J Incl Phenom Macrocycl Chem (2010) 66:393–402
DOI 10.1007/s10847-009-9656-0

ORIGINAL ARTICLE

Physicochemical characterization of terbinafine-cyclodextrin complexes in solution and in the solid state

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Received: 15 May 2009 / Accepted: 22 July 2009 / Published online: 15 August 2009
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Abstract Terbinafine (TB) is an allylamine derivative used as oral and topical antifungal agent. The physicochemical properties of the complexes between TB and different cyclodextrins (CDs): α-CD, β-CD, hydroxypropylβ-CD, methylβ-CD and γ-CD, have been studied in pH 12 aqueous solutions at 25 °C and in the solid state. Different phase solubility profiles of TB in the presence of CDs have been obtained: A_L type for TB with hydroxypropylβ-CD and γ-CD, A_P type for the complexes with methylβ-CD and α-CD, while a B_S profile was found for TB-β-CD. The apparent stability constants of the complexes were calculated at 25 °C from the phase solubility diagrams. The higher increase of TB solubility, up to 200-fold, together with the higher value of the stability constant were found for the complex with methylβ-CD. Solid systems of 1:1 drug:CD molar ratio were prepared and characterised using X-ray diffraction patterns, thermal analysis and FTIR spectroscopy. The coevaporation method can be considered the best method in preparing these solid complexes. The complexes of TB with natural CDs, except with α-CD, were crystalline, whereas the methyl and hydroxypropyl derivatives gave rise to amorphous phases. Dissolution rate studies have been performed with TB-β-CD and TB-HPβ-CD complexes, showing a positive influence of complexation on the drug dissolution.

Keywords Terbinafine · Cyclodextrins · Solubility diagrams · Solid complexes · Dissolution rate

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Introduction

Terbinafine (TB), [(2E)–6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalen-1-ylmethyl) amine hydrochloride (Fig. 1) is an allylamine derivative, used as oral and topical antifungal agent, which belongs to in a new chemical group of antifungal compounds, represented by naftifine (NF). Its mechanism of action is based on the specific inhibition of a fungal squalene epoxidase, blocking the biosynthesis of ergosterol, which is an essential component of fungal cell membranes [1]. The excellent absorption properties and a preferential distribution to the target tissue make TB an appropriate drug for antifungal therapy [2]. It is one of the main treatment options for dermatophyte infections [3]. Terbinafine is active against dermatophytes such as *Aspergillus* and *Scopulariopsis brevicauli*, the dimorphic fungi *Blastomyces dermatitidis* and *Histoplasma capsulatum* and also against *Candida albicans* [1].

Cyclodextrins (CDs) are torus shaped cyclic oligosaccharides made up of α-(1,4) linked glucose units, the most common CDs are α-CD, β-CD and γ-CD, which contain six, seven and eight glucose units, respectively. CDs are known to form inclusion complexes both in solution and in the solid state with a great variety of compounds. In general, the binding is led by the polarity of the guest molecule and its ability to fit closely within the CD cavity [4]. The formation of inclusion complexes has been widely used to improve the solubility of poorly water-soluble compounds, bioavailability, aqueous dissolution, permeability and stability of drugs [5].

Although natural CDs are hydrophilic, their aqueous solubility is rather limited in relation with their derivatives, especially for β-CD. It is thought to be associated to relatively strong intermolecular interactions and high

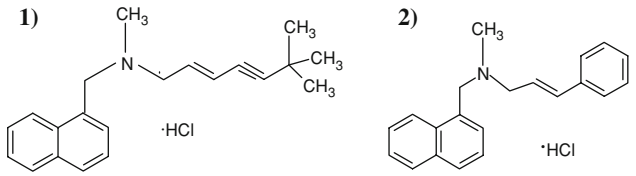

Fig. 1 Chemical structures of TB (**1**) and NF (**2**) hydrochlorides

crystallinity degrees. Random substitution of the hydroxyl groups, even by hydrophobic moieties such as methoxy functions, results in a certain solubility improvement, because the crystalline CDs transform into amorphous mixtures of isomeric derivatives. β-CD derivatives of pharmaceutical interest include the hydroxypropyl derivatives and the randomly methylated CDs [6]. Hydrophilic CDs (HPβ-CD, Mβ-CD) can enhance drug absorption and they are useful for immediate release and, on the other hand, the hydrophobic ones may be employed for prolonged release formulations [7]. In the literature there are several studies in which complexes between different antifungal agents, such as tolnaftate [8], miconazole [9], clotrimazole [10–12], ketoconazole [13–15], itraconazole [16, 17], econazole [18, 19], fluconazole [20], chlorhexidine [21], ciclopirox [22], griseofulvin [23] and CDs have been investigated in order to improve the physicochemical and biopharmaceutical properties of these drugs.

The aim of this paper is to investigate the complex formation of TB with natural (α-CD, β-CD and γ-CD) and substituted (HPβ-CD and Mβ-CD) cyclodextrins in solution and in the solid state, which could be useful to improve TB oral and topical formulations. The stability constants of the complexes have been determined according to the phase solubility studies. The inclusion complexes in the solid state have been prepared by kneading, coevaporation and coprecipitation methods. X-ray difractometry together with differential scanning calorimetry (DSC) and Fourier transform-infrared spectroscopy (FTIR) have been used to identify possible channel or cage-type crystalline structures as well as amorphous systems. The dissolution rate of amorphous and crystalline complexes has been evaluated by comparing with that of TB alone and with the corresponding physical mixture.

In a previous work we have studied the interactions between the antifungal drug NF and CDs. Taking into account that TB belongs to a chemical group of antifungal compounds represented by NF (Fig. 1), it results interesting to compare the complexation of TB and different CDs with the corresponding results obtained for NF [24], in order to elucidate the influence of the TB aliphatic side chain on the binding with the CD molecules and on the improvement of the bioavailability of both drugs.

Materials and methods

Materials

Terbinafine hydrochloride (molecular weight, 327.9) was kindly supplied by Novartis (Milan, Italy). β-CD, Mβ-CD and HPβ-CD were from Roquette S.A. (Lestrem, France), Cyclolab (Budapest, Hungary) and Sigma (Missouri, USA), respectively. Mβ-CD and HPβ-CD had average substitution degrees DS $\approx$ 12 and 4, respectively. γ-CD and α-CD were purchased from Wacker Chemie GmbH (Munich, Germany). All other reagents and solvents were from Panreac (Barcelona, Spain).

Methods

Determination of pK_a from the pH-solubility profile

The solubility as a function of pH was determined by adding excess amounts of terbinafine to different aqueous solutions ranging from pH 1.2 to 12.0. Depending on the desired pH value, the aqueous solutions were prepared using the following reagents: HCl, Na_2HPO_4, KH_2PO_4, $NaHCO_3$, NaOH and $KHC_8H_4O_4$. Later, the mixtures were shaken till equilibrium was reached. The solubility was determined by means of the absorbance measurement of filtered aliquots at 222 and 284 nm. The pK_a value was obtained from the solubility-pH profile using the Henderson-Hasselbalch equation.

Solubility assays of TB-CD systems

The solubility assays have been made in pH 12 aqueous solutions at 25 °C. This buffer solution was prepared from Na_2HPO_4 (0.05 M) and NaOH (1 M) solutions. The assays were carried out as it has been indicated in a previous work using NF [24].

The samples were measured at 222 nm considering that the molar absorptivity of TB at 25 °C was 40.0×10^3 M^{-1} cm^{-1}. The apparent stability constants and the stoichiometry of complexes were estimated from the phase solubility diagrams as it was reported by Connors [19].

Solid systems

Solid systems containing TB and the different cyclodextrins were prepared in 1:1 molar ratio. The physical mixtures (PM) were prepared by a careful mixing with a micro spatula for 15 min. The kneaded products (KN) were obtained by kneading a mixture of TB and cyclodextrin with a minimum volume of a 50% V/V ethanol/water solution to obtain a paste, which was subsequently dried at room temperature. The coevaporated systems (CE) were prepared by a slow

addition of aqueous alcoholic solutions (ethanol/water 50% V/V) of TB to aqueous solutions of the different cyclodextrins. These solutions were stirred and the solvent removed under vacuum in a rotatory evaporator at 25 °C; finally, the solid residue was dried at room temperature.

The coprecipitated product (CP) of TB and β-CD was obtained from the solid residue of the solubility assay at the highest CD concentration.

Characterization of solid systems

X-ray powder diffraction patterns were collected on a Bruker D8 Advance diffractometer (Karlsruhe, Germany), with a CuKα1 radiation, at a 40 kV voltage and a 30 mA current. The thermal analysis was performed with a simultaneous TGA/sDTA 851 Mettler Toledo thermoanalyzer (Schwerzenbach, Switzerland). The thermal behaviour was studied by heating about 15 mg of the sample at a scan rate of 5 °C/min in a pierced aluminium crucible under static air atmosphere from 25 to 250 °C. Infrared spectra were obtained with a Fourier transform infrared FTIR Nicolet Avatar 360 spectrophotometer (WI, USA)-with OMNIC ESP software, using the KBr pellet technique; the resolution was 2 cm^{-1} and the spectra used were the result of averaging 100 scans. Also, the accessory MKII Golden Gate (Speck), which presents attenuated total reflectance (ATR), was used for this study.

Dissolution studies

Preliminary dissolution assays of pure TB, TB-β-CD and TB-HPβ-CD physical mixtures and coevaporated products have been carried out. A constant amount (9 mg) of powdered TB or equivalent was suspended into 25 mL of pH 7.0 $\pm$ 0.3 phosphate buffer, as simulated intestinal medium, in sealed glass containers which were shaken at constant temperature (37.0 $\pm$ 0.5 °C). At regular time intervals, aliquots of 2.5 mL were taken out and filtered to determine spectrophotometrically the amount of TB dissolved at 222 nm. The volume of each sample taken out was replaced by fresh dissolution medium and the corresponding TB concentration was corrected. Each experiment was carried out in triplicate. Relative dissolution rates have been calculated as the ratio of the amount of drug dissolved at 300 min with respect to that obtained with the pure drug.

Results and discussion

Determination of pK_a from the pH-solubility profile

The solubility of TB is strongly dependent on pH as it is shown in Fig. 2; it diminishes down to 4.5 $\times$ 10^{-6} M at pH 9. From these results, a pK_a value of 6.7 $\pm$ 0.3 has been determined, by means of the Henderson-Hasselbalch equation. The weaker basic character of TB in relation to NF [24] can be explained by the influence of the aliphatic side chain of TB on the amine ionisation.

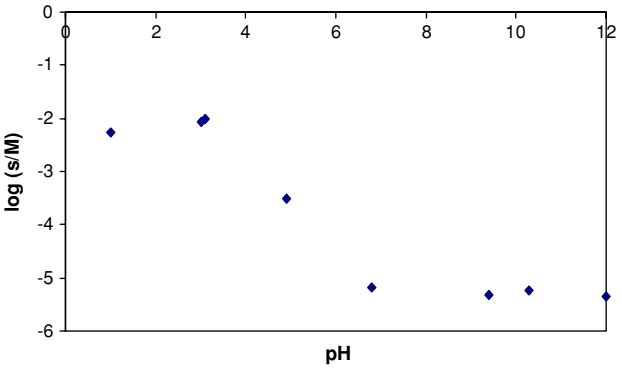

Fig. 2 pH-solubility profile of TB

Phase solubility diagrams

The solubility studies have been carried out in pH 12 aqueous solutions in order to investigate the complexation of TB neutral form with CDs, taking into account the low solubility of the drug in these conditions. The phase solubility diagrams for the interaction of TB with the different CDs are depicted in Fig. 3. Several phase solubility profiles were obtained with different CDs: A_L type for TB with HPβ-CD and γ-CD, A_P isotherm for the complexes with Mβ-CD and α-CD while a B_S profile resulted for TB-β-CD.

A solubility value of 2.3 $\pm$ 0.7 $\times$ 10^{-6} M was obtained for neutral TB from the intercept of these diagrams at pH 12. The solubility of TB increases up to 7 and 2-fold in the presence of 1.0 $\times$ 10^{-2} M solutions of α-CD and γ-CD, respectively; these enhancements can be attributed to the binding of TB with the CD molecules. In addition, the TB solubility rises up to 25 and 75-fold at the same aforementioned concentration of HPβ-CD and Mβ-CD, respectively, suggesting a strong influence of both hydroxypropyl and methyl groups on the TB-CD interactions, especially with the latter. On the other hand, the solubility of the TB-β-CD complex increases 10-fold with respect to that of free TB, although the complex solubility is limited, as shown in the B_S diagram obtained.

It has been observed that the solubility of the drug increases linearly as a function of HPβ-CD and γ-CD concentration (Fig. 3). This A_L isotherm often indicates that a hydrosoluble complex of 1:1 stoichiometry is formed. The stoichiometry with respect to the ligand for both complexes has been also confirmed by the slope value (1.1 and 1.0, respectively) of the plots of log $S_t - S_o/S_o$ versus log [CD] [25]. The apparent stability constants are

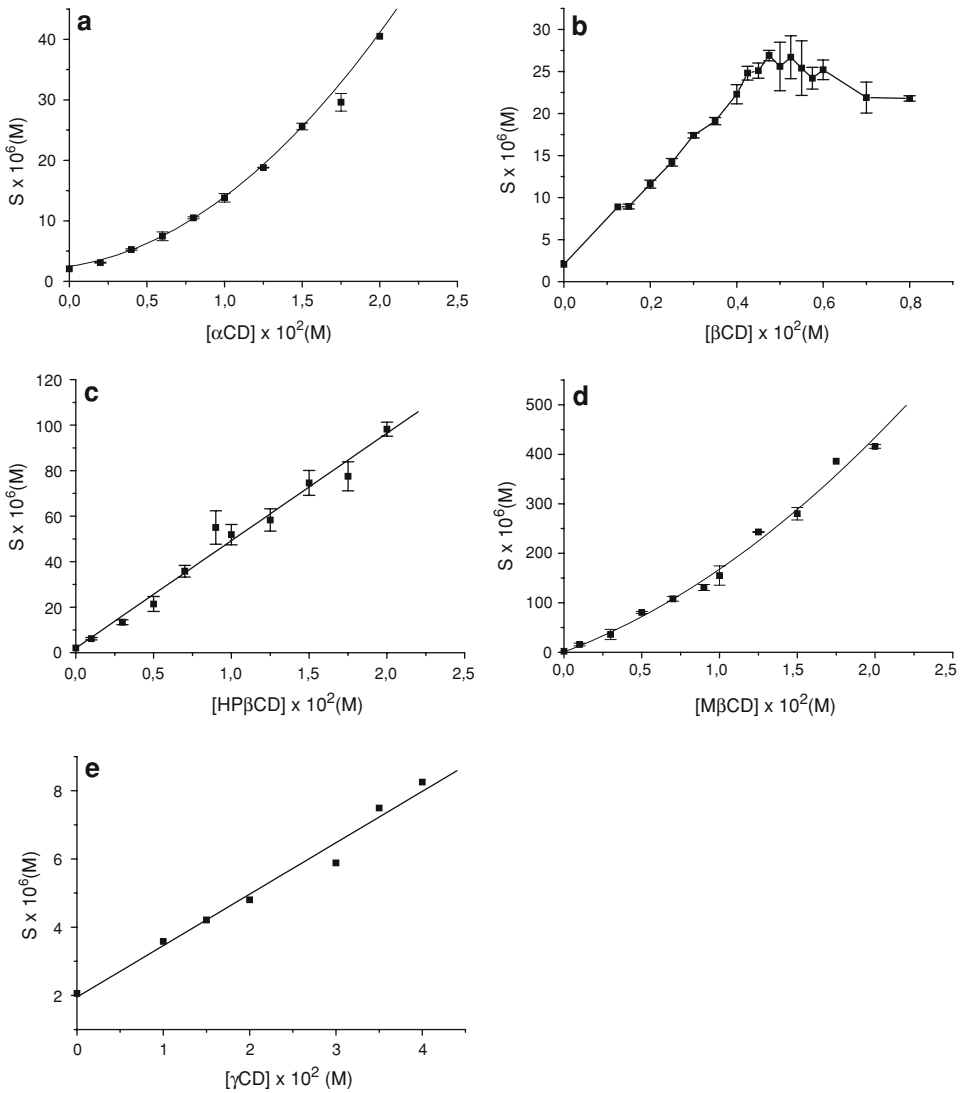

Fig. 3 Phase solubility diagrams of TB-CD systems in pH 12 aqueous solutions at 25 °C

indicated in Table 1. The stability constant for TB-γ-CD is the lowest one found and it points out the inability of the TB molecule to fit closely within the larger cavity of γ-CD. Moreover, a significant turbidity, probably caused by intermolecular aggregation [26], has been observed at high concentration of γ-CD. This turbidity makes the sample extraction difficult and leads into higher standard errors in the solubility measurements.

The phase solubility diagrams of TB with α-CD and Mβ-CD can be classified as A_p type according to Higuchi and Connors [27]. A nonlinear plot with concave-upward curvature means that at least one complex with stoichiometry >1 with respect to the ligand is formed. The solubility data as a function of CD concentration fit well to the equation obtained for the formation of 1:1 and 1:2 complexes [25]: $S_t - S_o/[CD] = K_{11}S_o + K_{11}K_{12}\ S_o[CD]$ and the respective values for K_{11} and K_{12} constants are collected in Table 1. The stability constants obtained for the interaction between TB and α-CD are relatively low. The small size of the α-CD cavity does not allow a complete inclusion of the naphthalene ring, in this case, but, other guests, such as aliphatic molecules, can fit adequately [28, 29]. Therefore, the complexation of TB with α-CD could be related to weak interactions of the TB aliphatic chain in the cavity of α-CD. In the case of TB-Mβ-CD interactions, the value of K_{11} is the highest found among the stability constants, showing the favourable influence of the methyl

Table 1 Stability constants[a] of TB-CDs inclusion complexes in pH 12 aqueous solutions at 25 °C

	α-CD	β-CD	HP β-CD	Mβ-CD	γ-CD
$K_{11} \times 10^{-2}$ (M^{-1})	2.8 ± 0.1	25 ± 1	23 ± 1	46 ± 3	0.66 ± 0.04
$K_{12} \times 10^{-2}$ (M^{-1})	1.1 ± 0.1	–	–	0.67 ± 0.12	–

[a] Values are the mean ± SE of three determinations

substituents of CD on complexation [30], as it was also observed for NF [24]. Likewise, the small value of K_{12} could be explained by the surfactant effects of Mβ-CD which facilitate the solubilization of TB [31] and also, by a loose inclusion of the *tert*-butyl moiety of TB inside the methylated derivative.

The phase-solubility diagram obtained for TB-β-CD is B_S type. It corresponds to the formation of a complex whose solubility is limited by the reduced aqueous solubility of natural β-CD (Fig. 3). The molar ratio TB:β-CD for the binding, calculated from the length of the plateau, is equal to 0.85. This deviation with respect to a 1:1 stoichiometry could be attributed to higher standard errors at the plateau region.

The apparent binding constants with β-CD and HPβ-CD are quite similar (Table 1). The slight differences could be related to a steric hindrance of the hydroxypropyl substituents, which prevent the guest molecule from entering the CD cavity [32], although specific interactions of the amine group with the outer surface of the natural or substituted cyclodextrin molecules could be involved as well.

As it was previously indicated, it is interesting to compare the complexation between TB with different cyclodextrins and the corresponding results recently obtained with NF [24]. From this analysis, it is possible to infer that the aliphatic moiety of TB is involved in the formation of the complex with α-CD, which is not formed with NF. Likewise, the K_{11} stability constants of TB-β-CD and TB-Mβ-CD are almost 4-fold higher than those obtained with naftifine and the K_{11} value of the complex TB-HPβ-CD is increased 3-fold. These differences can be affiliated to the length of the aliphatic chain, which probably allows a deeper inclusion of the naphthalene group inside the corresponding β-CD molecule. However, the binding can also be affected by less steric hindrance of the methyl groups at the end of the chain of TB in relation to the benzene ring of NF. Moreover, the methyl groups of the guest can increase the complex stability [30].

Besides, it is worthy of note the important role that seems to play the different conformation of the side chain of both drugs; comparing to the structure of an e-alkene of the side chain of NF, the ene-yne side chain of TB appears to be a highly restricted conformation, which could lead to more stable complexes.

Solid complexes

The possible complexation of TB with the different cyclodextrins in the solid state has been studied by comparison of kneaded (KN), coevaporated (CE) and coprecipitated (CP) products with the corresponding physical mixtures (PM).

X-ray diffraction

Figure 4 shows the powder X-ray diffraction patterns of single components and different TB-CD systems of 1:1 molar ratio, for comparative purposes.

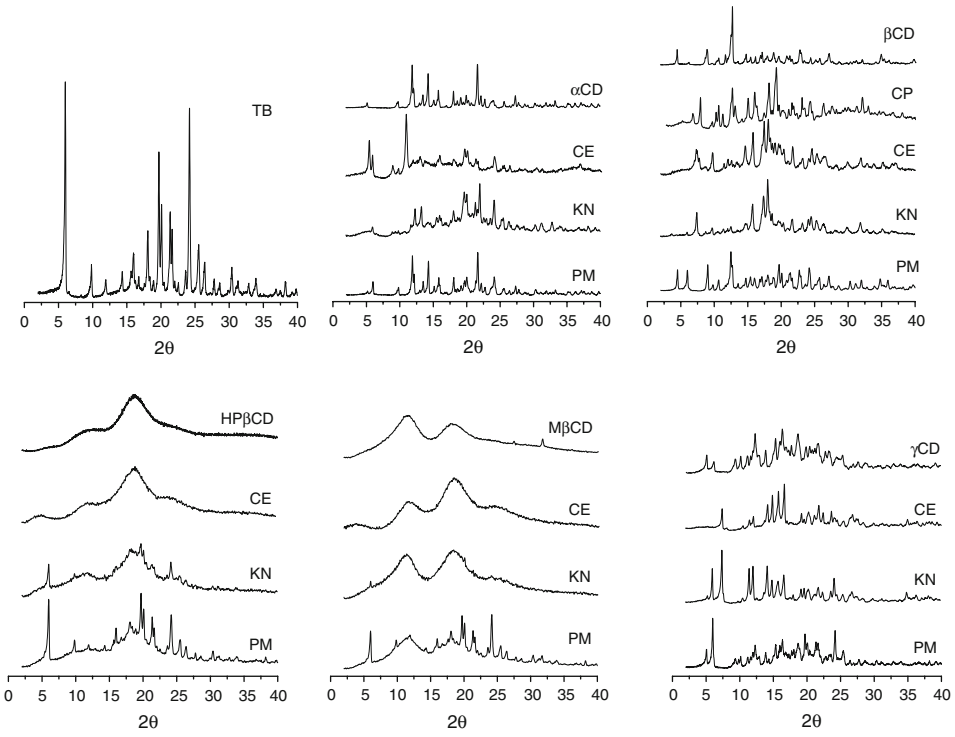

Fig. 4 X-ray diffraction patterns of single components and equimolar physical mixtures (PM), coevaporated (CE), kneaded (KN) and coprecipitated (CP) systems

The diffraction patterns of the TB-α-CD coevaporated, kneaded and physical mixture exhibit the main peaks of TB at $2\theta = 6.0°$, 19.7° and 24.2°; suggesting the presence of free terbinafine in the samples. In accordance to this, the FTIR spectra of all TB solid systems with α-CD are equivalent (Fig. 6), showing no evidence of an inclusion of the naphthalene ring in the host cavity. In relation with the thermal analysis of these samples, the endothermic peak associated to the melting of TB is clearly present in the DTA curve of PM, simultaneously with the decomposition process of TB and α-CD, but the TB melting is weakly detected in KN and CE products (Fig. 5). Regarding the main diffraction peaks of the cyclodextrin, pure α-CD and PM show the characteristic reflections of the cage-type packing at $2\theta = 12.0°$, 14.4° and 21.7° [33] and also exhibit three specific types of crystallisation water (Fig. 5) in the thermal analysis [34]. However, the X-ray pattern of TB-α-CD KN product suggests an intermediate structure for the α-CD crystals [33], with a specific arrangement of the hydration molecules (Fig. 5), in agreement with the crystals of pure α-CD obtained by kneading. This fact has been also observed in the kneading systems of NF with α-CD [24]. In addition, the X-ray pattern of the CE of TB-α-CD is different to that obtained by coevaporating single α-CD. The CE of pure α-CD presents the main peaks of the cage structure,

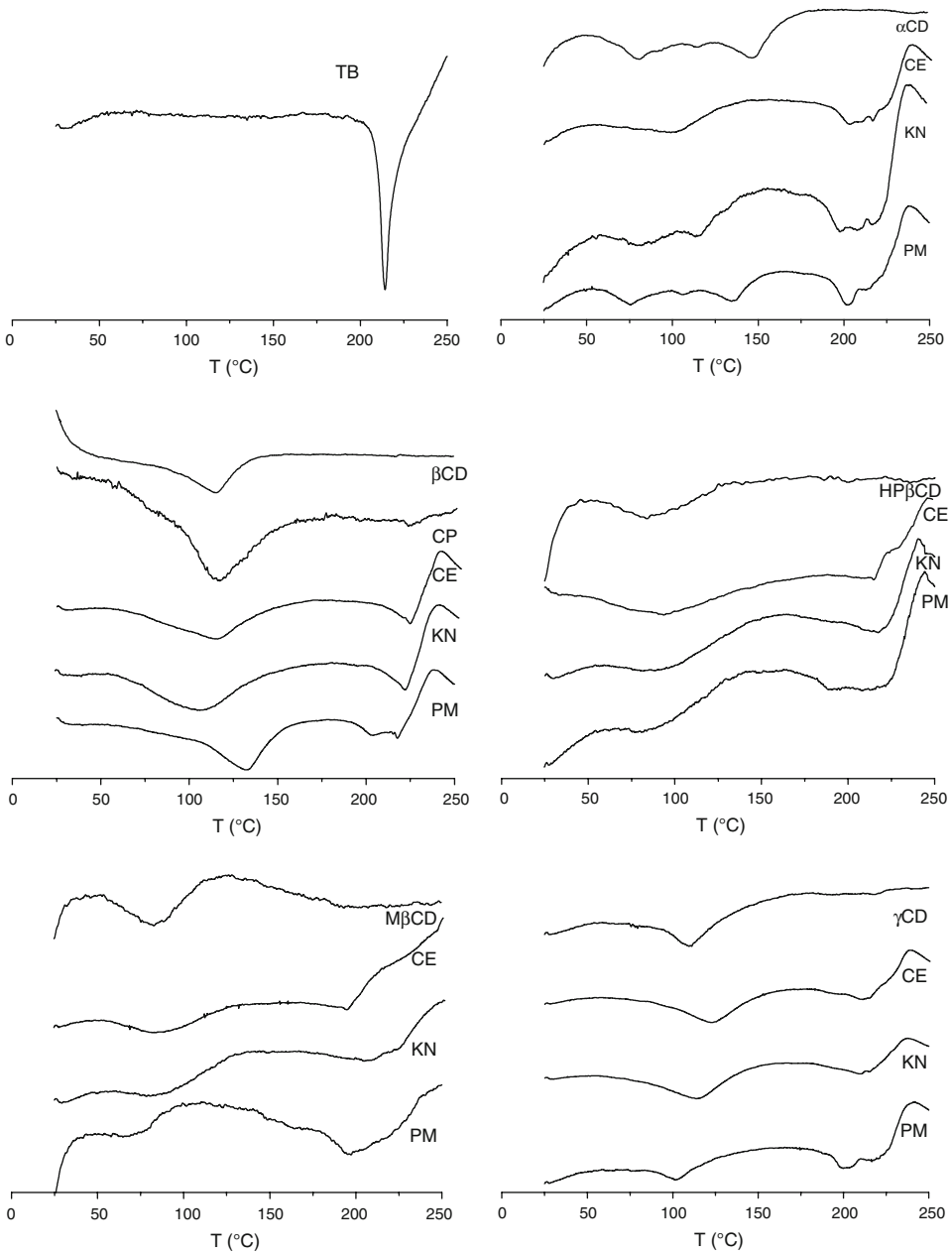

Fig. 5 Differential thermal analysis thermograms of TB, *β*-CD, HP*β*-CD, M*β*-CD and *γ*-CD, and their respective PM, CE, KN and CP systems

whereas in the TB-α-CD system these reflections are not observed.

In relation to the TB reflections, they are diminished in the CE system with respect to PM and KN products, showing a partial complexation by coevaporation. In this sense, a more complete complexation of TB and α-CD was evidenced by rapid coevaporation, which leads to an almost amorphous system, without the main TB reflections, and whose X-ray pattern is comparable with that obtained for complexes between cyclohexane and α-CD by vacuum drying [35].

Regarding the complexation with β-CD, the X-ray diffraction patterns of coevaporated and kneaded TB-β-CD products are different to that of the physical mixture. The main peaks of TB have disappeared in the CE but they weakly remain in the KN, indicating that the complex is formed in both cases, but more efficiently in the coevaporated product. In agreement with these results, the corresponding DTA curves (Fig. 5) and FTIR spectra (Fig. 6) are consistent with complex formation. In addition, while the CE and KN of pure β-CD lead to X-ray patterns similar to untreated CD, in the corresponding processes with TB-β-CD mixtures, the most interesting reflection of β-CD cage structure at $2\theta = 12.5°$ has disappeared, showing a possible channel-type crystalline structure of the complex.

In relation to the coprecipitated system, the X-ray diffraction pattern, the DTA curve and the FTIR spectrum point out the complex formation, but its X-ray pattern is different from that of the product obtained by coevaporation. Although it has been found difficult to distinguish characteristic peaks for β-CD which allow to differentiate between the cage and channel structures [36], the reflection at $2\theta = 12.1°$ in the CP product probably could

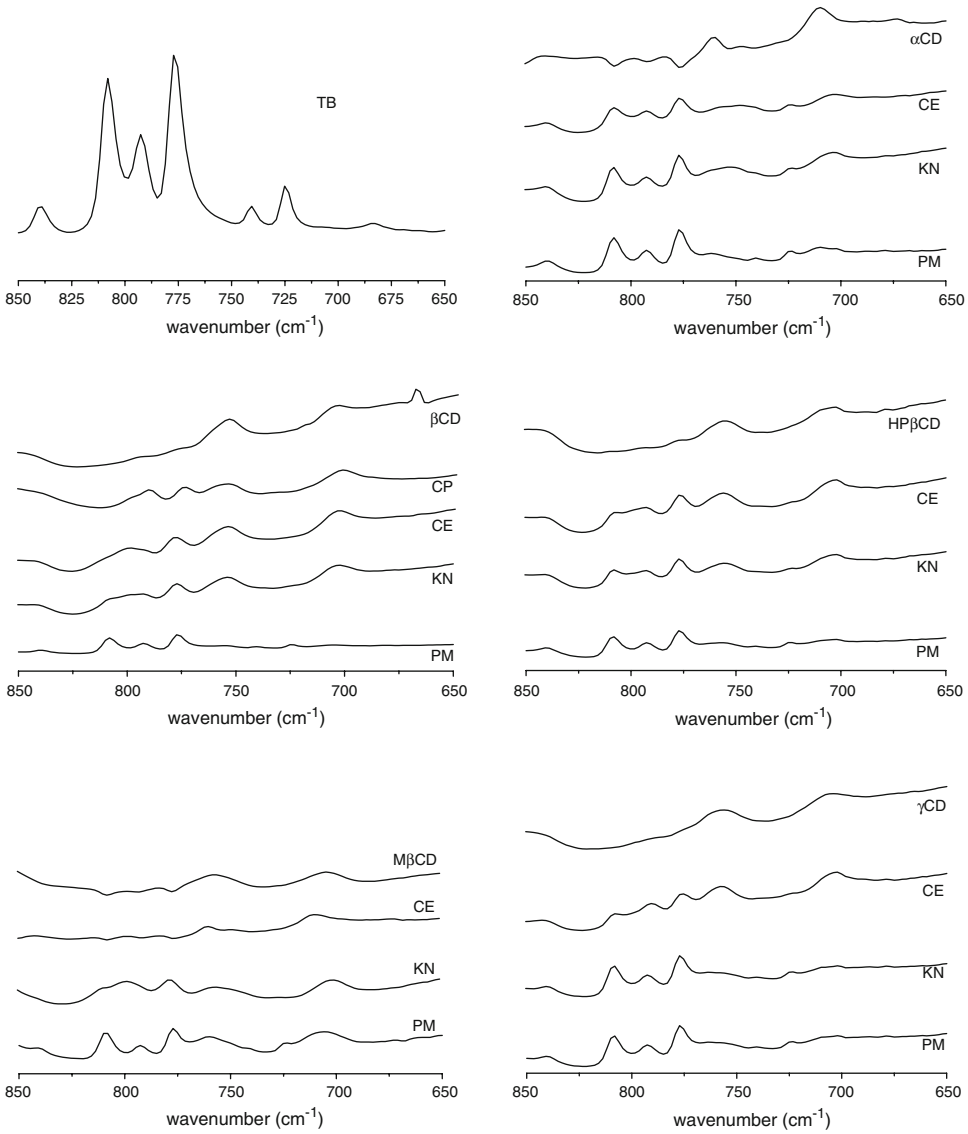

Fig. 6 Fourier transform infrarred spectra of TB, β-CD, HPβ-CD, Mβ-CD and γ-CD and their respective PM, CE, KN and CP systems

characterize the cage structure. In this sense, the complexes between β-CD and aromatic guests can be included in the cage structure as well as small molecules [37].

Finally, amorphous complexes of TB-β-CD were prepared by drying crystalline complexes at 70 °C. It has been indicated that the loss of crystallisation water results in amorphisation leading to solid complexes with high energy, which could be important in some pharmaceutical applications [38].

The X-ray pattern of pure γ-CD displays the specific peaks of the cage-type packing at $2\theta = 12.4°$ and 18.8° and, likewise, the physical mixture shows the cage γ-CD reflections together with those of pure TB. On the contrary, the characteristic reflection of the channel-type packing at $2\theta = 7.5°$ [34] was observed in the CE and KN products. Moreover, the channel structure, formed by void endless columns of two CD molecules consecutively superimposed, can be evidenced by the special disposition of the four peaks at $2\theta = 14.2°$, 14.9°, 15.8° and 16.7°, that always appear in this type of crystals. Although it is possible that the crystallisation of pure γ-CD in the channel structure occurs by rapid precipitation [36], the absence of the TB reflections evidences the channel complexation between TB and γ-CD by the CE method. The DTA curves (Fig. 5) and the FTIR spectra (Fig. 6) confirm the complexation by coevaporation. These results reveal once again the inability of the cage γ-CD structures to accommodate the guest molecule inside, because other close γ-CD molecules are partially included in it, blocking the CD molecular cavity [37]. Instead, the X-ray pattern of the KN system also presents the TB characteristic peaks, together with those of the channel γ-CD crystals; the similarity of the FTIR spectra of KN and PM (Fig. 6) seems to point out the separate crystallization of both components.

The coevaporated and kneaded TB-HPβ-CD and TB-Mβ-CD systems are amorphous, like the single cyclodextrins. The absence of TB reflections means that the complex is formed, although more completely in the coevaporated products. The FTIR spectra and the DTA curves are also in agreement with complex formation.

Thermal analysis

The DTA thermogram of TB shows a sharp endothermic peak at 214 °C which corresponds to the melting of the drug as it is depicted in Fig. 5. The corresponding TGA curve shows the drug decomposition during the melting. Likewise, the endothermic peaks of pure CDs below 160 °C are associated to dehydration processes of these cyclic oligomers.

By comparison with the physical mixtures, all the coevaporated and kneaded systems which lead to complex formation exhibit endothermic peaks, corresponding to the loss of water molecules, which broaden towards higher or lower temperatures. In addition, the endothermic of TB melting disappears in the aforementioned systems. These effects indicate a strong interaction between TB and CDs, with new arrangements of the water molecules in the complexes, although they do not present conclusive data to complex formation. On the other hand, the melting signal of TB in the physical mixtures is diminished in relation to pure TB because heating can induce specific interactions between the drug and CDs, mainly with the methyl and hydroxypropyl derivatives [39]. Yet, it is also possible that the melting of TB will be masked by the decomposition processes of CDs, which occur at lower temperature, starting around 200 °C, in systems containing TB in relation to pure cyclodextrin.

FTIR spectroscopy

The band at 772 cm^{-1} in the FTIR spectrum of TB corresponds to the bending vibration of the aromatic C–H bond [40] and can be used to elucidate the inclusion of the TB naphthalene ring inside the CDs. This band appears unchanged in the physical mixtures but it broadens and shifts to a higher frequency in the coevaporated and kneaded products for all the cyclodextrins, except for α-CD and the kneaded of TB-γ-CD (Fig. 6). The FTIR results evidence the inclusion of the naphthalene moiety inside the CD molecule when amorphous or crystalline complexes are formed, but they are unable to detect the inclusion of the aliphatic side chain.

Dissolution rate

In order to study the effect of solid state complexation on the dissolution rate of the drug, the dissolution profile of TB with β-CD and HPβ-CD was investigated. Both complexes exhibit similar apparent stability constants in solution, but their crystallinity, as explained before, is different, so the influence of this parameter on the dissolution rate was studied. The dissolution values were plotted as μg/mL of TB dissolved from coevaporate, physical mixture and pure TB versus time (Fig. 7).

From these curves, it can be observed that all the CDs displayed a drug dissolution rate higher than that of the pure drug. The relative dissolution rate values in relation to pure TB at 300 min were found to be 2.4 and 1.5 for CE systems of TB-β-CD and TB-HPβ-CD, respectively, and 1.8 and 1.1 for the corresponding physical mixtures. The increase in the dissolution rate observed for physical mixtures might be mainly attributed to the hydrophilic effect of cyclodextrins, which increase the drug solubility in the solid-liquid interface and can reduce the interfacial tension between TB and the dissolution medium, thus

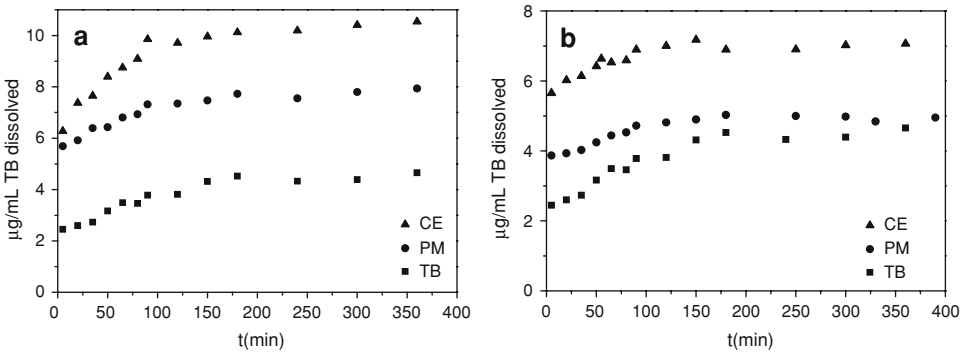

Fig. 7 Dissolution curves of TB alone (*Square*) and TB-β-CD (**a**) and TB-HPβ-CD (**b**) equimolar systems: PM (*Circle*) and CE products (*Triangle*)

leading to a higher dissolution rate [41, 42]. Compared to the physical mixtures, the TB release from the coevaporated products was faster. Several mechanisms have been proposed to account for the increase in the dissolution kinetics of drugs from solid dispersions; decreased crystallinity, increased wettability, reduction of drug particle size and complex formation are considered to be predominant factors [41, 43]. In agreement with complex formation [44], the dissolution rates of CE systems with β-CD and HPβ-CD are related to their stability constants; although the K_{11} value is only slightly higher with β-CD, it seems sufficient in improving the dissolution rate values with respect to HPβ-CD. The amorphous character of HPβ-CDs, which contributes to a higher aqueous solubility, has a scarce influence on the dissolution rate of TB.

It was not possible to compare the dissolution process of TB and NF [24] because of their differences in the ionisation degree at pH 7.0, by considering the pKa values of both drugs (6.7 and 8.0, respectively).

Conclusions

It has been found that the antifungal drug TB can form complexes with all the CDs studied in this work, both in solution and in the solid state. The highest stability constant of the complexes in solution is that of TB-MβCD. In relation to the solid state, the coevaporation method can be considered as best in preparing the complexes and it has been observed that complex formation has a positive influence on the drug dissolution.

Referring to the comparison of the results obtained in this study with those obtained for NF in a previous work [24], the stability constants calculated for the complexes of TB are higher than those of NF complexes, which can be attributed to a more favourable inclusion of TB related to the aliphatic chain of this drug.

Acknowledgements Authors are grateful to Comisión Interministerial de Ciencia y Tecnología (Project MAT2003-08390-C02-01) for financial support and to Gobierno de Navarra for M. Uzqueda's grant.

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