of inclusion complexes with βCD in the solid state, were confirmed by Differential scanning calorimetry (DSC), Fourier Transform Infrared spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) studies, and comparative studies on the in vitro dissolution of CEF were carried out. Characterization of binary system by DSC, FTIR 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 binary systems MWI products were prepared in least time with better yield and highest dissolution rate.

Keywords Cefdinir · β-cyclodextrin · Complexation · Dissolution rate · Microwave irradiation method

Introduction

Cefdinir (CEF) is a semi synthetic third generation oral cephalosporin with an extended antibacterial spectrum and it is characterized by a vinyl group at C-3 and a (Z)-2-(2-amino-4-thiazolyl)-2-(hydroxyimino) acetyl moiety at C-7 which results in increase in its antimicrobial activity against gram-negative and gram-positive bacteria [1–4]. The absorption of orally administrated CEF is low with an oral bio-availability of 21–26% [5] which is mainly due to its poor aqueous solubility and slow dissolution rate. One of the methods to increase solubility is to prepare inclusion complexes with cyclodextrins. Such complexes have the capability to increase the solubility, dissolution rate, bio-availability and stability of drugs, to reduce bitterness and to decrease tissue irritation upon dosing [6, 7].

Currently, the widely used methods to prepare inclusion compounds are co-grinding, kneading, co-evaporation, spray drying and freeze drying [8]. These methods often involve time-consuming manufacturing processes and generally require large amounts of solvents. According to a very recent report, carrying out the inclusion reactions using microwave irradiation (MWI), as opposed to conventional methods, has the major advantages of shorter reaction times and higher yield of products [9, 10]. Complexation with cyclodextrin by MWI method has been proved effective in improving the solubility of poorly soluble drugs. Similar results have been reported by many researchers. Inclusion complexes of Gossypol with βCD prepared by microwave irradiation have been described by Shen et al. They have reported an increase in apparent solubility of gossypol [11]. Wen et al. have reported the formation of 1:2 inclusion complex of Carvedilol with βCD, wherein they have found that stable, true inclusion complexes of the drug could be obtained by MWI method [12].

Aleem et al. have reported increase in the solubility of CEF by complexing it with β-cyclodextrin (βCD) and hydroxypropyl β-cyclodextrin (HPβCD) by kneading method [13]. Ren et al. have filed a patent for the

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complexation of CEF with pharmaceutically acceptable CDs such as βCD, sulfobutyl ether βCD, HPβCD and sulfobutyl ether HPβCD by conventional techniques [14].

The aim of present work was to evaluate the usefulness of the microwave irradiation (MWI) method for preparation of CEF–βCD complexes. In order to prove the advantage of this method, complexes were also prepared by widely used methods like kneading (KN), co-evaporation (CE) and spray drying (SD) method. The complexes were characterized by Fourier Transform InfraRed spectroscopy (FTIR), Scanning Electron Microscopy (SEM) and Differential Scanning Calorimetry (DSC). Dissolution studies were performed with paddle method, in which dissolution properties of inclusion complex prepared by MWI method were evaluated and compared with those of CEF alone, PM and the complexes prepared by other methods.

Experimental

Materials

CEF was kindly gifted by Alkem Research Lab. Ltd (India), βCD (MW-1135) was gifted by the Signet Chemical Corporation (India). These chemicals were used as received without further treatment. All other reagents were of analytical reagent grade purity. Double distilled water was used throughout the study.

Phase-solubility studies

Phase-solubility studies were carried out in water according to the method described by Higuchi and Connors [15]. An excess amount of CFE (20 mg) was added to 5 ml of aqueous solution containing various concentrations of βCD (0–10 mM) in a sealed glass container. The suspensions were shaken at room temperature for 48 h. After equilibrium was achieved, the samples were filtered and properly diluted. The concentration of CEF was determined spectrophotometrically using UV–visible spectrophotometer-(Shimadzu model UV-1601) at 287 nm [16]. The study was carried out in triplicate. The apparent stability constant K_s was calculated from the phase-solubility diagram according to the following equation.

$$K_s = \frac{\text{slope}}{S_0(1 - \text{slope})}$$

S_o is the solubility of CEF in absence of βCD.

Preparation of solid binary system

Following binary systems of CEF with βCD were prepared in 1:1 molar ratio.

Physical mixture (PM)

PM of CEF-BCD in 1:1 molar ratio were prepared by mixing individual components that had previously been sieved through sieve no 80.

Kneading method (KN)

CEF and βCD were accurately weighed, placed in the mortar and triturated for 20 min. The mixture was then kneaded with 66% alcohol for 45 min and resulting paste was kept in vacuum desiccator overnight. The dry mass so obtained was powdered and passed through sieve no. 80.

Co-evaporation method (CE)

Equimolar amounts of CEF and βCD were added to minimum volume of 66% alcohol and then sonicated for 5 min to get clear solution. The final solution was stirred with the help of magnetic stirrer at 60 °C.The pasty mass obtained was dried at 60 °C, passed through sieve no. 80 and stored overnight in desiccator [17].

Spray drying method (SD)

For preparation of spray dried product, the method reported by Esclusa-Diaz et al. with some modification was used [18, 19]. Equimolar amounts of CEF and βCD were dissolved in 100 ml of 66% alcohol and the solution was spray dried in Spraymate LSD 48 apparatus (flow rate 4 ml/min, inlet temperature 95 °C outlet temperature 55 °C atomizing pressure 2 kg/cm^2). The dry mass was passed through sieve no. 80.

Microwave irradiation method (MWI)

Zhao et al. have prepared complex of Andrographolide with βCD using microwave irradiation method [9, 20]. For preparation of CEF–βCD complexes this method was used. Homogenous powder mixture of CEF and βCD was prepared in molar ratio 1:1. Minimum volume of 66% alcohol was added to homogenous mixture of CEF and βCD, sonicated for 5 min and subjected to microwave irradiation in a scientific microwave oven (CATA-4R). The process was carried out at power 245 watt and at 60 °C for 90 s. After the reaction was completed, adequate amount of solvent (66% alcohol) was added to remove the residual βCD and CEF, then the precipitate was filtered and sample was then dried under vacuum.

Efficiency and yield of complexation methods

The total amount of CEF and βCD used in the beginning of preparation method and the time required for complexation of the processes were noticed. The amount of product obtained at the end of process was determined. These parameters were used to calculate percentage yield and to understand efficiency of the process in terms of time.

Analysis of drug content in binary mixture

Samples of each binary mixture were assayed for drug content by dissolving 50 mg equivalent in 100 ml of methanol with the help of sonication and with subsequent suitable dilution. The drug content was determined spectrophotometrically at 287 nm.

Characterization of CEF–βCD complexes

Differential scanning calorimetry

The DSC records were obtained with a Mettler Toledo DSC 882 apparatus. Between 2 and 6 mg of sample was crimped in a sealed aluminium pan and heated at 10 °C/min in the range of room temperature to 300 °C using an empty sealed pan as a reference.(Dry nitrogen was used as purge gas.)

Fourier transformed infrared spectroscopy

The sample with a CEF content of 0.5 mg was ground and mixed with 50 mg of dry KBr in an agate mortar and the mixture was then compressed into a disc. Each disc was scanned 50 times at a resolution of 4 cm^{-1} over the wavelength region 4,000–400 cm^{-1}.

Scanning electron microscopy

The surface morphology of CEF and CEF–βCD physical mixture and complexes prepared by each method were examined using a Scanning Electron Microscope.(JSM-5510, JEOL, USA).The samples were precisely fixed on a brass stub using double sided adhesive tape and then were made electrically conductive by coating in a vacuum with a thin layer of gold. The photographs were taken at an acceleration voltage of 20 KV.

^1H nuclear magnetic resonance spectroscopy

^1H nuclear magnetic resonance (^1H NMR) spectra of CEF, βCD and MWI system were taken at 25 °C by a Bruker DPX Digital Nuclear Magnetic Resonance Model (USA) operating at a proton frequency of 400 MHz using 5 ppm sample tubes. DMSO [2.5 ppm from tetramethylsilane (TMS)] was used as a 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.

Dissolution studies

The dissolution rate studies of CEF alone and from various CEF–βCD systems were conducted using USP XXIII dissolution apparatus type-II (6 stations VDA-6DR Veego Scientific, India) at 37 ± 0.5 °C stirring at 50 rpm. 125 mg of CEF or its equivalent amount of CEF–βCD binary system was added to 900 ml of phosphate buffer pH 6.8. The aliquots of 5 ml were withdrawn at time intervals of 10, 20, 30, 45, 60, 90, 120, 150 and 180 min, diluted appropriately and analysed spectrophotometrically at 287 nm.

Results and discussion

Phase solubility studies

The phase-solubility graph of CEF–βCD is shown in Fig 1. The plot showed that aqueous solubility of the drug increased linearly as a function of βCD. According to Higuchi and Connors, the phase solubility profile can be considered as A_L type. The slope calculated was 0.0944 ± 0.00036 which is less than 1, thus 1:1 stoichiometry was suggested [15]. The value of the stability constant was found to be 119.8 ± 5.06 M^{-1}. A similar stability constant of 120.38 M^{-1} has been reported by Aleem et al. in their phase solubility study of CEF and βCD [13]. The stability constant between the range of 100 and 1000 M^{-1} is considered as an ideal value, smaller values indicate weak interaction between drug and cyclodextrin, while large value indicate incomplete drug release from the inclusion complex [21].

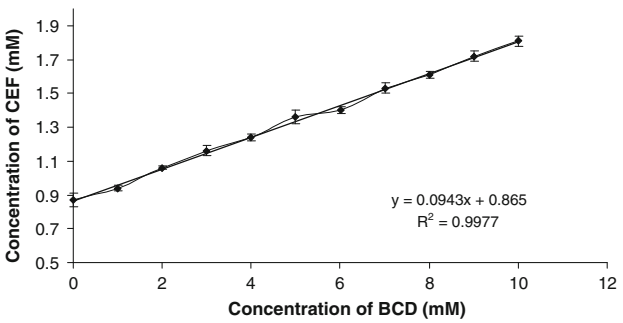

Fig. 1 Phase solubility profile CEF–βCD in water

Efficiency and yield of complexation method

The time required for complexation by various methods and percentage yield obtained are shown in Table 1. It can be seen that MWI method required the least time (6.5 min), whereas CE method took the longest period (95 min). SD method gave least yield of 55.62% as compared to maximum yield of 72.9% obtained by MWI method. Thus MWI process proved to be less time consuming and yielding maximum amount of the product.

Analysis of drug content in binary mixture

The results of the assay indicated that the content in the binary mixture was in the range of 97–100%. Individual values obtained were as described in Table 2.

Characterization of CEF–βCD complexes

Differential scanning calorimetry

Figure 2 represents the DSC thermograms of drug, βCD and binary mixtures. DSC thermogram of CEF (Fig. 2a) showed a sharp exothermic peak at 227.59 °C, an observation similar to that made by Walter Cabri et al. [1]. A broad endothermic peak at 130.78 °C was observed for βCD (Fig. 2b), indicating the loss of water molecule. The thermograms of the PM (Fig. 2c), KN (Fig. 2d) and CE (Fig. 2e) products were superimpositions of the raw materials, with a slight decrease in the intensity of the drug peak and a slight shifting of the peak to 227.69, 224.17 and 226.05 °C, respectively. This indicated that the complex

Table 1 Efficiency and yield of complexation with following methods

Complexation method	Time required (min)	Percentage yield
Kneading	65	63.34
Co-evaporation	95	67.58
Spray drying	25	55.62
Microwave irradiation	6.5	72.9

Table 2 Percentage drug content of various binary systems of CEF–βCD

Binary system	% Drug content
Physical mixture	99.60
Kneaded product	97.28
Co-evaporated product	97.72
Spray dried product	98.30
Microwaved product	100.2

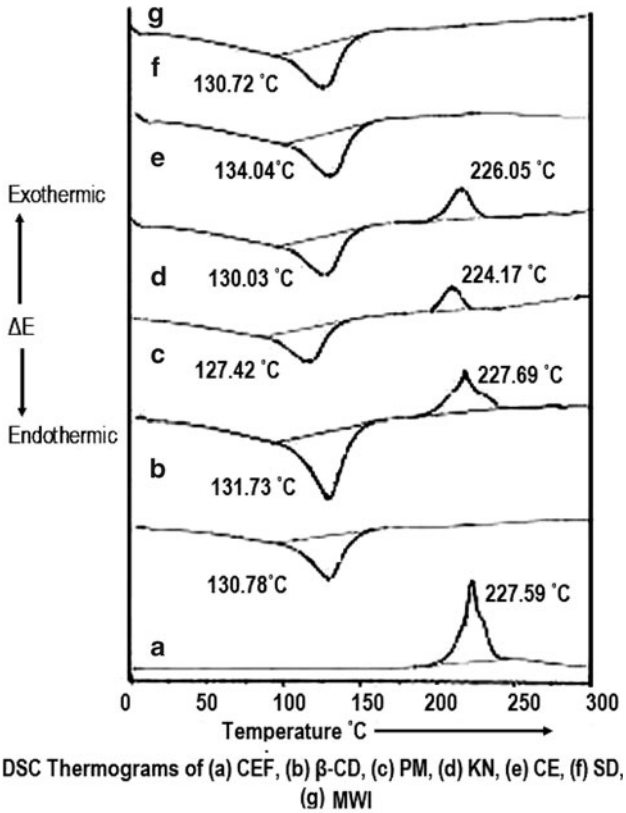

Fig. 2 DSC thermograms of CEF: βCD systems: Cefdinir (*a*), βCD (*b*), CEF: βCD PM (*c*), CEF: βCD KN (*d*), CEF: βCD CE (*e*), CEF: βCD SD (*f*) and CEF: βCD MWI (*g*) systems

formation was not complete. The disappearance of peak of drug in SD and MWI products can be attributed to the inclusion of CEF in the βCD cavity which provided evidence that the complexes prepared by SD and MWI method were true inclusion complexes [22].

Fourier transformation infrared spectroscopy

Figure 3 illustrates the FTIR spectra of CEF, βCD and their binary mixtures prepared by different methods such as KN, CE, SD and MWI method. The FTIR spectrum of CEF (Fig. 3a) 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 βCD showed prominent peaks at 3396.41 cm^{-1} (O–H stretching), 2925.81 cm^{-1} (C–H stretching), 1637.45 cm^{-1} (H–O–H bending), 1159.14 cm^{-1} (C–O stretching of COOH group) and 1026.06 cm^{-1} (C–O–C bending). The IR spectrum of the PM was found to be a superimposition of the two parent

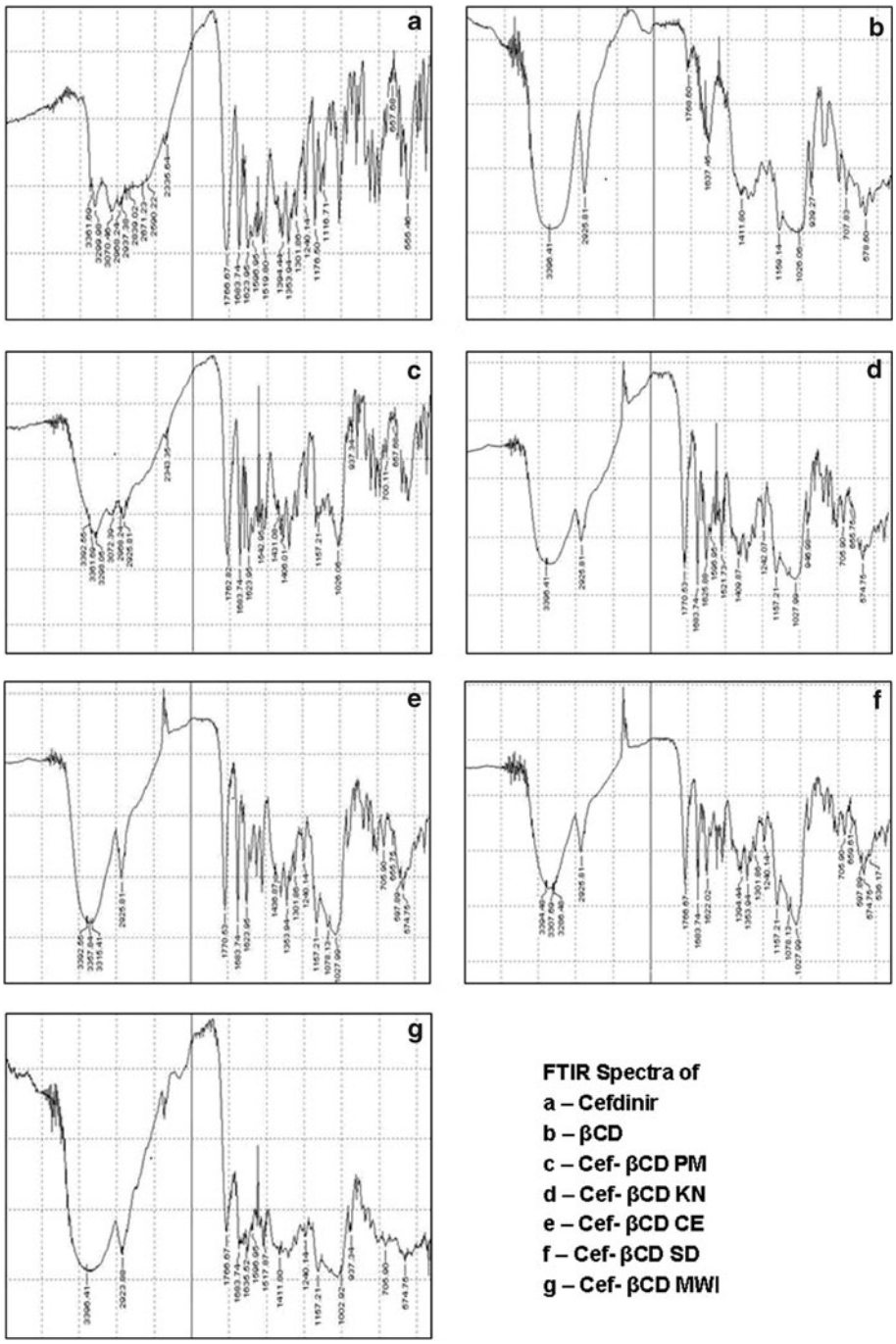

Fig. 3 FTIR spectra of CEF: βCD systems: Cefdinir (**a**), βCD (**b**), CEF: βCD PM (**c**), CEF: βCD KN (**d**), CEF: βCD CE (**e**), CEF: βCD SD (**f**) and CEF: βCD MWI (**g**) systems

compounds with the peaks of both the substances appearing with some peaks having lower intensities. Slight shifts were observed in certain peaks mainly 3299.98, 2968.24 and 657.68 cm^{-1} of CEF indicating an interaction between the drug and cyclodextrin. In cases of inclusion complexes prepared by KN, CE and SD methods there was even further decrease in the intensities of the peaks of the drug but the peaks were still visible indicating incomplete complex formation. In case of the inclusion complex made by MWI technique, the above mentioned three peaks of the drug disappeared completely indicating the entrapment of drug within the βCD cavity. The peaks 3299.98, 2968.24 and 657.68 cm^{-1} corresponds to the cephem ring along with carboxylic group. This reflected that cephem ring with COOH functionality to be the guest moiety which has been entrapped in the hydrophobic cyclodextrin cavity. A similar observation has been made by Aleem et al. in their CEF–βCD complexation study [13]. The FTIR observations were in concurrence with those obtained in DSC studies.

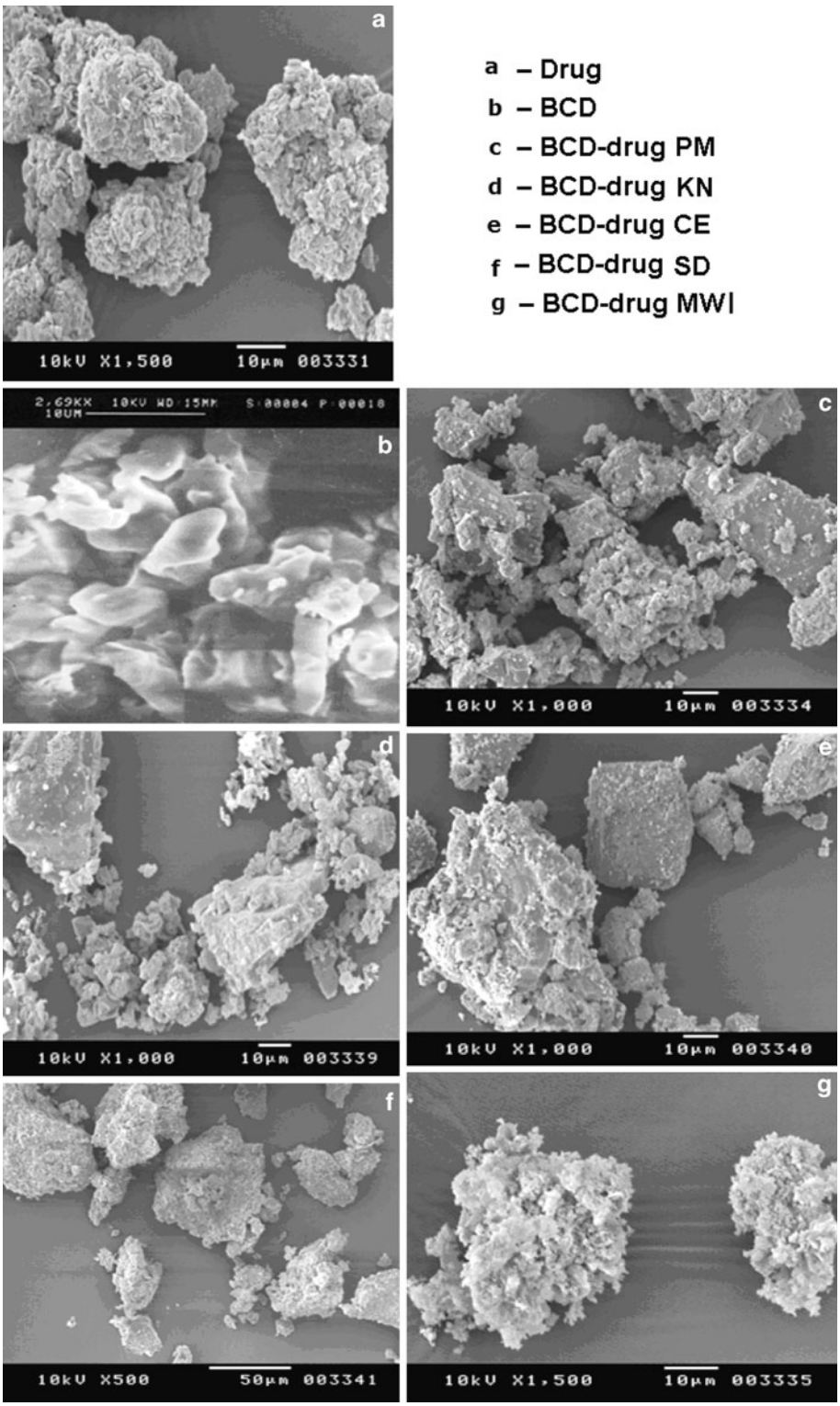

Fig. 4 SEM microphotographs of CEF: CEF systems: Cefdinir (**a**), βCD (**b**), CEF: βCD PM (**c**), CEF: βCD KN (**d**), CEF: βCD CE (**e**), CEF: βCD SD (**f**) and CEF: βCD MWI (**g**) inclusion complexes

Scanning electron microscopy

Figure 4 illustrates the observations of SEM. CEF was observed to have irregular-shaped crystals whereas βCD showed a parallelogram shape. The CEF–βCD PM showed bulky unmodified particles of βCD covered with adhering smaller drug particles. The comparison of the PM with the pure component revealed that apparently no interaction between CEF and βCD has taken place in solid state. In the KN, CE and SD products some agglomerates were visible

in which the two parent components were indistinguishable but some particles of βCD on which adhering drug particles were visible. This indicated that though there was some complex formation, it was not complete as parent components were still visible. In the product obtained by MWI original morphology of the raw material disappeared and it was not possible to differentiate between the components. The microwave product appeared as agglomerates. This change, indicative of the new solid state phase, could be simply a consequence of crystalline pattern change in this system and supported the existence of new single solid phase.

^{1}H nuclear magnetic resonance spectroscopy

NMR spectroscopy has been previously used to establish inclusion modes and stoichiometries [23]. In the present work ^{1}H NMR was performed to elucidate the structure of CEF–βCD inclusion complex. The ^{1}H NMR chemical shift values of βCD in the free and complexed form are shown in Table 3. The chemical shifts of βCD protons showed noteworthy, upfield changes of proton H-3 (0.107 ppm) and H-5 (0.074 ppm) which are located on the inner surface of the βCD 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.

In order to further confirm the inclusion complexation, ^{1}H NMR spectroscopy data of CEF was evaluated. Figure 5 gives the 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 βCD cavity. It can thus be deduced that cephem ring along with COOH functionality entered the βCD cavity. This observation is in concurrence with that obtained from FTIR data.

Table 3 ^{1}H NMR chemical shift values of βCD in the absence and presence of CEF

Proton no.	βCD (δ_0)	βCD–CEF (δ)	$\Delta\delta$ (δ–δ_0)
H 1	4.819	4.800	−0.013
H 2	3.290	3.272	−0.018
H 3	3.627	3.520	−0.107
H 4	3.391	3.327	−0.064
H 5	3.565	3.491	−0.074
H 6	3.640	3.572	−0.068

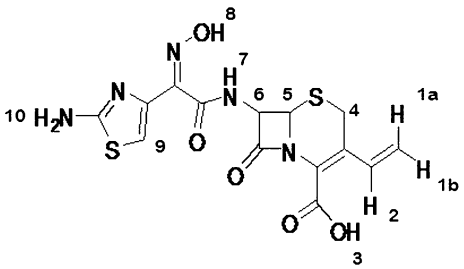

Fig. 5 Chemical structure of Cefdinir

Dissolution rate studies

The dissolution curves of CEF and CEF–βCD binary systems in pH 6.8 phosphate buffer at 37 ± 0.5 °C are shown in Fig. 6. According to these results, the amount of drug released from PM was not significantly different than that of CEF alone. But the amount of drug released from binary mixtures prepared by various methods like CE, KN, SD and MWI was 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 for plain drug. Complete drug release was obtained in 60 min in case of complexes prepared by MWI method, indicating the effectiveness of MWI method in improving dissolution characteristics of drug. Zingone et al. have compared the release of Warfarin complexed with βCD by various techniques such as KN, CE and FD. They observed that the release of the drug from KN and CE inclusion complexes was lesser as

Table 4 ^{1}H NMR chemical shift values of CEF in the absence and presence of βCD

Proton no.	CEF (δ_0)	βCD–CEF (δ)	$\Delta\delta$ (δ–δ_0)
H 3	12.564	12.613	0.049
H 4	3.164	3.228	0.064
H 5	5.172	5.283	0.111
H 6	5.466	5.517	0.051

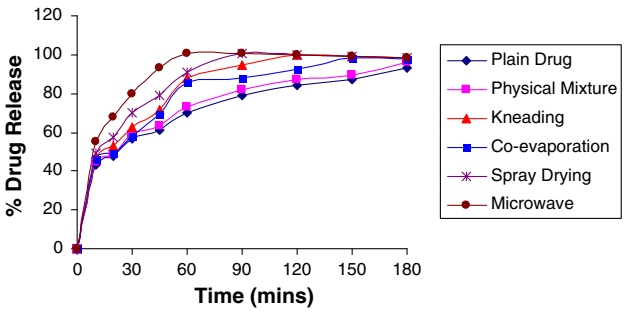

Fig. 6 Dissolution diagram of CEF–βCD systems: (◆) Cefdinir (CEF) (■) Physical mixture of CEF: βCD, (▲) Kneading mixture of CEF: βCD, (■) Co-evaporated mixture of CEF: βCD, (×) Spray dried mixture of CEF: βCD, (●) Microwaved mixture of CEF: βCD

compared to the FD complex. Our observation is similar to theirs in respect that CEF–βCD inclusion complex prepared by KN and CE methods showed a lower rate of dissolution as compared to those prepared by SD and MWI. Results of instrumental characterisation which suggested that true complexation occurred only in case of SD and MWI, might be responsible for their better dissolution behaviour [24]. Similar observations have been reported by Obaidat et al. who got better dissolution from binary systems prepared by SD method over those prepared by KN method [25].

There have recently, been reports of synthesis of modified CDs with the assistance of microwave. Trotta et al. have reported the use of ultrasound and microwave for the synthesis of CD derivatives such as 6^{I}-monotosyl-βCD, 6^{I}-monoazido-6^{I}-monodeoxy-βCD, 6^{I}-monoamino-6^{I}-monodeoxy-βCD and 2^{I}-O-mono(methylamino)alkyl-βCD [26].

The inclusion complex of CEF with βCD in this work was also prepared by microwave technique. But there are differences in the two methods with respect to reaction time, temperature and use of specialised reagents. Time and temperature required to synthesize substituted CDs was higher than that used in the present work. Also no special reagent or solvents were used. Thus it would not lead to generation of substituted CDs.

Generation of inclusion complex has also been irrevocably proven by various characterisations carried out. FTIR, DSC and NMR have conclusively proved that there is only an entrapment of cephem ring with COOH functional group of CEF within the hydrophobic cavity of βCD. There are no observations made for the appearance of a new chemical entity. Thus it can be emphatically concluded that MWI generated the true CEF–βCD inclusion complex.

Conclusion

The phase solubility study of CEF–βCD indicated formation of inclusion complexes of 1:1 stoichiometry. Characterisation of binary systems by DSC, SEM confirmed true inclusion complexation by SD and MWI method. FTIR and ^{1}H NMR studies of MWI binary system indicated inclusion of cephem moiety of Cefdinir inside the βCD cavity. Two distinct advantages of MWI method on large scale are shorter drying time and exclusion of large quantities of potentially hazardous organic solvents. Thus it can be concluded that MWI method can be used efficiently to prepare CEF–βCD complex with better yield on industrial scale.

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References

1. Cabri, W., Ghetti, P., Alpegiani, M., Pozzi, G., Justo-Erbez, A., Perez-Martinez, J.I., Villalon-Rubio, R., Monedero-Perales, M.C., Munoz-Rubio, A.: Cefdinir: a comparative 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. Neu, H.C., Saha, G., Chin, N.X.: Comparative in vitro activity and beta-lactamase stability of FK482, a new oral cephalosporin. Antimicro. Agents chemother. **33**, 1795–1800 (1989)
4. Mine, Y., Yokota, Y., Wakai, Y., Kumimura, T., Tawara, S., Shibayama, F., Kikuchi, H., Kuwahara, S.: In vivo antibacterial activity of FK482, a new orally active cephalosporin. J. Antibiot. **41**, 1888–1895 (1988)
5. Perry, C.M., Scott, L.J.: Cefdinir: a review of its use in the management of mild-to-moderate bacterial infections. Drugs **64**, 1433–1464 (2004)
6. Miller, L.A., Carrier, R.L., Ahmed, I.: Practical considerations in development of solid dosage forms that contain cyclodextrin. J. Pharm. Sci. **96**, 1691–1707 (2007). doi:10.1002/jps.20831
7. Duchene, D., Wouessidjewe, D.: Pharmaceutical uses of cyclodextrins and derivatives. Drug Dev. Ind. Pharm. **16**(17), 2487–2499 (1990)
8. Szente, L., Atwood, J.L., Davies, J.E.D., MacNicol, D.D., Vogtle, F.: Comprehensive supramolecular chemistry, vol 3, p. 243. Elsevier Science Ltd, New York (1996)
9. Zhao, D.Y., Yang, S.G., Hu, M., Ma, X.Y.: Structural study of inclusion complex of andrographolide with β-cyclodextrin prepared under microwave irradiation. Chin. Chem. Lett. **14**, 155–158 (2003)
10. Zhao, D., Liao, K., Ma, X., Yan, N.: Study of supramolecular inclusion of β-cyclodextrin with andrographolide. J. Incl. Phenom. Macrocycl. Chem. **43**, 259–264 (2002)
11. Shen, Y., Yang, S., Wu, L., Ma, X.: Study on structure and characterisation of inclusion complex of gossypol/beta cyclodextrin. Spectrochem. Acta A **61**, 1025–1028 (2005)
12. Wen, X., Tan, F., Jing, Z., Liu, Z.: Preparation and study the 1:2 inclusion complex of carvedilol with β-cyclodextrin. J. Pharm. Biomed. Anal. **34**, 517–523 (2004)
13. Aleem, O., Kuchekar, B., Pore, Y., Late, S.: Effect of β-cyclodextrin and hydroxypropyl β-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
14. 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)
15. Higuchi, T., Connors, K.A.: Phase-solubility techniques. Adv. Anal. Chem. Instrum. **4**, 117–212 (1965)
16. Hirlekar, R., Kadam, V.: Preparation and characterization of inclusion complexes of carvedilol with methyl-β-cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. **63**, 219–224 (2009). doi:10.1007/s10847-008-9506-5
17. Nie, S., Fan, X., Peng, Y., Yang, X., Wang, C., Pan, W.: In vitro and in vivo studies on the complexes of vinpocetine with hydroxypropyl-β-cyclodextrin. Arch. Pharm. Res. **30**, 991–1001 (2007)
18. Esclusa-Diaz, M.T., Torres-Labandeira, J.J., Kata, M., Vila-Jato, J.L.: Inclusion complexation of glibenclamide with 2-hydroxypropyl-β-cyclodextrin in solution and in solid state. Eur. J. Pharm. Biopharm. **1**, 291–296 (1994)

19. Bodmeier, R., Chen, H.: Preparation of biodegradable poly(±)lactide microparticles using a spray-drying technique. J. Pharm. Pharmacol. **40**, 754–757 (1988)
20. Moneghini, M., Bellich, B., Baxa, P., Princivalle, F.: Microwave generated solid dispersions containing ibufrofen. Int. J. Pharm. **361**, 125–130 (2008)
21. Manca, M.L., Zaru, M., Ennas, G., Valenti, D., Cinico, C., Loy, G., Fadda, A.M.: Diclofenac-β-cyclodextrin binary systems: physicochemical characterization and in vitro dissolution and diffusion studies. AAPS PharmSciTech. **6**(3), 58 (2008)
22. Mura, P., Maestrelli, F., Cirri, M., Furlanetto, S., Pinzauti, S.: Differential scanning calorimetry as tools in the study of drug–cyclodextrin interactions. J. Therm. Anal. Calorim. **74**, 769–777 (2003)
23. Benesi, H., Hildebrand, J.: A spectrophotometric investigation of the interaction of iodine with aromatic hydrocarbon. J. Am. Chem. Soc. **71**, 2701–2705 (1949)
24. Zingone, G., Rubessa, F.: Preformulation study of the inclusion complex warfarin-β-cyclodextrin. Int. J. Pharm. **291**, 3–10 (2005)
25. Obaidat, A.A., Khanfar, R.A., Khawam, M.N.: The effect of *b*-cyclodextrin on the solubility and dissolution rate of meloxicam and investigation of the driving force for complexation using molecular modelling. J. Incl. Phenom. Macrocycl. Chem. **63**, 273–279 (2009). doi:10.1007/s10847-008-9517-2
26. Trotta, F., Martina, K., Robaldo, B., Barge, A., Cravotto, G.: Recent advances in the synthesis of cyclodextrin derivatives under microwaves and power ultrasound. J. Incl. Phenom. Macrocycl. Chem. **57**, 3–7 (2007)