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Research Article

Preparation and Solid-State Characterization of Inclusion Complexes Formed Between Miconazole and Methyl-β-Cyclodextrin

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Abstract. The aim of this study is to confirm the formation of inclusion complexes between miconazole (MCZ) and two derivatives of beta-cyclodextrin, methyl-beta-cyclodextrin (MβCD) and 2-hydroxypropyl-beta-cyclodextrin (HPβCD) in aqueous solution by phase solubility studies. Inclusion complexes with MβCD in the solid state were then prepared by different methods, i.e., kneading, coevaporation (COE), spray-drying (SD), and lyophilization (LPh). The physicochemical properties of these complexes were subsequently studied by means of differential scanning calorimetry, Fourier transform infrared spectroscopy, scanning electron microscopy, and X-ray diffraction techniques. Phase solubility diagrams with MβCD and HPβCD were classified as A_P type, indicating the formation of 1:1 and 1:2 stoichiometric inclusion complexes. The apparent stability constants (K_S) calculated from the phase solubility diagram were 145.69 M^{-1} ($K_{1:1}$) and 11.11 M^{-1} ($K_{1:2}$) for MβCD and 126.94 M^{-1} ($K_{1:1}$) and 2.20 M^{-1} ($K_{1:2}$) for HPβCD. The method of preparation of the inclusion complexes in the solid state was shown to greatly affect the properties of the formed complex. Hence, the LPh, SD, and COE methods produce true inclusion complexes between MCZ and MβCD. In contrast, crystalline drug was still clearly detectable in the kneaded (KN) product.

KEY WORDS: cyclodextrins; 2-hydroxypropyl-β-cyclodextrin; inclusion complexes; methyl-β-cyclodextrin; miconazole.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides produced from starch by the action of glycosyltransferases. The four natural cyclodextrins, α-, β-, γ-, and δ-cyclodextrins, with 6, 7, 8, or 9 glucose units, respectively, differ in their ring size and solubility (1). Complexation with CDs has been reported to enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs (1,2). The internal hydrophobic cavity in the CDs allows the inclusion of lipophilic entities, resulting in enhanced water solubility (3,4). Beta-cyclodextrin (β-CD) is the natural cyclodextrin with higher commercial interest; however, the practical utility of this compound can be limited by its solubility in aqueous systems. The rigid structure of the beta-cyclodextrin β-CD makes it more susceptible to crystallization. For the above reasons, the beta-cyclodextrin β-CD should be modified, both to improve solubility and to prevent its crystallization, as well as to reduce its toxicity (5). For instance, chemical modification through random methylation or hydroxyalkylation has resulted in amorphous derivatives with improved water solubility and greater solubilizing and complexing power than the parent beta-cyclodextrin β-CD (6). Hydrophilic cyclodextrins, which are considered a new class of penetration enhancers, improve drug delivery through the membranes by increasing the availability of dissolved drug close to the membrane surface (7,8). Methylated β- cyclodextrin interacts strongly with lipids and modify mucosa permeability (9). Some toxicological effects can be expected if higher concentrations of CDs are used due to its high affinity to lipids (10). However, cyclodextrin is very effective as penetration enhancers at low concentrations ranging from 2% to 5% (7) therefore avoiding harmful effects (9). The modified methyl-β-cyclodextrin (MβCD) offers a significant advantage, as a host molecule, over the beta-cyclodextrin β-CD since its solubility in aqueous solution at room temperature (>2,000 mg/mL) is significantly higher than the latter one (18.5 mg/mL) (6). It is expected that the higher solubility of MβCD in aqueous solution will contribute to a higher solubility of the drug when in the complexed state (11).

Miconazole (MCZ; ((1-2-(2, 4-diclhorophenyl)-2-(2, 4-diclhorophenyl)-methoxy) ethyl)-1-imidazole; Fig. 1) is a broad-spectrum antifungal agent of the imidazole group (12), a compound well known for its poor aqueous solubility (13). MCZ is used primarily as a topical drug for cutaneous mycoses (14). Antimycotic imidazole derivatives are lipophilic drugs, and complexation of these drugs with different types of cyclodextrins CDs has been previously studied (12–17). However, complexation of MCZ with this particular cyclodextrin, MβCD, has never been investigated. MCZ inclusion complexes with MβCD can be very interesting due to

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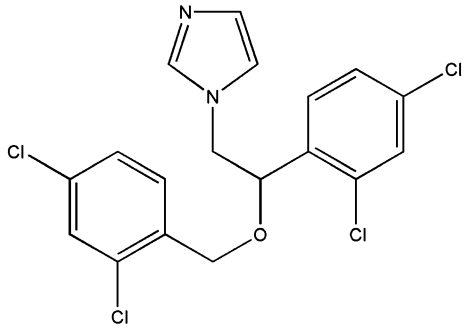

Fig. 1. MCZ chemical structure

superior solubility of this cyclodextrin, enhancing permeation effect through biological membranes (18) and an overall improvement of the efficacy of drug delivery systems. MβCD has been shown to be an effective promoter of drug absorption by increasing drug penetration through the skin and nasal (8) and buccal mucosa (9).

The aim of this study was to investigate and to confirm the formation of an inclusion complex between MCZ and MβCD. Drug–cyclodextrin interactions in solution were investigated by phase solubility diagrams. Furthermore, another modified cyclodextrin, the 2-hydroxypropyl-β-cyclodextrin (HPβCD), was used in a comparative way, to ascertain the usefulness of the MβCD to form complexes with MCZ in solution.

Inclusion complexes between MCZ and MβCD in solid state were prepared by kneading (KN), coevaporation (COE), spray-drying (SD), and lyophilization (LPh) methods. Binary systems in solid state were characterized by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and X-ray diffraction (XRD) techniques.

MATERIAL

Methyl-β-cyclodextrin (Lot 781144; MW=1,190 and an average degree of substitution, DS=0.5) and 2-hydroxypropyl-β-cyclodextrin (Lot E812M; MW=1,480 and an average degree of substitution, DS=0.63) were kindly donated by Roquette (Lestrem, France). Miconazole (MCZ) (Lot 00478343; MW=416.13) base was kindly donated by Janssen Pharmaceutica (Beerse-Belgium). All others reagents were of analytical reagent grade.

EXPERIMENTAL METHODS

Phase Solubility Studies

The determination of the phase solubility diagram is a widely accepted method for evaluation of the effect of cyclodextrin complexation on the drug solubility. The phase solubility studies were performed by the method reported by Higuchi and Connors (19). Increasing concentrations of MβCD (0–0.23 M) or HPβCD (0–0.2 M) were added to excess amounts of MCZ. Suspensions were stirred at room temperature (25°C±2) during 6 days until reaching the equilibrium. All suspensions were filtered through a 0.45-μm membrane filter (Millipore), suitably diluted with ethanol and analyzed spectrophotometrically (UV-1603, Shimadzu, Japan) at 272 nm (20). The stability constants ($K_{1:1}$ and $K_{1:2}$) for the complexation were calculated using Eq. 1, from the straight line of the phase solubility diagrams and Eq. 2, where [*S*0] is the intrinsic solubility of MCZ, and [*St*] and [*Lt*] are the concentrations of MCZ and MβCD in solution, respectively (4).

$$K_{1:1} = \frac{\text{Slope}}{\text{Intercept}(1 - \text{Slope})} \tag{1}$$

$$\frac{([St] - [S0])}{[Lt]} = K_{1:1}[S0] + K_{1:1}K_{1:2}[S0][Lt] \tag{2}$$

Preparation of Solid Binary Systems

Solid systems were prepared with equimolar ratio of MCZ and MβCD, according the results obtained in phase solubility studies by four different techniques, namely KN, COE, SD, and LPh. Physical mixture (PM) was prepared and used as reference.

Physical Mixture

PM was prepared by blending MCZ and MβCD (1:1 molar ratio), previously sieved (125 μm) in a ceramic mortar.

Kneaded System

MβCD was wetted in a ceramic mortar. The required amount of MCZ was then slowly added and the slurry was kneaded for about 45 min. During this process, an appropriate quantity of hydroalcoholic solution (1:3; water–ethanol) was added in order to maintain a suitable consistency of MCZ. The final product was then allowed to equilibrate at 25°C during 24 h.

Coevaporated System

Equimolar amounts of MCZ and cyclodextrin (1:1 molar ratio) were dissolved in ethanol and hydroalcoholic solution (1:4 ethanol–water), respectively, mixed and stirred during 24 h, until a clear solution was obtained. Then, the solvents were evaporated in a vacuum oven at 50°C using Laborota, 40001 (Heidolph), until complete drying was obtained checked by constant weight.

Spray-Dried System

Equimolar quantities of MCZ and MβCD were dissolved in ethanol and distilled water, respectively, and mixed. The mixture was agitated in an orbital shaker during 24 h. The final clear solution was spray-dried in a LabPlant SD-05, under the following conditions: inlet temperature150°C, outlet temperature 77°C, flow rate of the solution 400 mL/h, airflow rate 40–50 m^3/h, and atomizing air pressure 1.5 bar.

Lyophilized System

Equimolar amounts of MCZ and corresponding cyclodextrin were dissolved in distilled water. The solution was

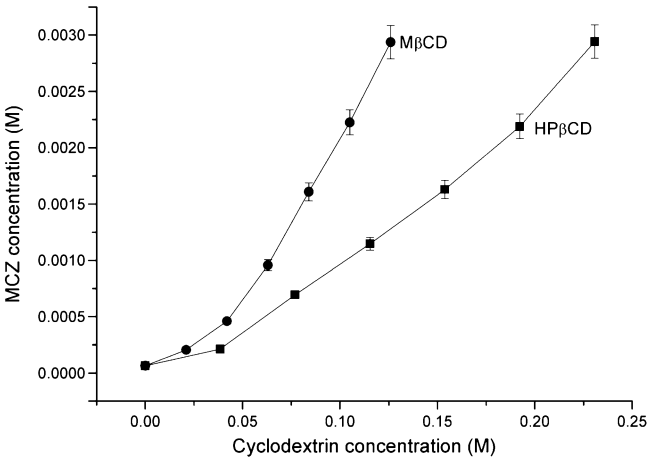

Fig. 2. Phase solubility diagrams of MCZ with CDs, in aqueous solution at 25±2°C. Values are mean±SD (n=3)

acidified with a few drops of hydrochloric acid (0.1 M) until a clear solution was attained. The mixture was agitated in an orbital shaker during 24 h at room temperature and filtered through a 0.45-μm membrane filter (Millipore). The filtrate was frozen by immersion in an ethanol bath at −50°C (Shell Freezer, Labconco, Freezone®—model 79490) and then lyophilized in a freeze-dryer (Lyph-lock 6 apparatus, Labconco) for 48 h.

The obtained powders were sieved (125 μm) and kept in a desiccator until used and the content of the drug was determined by UV assay.

Thermal Analysis

DSC measurements of the pure materials and binary systems were carried out using a Shimadzu DSC-50 System (Shimadzu, Kyoto, Japan) equipped with a computerized data station TA-50WS/PC. The thermal behavior was studied by heating the samples (1–2 mg) in a sealed aluminum pan from 30° C to 250°C, at a rate of 10°C/min, and under a nitrogen flow of 20 cm^3/min. An empty pan was sealed and used as a reference.

Indium (99.98%, mp 156.65°C, Aldrich®, Milwaukee, USA) was used as standard for calibrating the temperature.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectra were obtained by Nicolet Magna IR-750. Spectra acquisitions were performed directly in powder samples with the application of 16 scans at a resolution of 4 cm^{-1} over the range 4,000–400 cm^{-1}.

Scanning Electron Microscopy

The morphology of the samples was determined using a scanning electron microscope (JEOL JSM-5310, Tokyo, Japan). The samples were fixed on a brass stub using double-sided tape and then made electrically conductive by coating in a vacuum with thin layer of gold. The photographs were taken with a Pentax (model K100D) camera at an excitation voltage of 20 kV and magnification factors of 500 until ×3,500.

X-ray Diffraction

The structural analysis of MCZ, MβCD, and binary systems were performed using an X-ray diffractometer (Philips X'Pert diffractometer system) with Bragg-Brentano geometry and a Cobalt X-ray source, using a voltage of 40 kV and a current of 35 mA. The angular range (2θ) covered was between 5° and 60°, with a step size of 0.025° and a counting time per step of 0.5 s.

The relative degree of crystallinity (RDC) was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with a reference, as follows:

$$(\mathrm{RDC}) = \frac{I_{\mathrm{SA}}}{I_{\mathrm{REF}}} \tag{3}$$

where I_{SA} is the peak height of the sample under investigation and I_{REF} is the peak height of the same angle for the reference, with the highest intensity. MCZ was used as a reference sample for calculating RDC values of binary systems (21,22).

RESULTS AND DISCUSSION

Phase Solubility Diagrams

According to the classification introduced by Higuchi and Connors (19), phase solubility diagrams can be divided into two major categories, type "A" and type "B." The type "A" solubility curves are obtained when the apparent solubility of the substrate increases with increasing ligand concentration over the entire concentration range. A linear relationship is designated as an A_L-type, A_P-type curves exhibiting positive and A_N-type a negative curvature. When

Table I. K_S Values of the Inclusion Complexes

Inclusion complexes	Type of diagram	S_t (10^{-5} M)[a]	S_2 (10^{-3} M)[b]	SE[c]	$K_{1:1}$ (M^{-1})[d]	$K_{1:2}$ (M^{-1})[e]
MCZ–MβCD	A_P	6.5±0.57	2.94±0.02	45.10	145.69±4.1	11.11±0.5
MCZ–HPβCD	A_P	6.5±0.64	2.94±0.008	45.18	126.94±4.4	2.20±0.4

Values are mean±SD (n=3)
[a] MCZ solubility in aqueous solution
[b] MCZ solubility in CD solutions (0.12 M MβCD and 0.23 M HPβCD)
[c] Efficiency of solubilization (coefficient between MCZ solubility in the absence and in the presence of cyclodextrin)
[d] Determination of (K_S) by phase solubility studies for stoichiometry 1:1
[e] Determination of (K_S) by phase solubility studies for stoichiometry 1:2

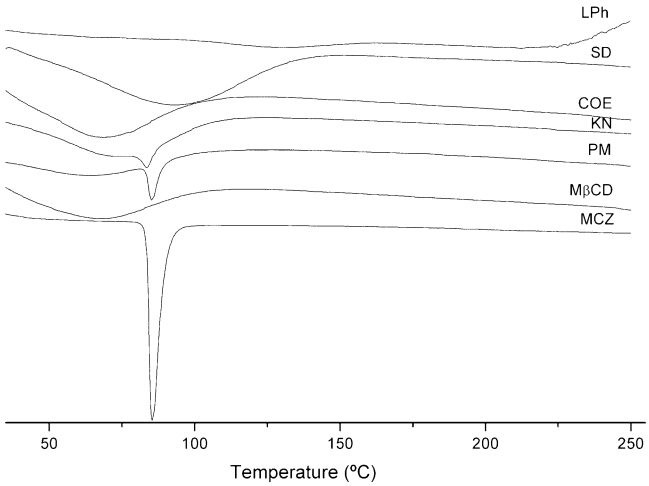

Fig. 3. DSC thermograms of miconazole (*MCZ*), methyl-beta-cyclodextrin (*MβCD*), physical mixture (*PM*), kneaded (*KN*), coevaporated (*COE*), spray-dried (*SD*), and lyophilized (*LPh*) systems

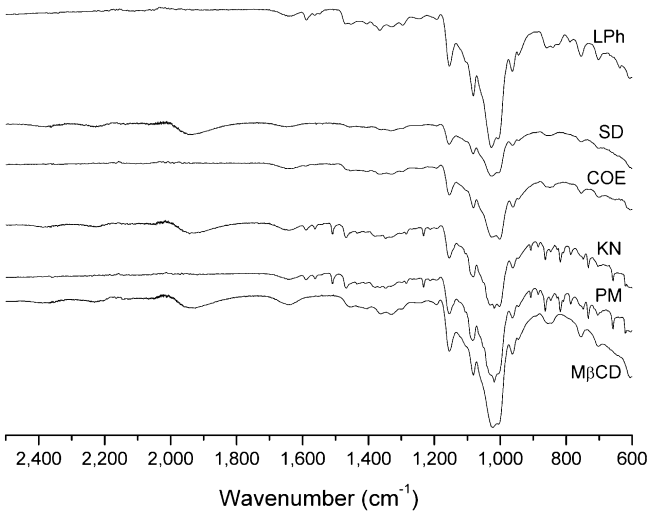

Fig. 5. FTIR spectra of methyl-beta-cyclodextrin (*MβCD*), physical mixture (*PM*), kneaded (*KN*), coevaporated (*COE*), spray-dried (*SD*), and lyophilized (*LPh*) systems

in the solubility curve a plateau region of the substrate is observed, it is a type "B" diagram, and the curve is designated B_S if an initial increase in the apparent solubility is observed before the plateau region is reached (23). The phase solubility diagrams of MCZ with the MβCD or HPβCD are shown in Fig. 2. Table I summarizes the type of phase solubility diagram, apparent stability constants (K_S), efficiency of solubilization, and solubility values in aqueous solution (S_t) and in the presence of the maxima concentration of cyclodextrin (S_2), for both cyclodextrins CDs. The solubility value of the MCZ in the cyclodextrin solution stands for the maximum solubility value of the drug when the cyclodextrin concentrations are also at a maxima value.

The diagrams are classified by Higuchi and Connors as A_P type. The results are in agreement with the general observations by Pedersen *et al.* (13), which also achieved A_P-type diagrams with βCD and HPβCD in water. Jacobsen *et al.* (24) attained A_P-type diagrams with αCD when the medium was 0.05-M phosphate buffer, pH 7.1.

The diagram profile suggests the formation of inclusion complexes between MCZ and MβCD or HPβCD in a stoichiometry of 1:1 and 1:2 over the concentration range studied (0–0.12 and 0–0.23 M, respectively). However, in both cases, the considerably higher K_S values attained within the stoichiometry of 1:1 suggest that the complex is preferably formed under this condition. In addition, the K_S value in purified water demonstrates that the cavity of those cyclodextrins CDs is able to accommodate the molecular portion of MCZ involved in the inclusion. The complexation of MCZ with both cyclodextrins CDs significantly increased its aqueous solubility as seen by the high efficiency of solubilization attained (see Table I). The efficiency of solubilization was similar for both cyclodextrins here investigated. However, it has to be pointed out that the concentration of MβCD used was nearly half of the concentration of HPβCD suggesting that the former CD cyclodextrin can be used to form inclusion complexes with this drug in a more efficient manner. For this reason, the MβCD was chosen to continue the studies of the inclusion complexes in the solid state.

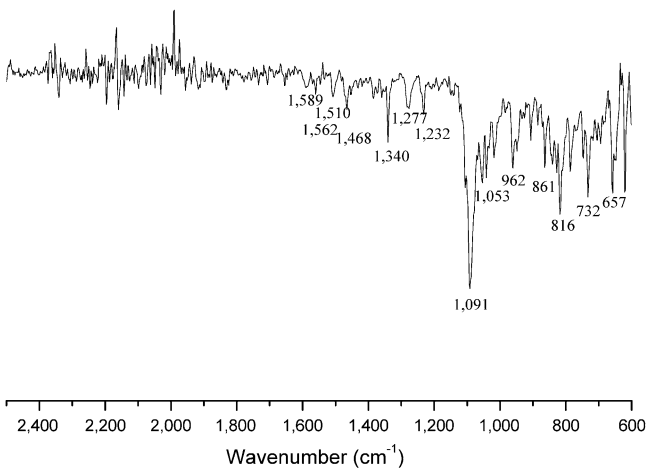

Fig. 4. FTIR spectra of MCZ

Thermal Analysis

DSC analysis has been shown to be a very powerful analytical tool in the characterization of solid-state interactions between drugs and CDs (25) and is a rapid analytical technique commonly used for evaluating drug–excipient interactions through the appearance, shift, or disappearance of endothermal or exothermal effects and/or variations in the relevant enthalpy values (26). The thermal curves of pure components and binary systems are shown in Fig. 3. MCZ is characterized by a single endothermic peak at 85.2°C due to the fusion of the compound (23). The DSC curve of MβCD shows a broad endothermic effect around 40°C and 100°C associated with water loss of the crystal (27). In the PM system, the peak characteristic of the drug is maintained despite appearing reduced in intensity which indicates that no complexation occurs between MCZ and MβCD in this system. Considering KN system, there is a substantial size reduction, a broadening, and a shift to lower temperatures of the drug melting point. Comparing with PM system, it could

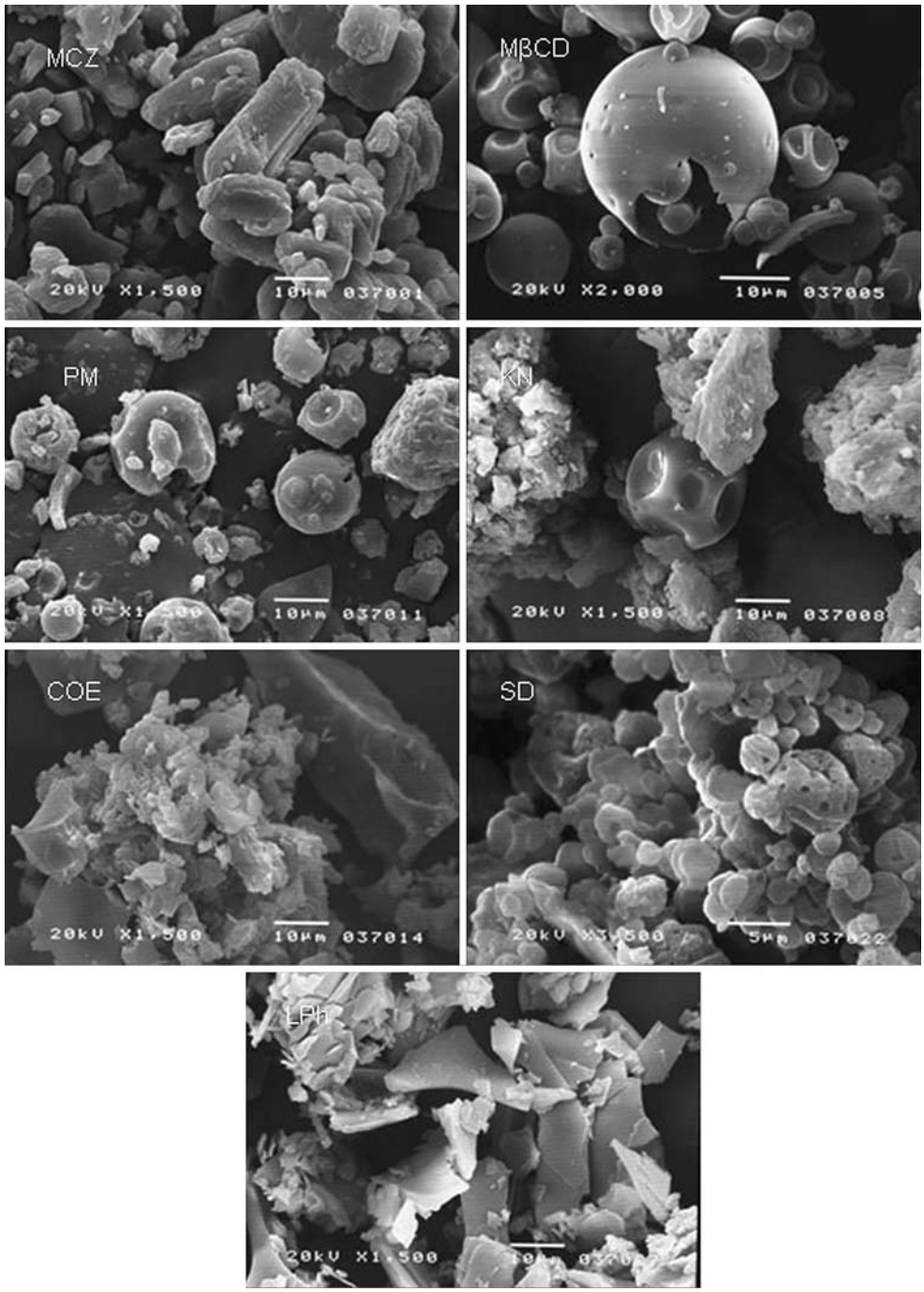

Fig. 6. Scanning electron microphotographs of miconazole (*MCZ*), methyl-beta-cyclodextrin (*MβCD*), physical mixture (*PM*), kneaded (*KN*), coevaporated (*COE*), spray-dried (*SD*), and lyophilized (*LPh*) systems

be ascribed to some drug–cyclodextrin interaction or loss of drug crystallinity. However, the absence of this peak in the COE, SD, and LPh systems suggests the formation of an amorphous inclusion complex through molecular encapsulation of the drug inside the MβCD cavity.

Fourier Transform Infrared Spectroscopy

For a structural characterization of the chemical entities, infrared spectroscopy is a standard method. The infrared assignments of MCZ have not yet been reported. For large molecules, quantum chemical calculations predicting harmonic frequencies and spectral intensities are essential when interpreting experimental infrared spectra. MCZ is made of 39 atoms giving rise to 111 vibrational degrees of freedom (28). The spectrum for the drug is presented in Fig. 4 and spectra of the MβCD and binary systems are presented in Fig. 5. In the mid-wavenumber region, some characteristic bands are observable. Barillaro *et al*. summarized the most important bands of the MCZ spectra. For instance, the bands

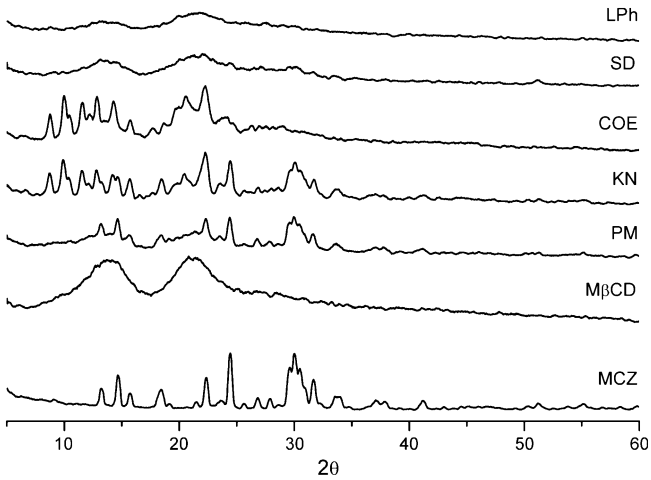

Fig. 7. X-ray diffractograms of miconazole (*MCZ*), methyl-beta-cyclodextrin (*MβCD*), physical mixture (*PM*), kneaded (*KN*), coevaporated (*COE*), spray-dried (*SD*), and lyophilized (*LPh*) systems

at 1,589 and 1,561 cm^{-1} in the experimental spectrum are assigned to the C–C stretching vibration of the two dichlorobenzene groups. The band at 1,510 cm^{-1} corresponds to C–C stretching vibration of the imidazole group as well as the CH bending of the imidazole group, the C6 of the aliphatic part of miconazole MCZ. The band at 1,468 cm^{-1} corresponds to the CH bending of the two dichlorobenzene groups and to the CH bending of the C6 and C17 (28).

The characteristic band of the MβCD at 1,021 cm^{-1} is present in all binary systems. Conversely, the typical bands of the MCZ at 1,053 and 1,091 cm^{-1} do not appear in any of the binary systems. Even in the PM where no complexation is expected and therefore those drug bands should appear, the bands are not detectable. This might suggest that those bands are masked by the very broad and intense bands of the MβCD within the same wavelength range. Therefore, the analysis of the complexation between the cyclodextrin and the drug was based on the other characteristic bands of the MCZ (657, 732, 816, 861, 962, 1,232, 1,277, 1,340, 1,468, 1,510, 1,562, and 1,589 cm^{-1}). In the PM and KN, the bands of the MCZ at 733, 861, 1,232, 1,469, and 1,562 cm^{-1} are present, whereas, in the COE, SD, and LPh products, the bands practically disappeared. In the spectrum of the LPh, one can observe one peak of MCZ, with small intensity, at 1,589 cm^{-1}. The FTIR spectrum of COE, SD, and LPh products, on the other hand, shows the strong reduction or the complete disappearance of the characteristic MCZ bands, indicative of strong drug–cyclodextrin interactions and possibly inclusion complexation of the drug, thus substantially confirming the results previously obtained by DSC, SEM, and XRD. The changes observed in the FTIR spectra of the various samples, such as shift of peaks or their reduction in intensity up to

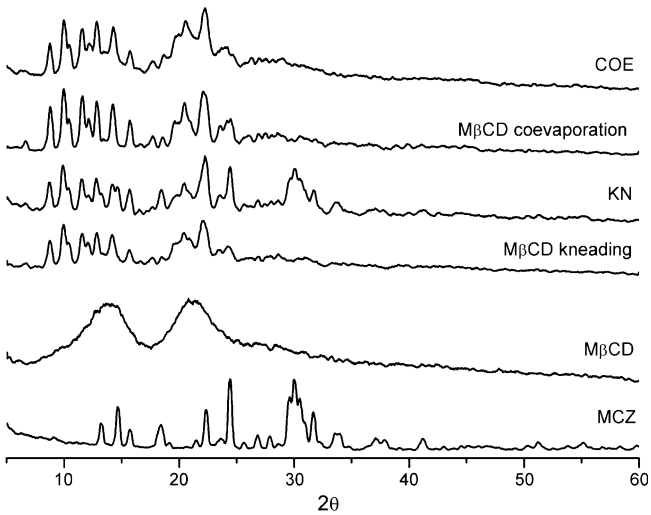

Fig. 8. X-ray diffractograms of miconazole (*MCZ*), methyl-beta-cyclodextrin (*MβCD*), MβCD kneading, kneaded (*KN*) system, MβCD coevaporation, and coevaporated (*COE*) system

Table II. Peak Intensities and RDC Values for MCZ:MβCD Systems

	MCZ	PM		KN		COE		SD		LPh	
2θ	PI	PI	RDC	PI	RDC	PI	RDC	PI	RDC	PI	RDC
14.738	146	126	0.863	88	0.602	91	0.623	79	0.541	60	0.410
24.438	276	128	0.463	139	0.503	83	0.300	71	0.257	68	0.246
29.537	159	145	0.911	109	0.685	81	0.509	77	0.484	59	0.371
30.563	151	106	0.701	102	0.675	63	0.417	49	0.324	56	0.370
31.662	137	95	0.693	72	0.525	71	0.518	53	0.386	41	0.299

PI peak intensity

almost complete disappearance, depended on their preparation method, suggesting different degrees of interaction and or amorphization in the different products.

Scanning Electron Microscopy

SEM is a qualitative method used to study the structural aspect of raw materials (29). Even if there is a clear difference in crystallization state of the raw materials and the products, this study is inadequate to confirm inclusion complexation but nevertheless helps to assess the existence of a single component in the preparations obtained. The morphology and particle size of MCZ, MβCD, and binary systems were analyzed by SEM and are represented in Fig. 6. MCZ appears as regular parallelogram-shaped crystals. MβCD is composed by spherical particles (30) with an amorphous character (27). The SEM image of the PM system shows clearly the characteristic MCZ crystals, mixed with the cyclodextrin particles or adhered to their surface, thus confirming the presence of crystalline drug. In contrast, a drastic change in the morphology and shape of the drug particles were observed in the COE-, SD-, and LPh-processed MCZ–MβCD complex; it was no longer possible to differentiate the two components, drug and cyclodextrin, revealing an apparent interaction between the drug and the cyclodextrin in those systems.

In the KN product, although one can detect the formation of a new solid phase with an evident particle size reduction and loss of crystallinity with respect to the original components, it is still possible to observe some isolated cyclodextrin particles. The particle size of the product formed by SD was smaller in size than that of the product formed by COE. The SD system shows the presence of amorphous and homogeneous aggregates of small spherical particles, a particular aspect of this type of systems (11). The LPh technique gave rise to amorphous and small irregular-shaped with a lamellate aspect.

X-ray Powder Diffraction

Powder X-ray diffractometry is a useful method for the detection of cyclodextrin complexation in powder or microcrystalline states. The diffraction pattern of the complex should be clearly distinct from that of the superimposition of each of the components if a true inclusion complex has been formed (31). Power X-ray diffractometry was used to investigate in more depth the differences in the solid state between MCZ and MβCD products prepared by different methods. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference. The X-ray diffraction patterns of MCZ, MβCD, and binary systems are represented in Fig. 7. In the X-ray diffractogram of MCZ is possible to observe several sharp peaks at the following diffraction angles (2θ) of 13.2°, 14.7°, 22.3°, 24.4°, 29.5°, 30.0°, 30.5°, and 31.6° suggesting that the drug is present in a crystalline form. In agreement with the DSC results, the XRD pattern of the unprocessed pure materials confirms that MCZ is in the crystalline state. On the other hand, the XRD pattern of MβCD confirms its amorphous form (32). In the case of the PM, the XRD spectrum is simply the superposition of those of the single components. A decrease in the peak intensity, crystallinity loss, was observed in the PM diffractogram, probably due to the amorphous character of the cyclodextrin used. In the KN and COE systems, new peaks were observed and in KN systems some characteristic MCZ peaks were still detectable. This can be due to cyclodextrin crystallization induced (33) by those two techniques. In order to comprehend such changes, MβCD without drug were subjected to a kneading and coevaporating process under the same conditions. The products obtained and MβCD (Fig. 8) show completely different X-ray diffraction patterns, peak relative intensities, and shape, suggesting that those techniques promote crystallization of the cyclodextrin (33). The total drug amorphization observed was induced by the COE, SD, and LPh methods.

Table II shows the RDC for the various binary systems. A decline in the relative crystallinity of all systems was observed. The decrease of the RDC in most of the cases follows the same pattern: PM > KN > COE > SD > LPh. The observations are in agreement with powder diffractograms.

Thus, the results obtained by DSC, FTIR, and SEM and the disappearances of the MCZ diffraction in the COE, SD, and LPh systems indicate again the possible formation of inclusion complexes between MCZ in those systems.

CONCLUSION

The results reported in the present study show that MCZ forms inclusion complexes with MβCD or HPβCD in solution in a stoichiometry of 1:1 and 1:2. Phase solubility profiles indicate that the solubility of the MCZ is significantly increased in the presence of MβCD dimer.

Information obtained from the DSC, FTIR, SEM, and XRD studies showed that solid MCZ–MβCD inclusion complexes can be prepared at a 1:1 molar ratio by COE, SD, and LPh methods. Data of this study demonstrate that SD and LPh can be efficient methods for inclusion complex formation between MCZ and MβCD.

Lyophilization was shown to be a promising method for preparation of inclusion complexes in the solid state between the MCZ and MβCD because it is an effective and economic method that allows the formation of solid complexes with easy and with a high yield, therefore very attractive for the pharmaceutical industry.

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