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Improvement in the Physicochemical Properties of Ketoconazole through Complexation with Cyclodextrin Derivatives

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Abstract

Highly-soluble cyclodextrin derivatives, such as hydroxypropyl-β-cyclodextrin (HP-β-CD) and methyl-β-cyclodextrin (MEB), were tested as solubilizing agents for ketoconazole, with the aim of improving the physicochemical and biopharmaceutical properties of this lipophilic imidazole antifungal agent. Products were prepared in four molecular ratios by physical mixing, kneading and spray-drying methods. The kneaded products in a ratio of 1:2 and the spray-dried products exhibited the highest dissolution rates. The phase solubility diagrams of ketoconazole with these cyclodextrins at 25 °C in water and in simulated intestinal medium were constructed. A solubility diagram of A_L type was obtained with HP-β-CD, and one of A_P type with MEB. The complexes were characterized by thermal methods (DSC, TG, DTG and DTA). Multicomponent systems were prepared with tartaric acid. The effects of water-soluble polymers, e.g., polyvinylpyrrolidone, on the aqueous solubility of ketoconazole were investigated. Particle size distribution, surface area, partition coefficient, heat of dissolution and wettability studies were also carried out. The formation of inclusion complexes was observed by means of thermoanalytical studies.

Introduction

Ketoconazole (KET) is an imidazole antifungal agent which interferes with the synthesis of ergosterol and therefore alters the permeability of the cell membrane of sensitive fungi [1]. It is a broad-spectrum antimycotic, which is administered topically or by mouth; it is practically insoluble in water [2].

The cyclodextrins (CDs) are a group of structurally related saccharides that are formed by the enzymatic cyclization of starch. They are cylindrical-shaped molecules with a hydrophilic outer surface and a rather hydrophobic cavity in the center. The CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity. Such molecular encapsulation will affect many of the physicochemical properties of the drug, such as its chemical stability and solubility [3–5].

The present study is mainly concerned with whether the aqueous solubility of KET can be increased by inclusion complexation with different CD derivatives, and with examination of their effects on the physicochemical properties of KET.

Table 1. Enhancement of aqueous solubility KET in binary and ternary systems with ratios of 1:1 and 1:1:1

1. Ketoconazole (KET)	1.00
2. KET + α-CD	15.4
3. KET + β-CD	35.79
4. KET + γ-CD	20.57
5. KET + HP-β-CD	**40.66**
6. KET + MEB	**77.88**
7. KET + RAMEB	81.15
8. KET + TA	89.27
9. KET + DIMEB	126.34
10. KET + TA + HP-β-CD	111.07
11. KET + TA + MEB	135.85

Experimental

Preliminary experiments were carried out to ascertain which CD derivative increases the solubility of the active ingredient most. Products were prepared in four molecular ratios (drug:CD molecular ratio = 2:1, 1:1, 1:2 or 1:3) by physical mixing (PM), kneading (KP) and spray-drying (SD) (Niro Atomizer). The dissolution studies were carried out by using the USP dissolution apparatus, with a modified

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Table 2. Partition coefficients, surface tensions and wetting angles of materials and products

Materials and products	$C_{octanol}$ (mg/mL)	C_{water} (mg/mL)	Partition coefficient [KET] in octanol/[KET] in water	Wetting angle (°) ± SD	Surface tension (mN/m)
Ketoconazole (KET)	13.81	0.026	531.1	34.3 ± 8.6	60.0
HP-β-CD	>60	>3000	>0.02	–*	59.5
MEB	190	>4000	0.048	46.0 ± 1.4	60.0
KET: HP-β-CD (2:1) PM	4.93	1.23	4.0	31.3 ± 2.5	60.5
KET: HP-β-CD (1:1) PM	13.96	1.70	8.2	37.3 ± 4.9	58.2
KET: HP-β-CD (1:2) PM	11.11	3.29	3.4	29.6 ± 7.6	64.5
KET: HP-β-CD (1:3) PM	13.11	5.6	2.4	34.6 ± 3.1	60.2
KET: HP-β-CD (2:1) KP	10.33	0.79	13.1	43.0 ± 2.6	60.2
KET: HP-β-CD (1:1) KP	13.37	1.41	9.5	29.6 ± 4.7	63.5
KET: HP-β-CD (1:2) KP	7.33	3.66	2.00	30.6 ± 5.8	64.7
KET: HP-β-CD (1:3) KP	5.93	6.74	0.88	41.0 ± 1.7	61.2
KET: HP-β-CD (1:1) SD	9.85	1.53	6.4	10.0 ± 0	62.5
KET: HP-β-CD (1:2) SD	3.59	4.27	0.84	–*	65.0
KET:MEB (1:1) PM	23.41	2.68	8.7	44.0 ± 1.4	59.0
KET:MEB (1:2) PM	69.44	5.65	12.3	41.0 ± 5.6	59.0
KET:MEB (1:1) KP	24.44	3.00	8.1	46.6 ± 1.2	60.0
KET:MEB (1:2) KP	19.74	4.63	4.3	45.6 ± 4.5	59.0

*The wetting angles were too small to be measured (nearly zero).

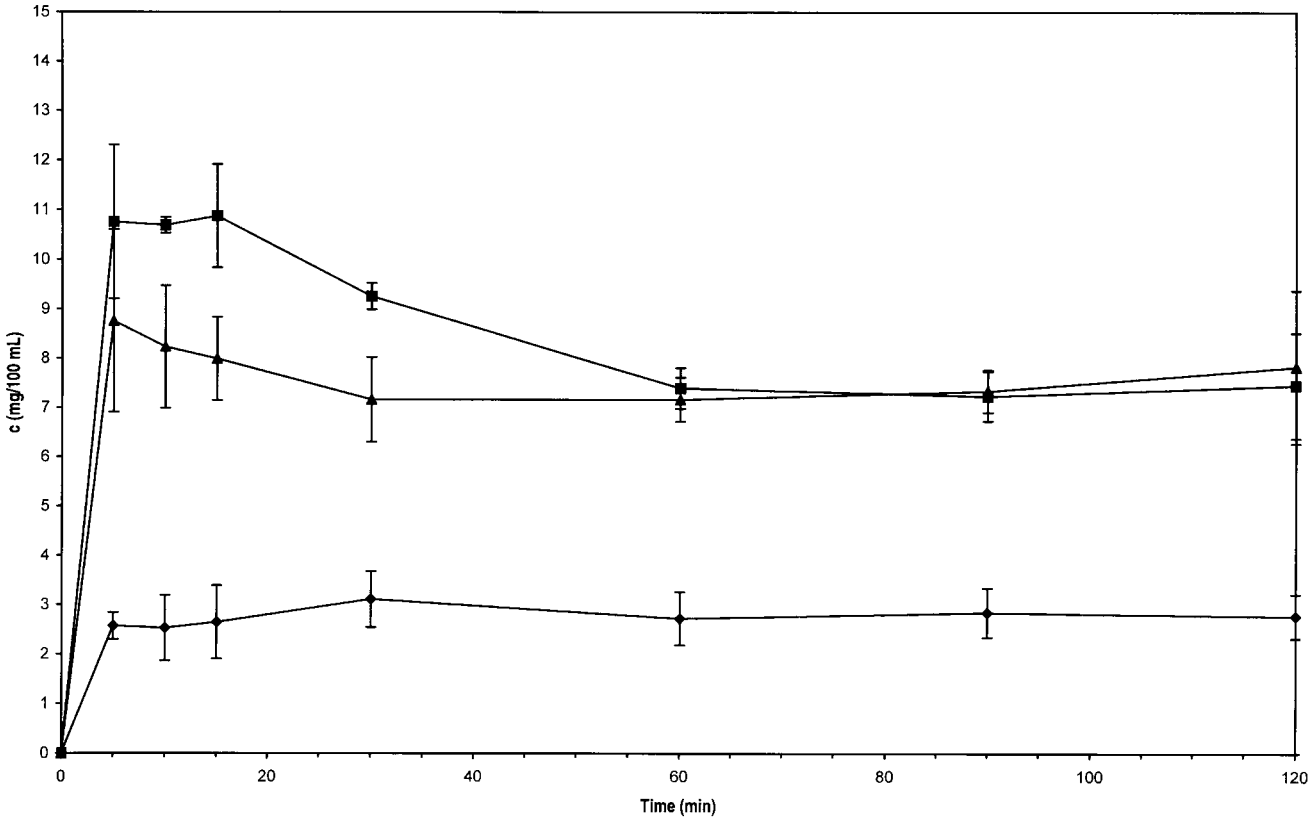

Figure 1. Dissolution profiles of SD products in SIM at 37 °C. ♦ SD KET; ■ SD 1:1; ▲ SD 1:2.

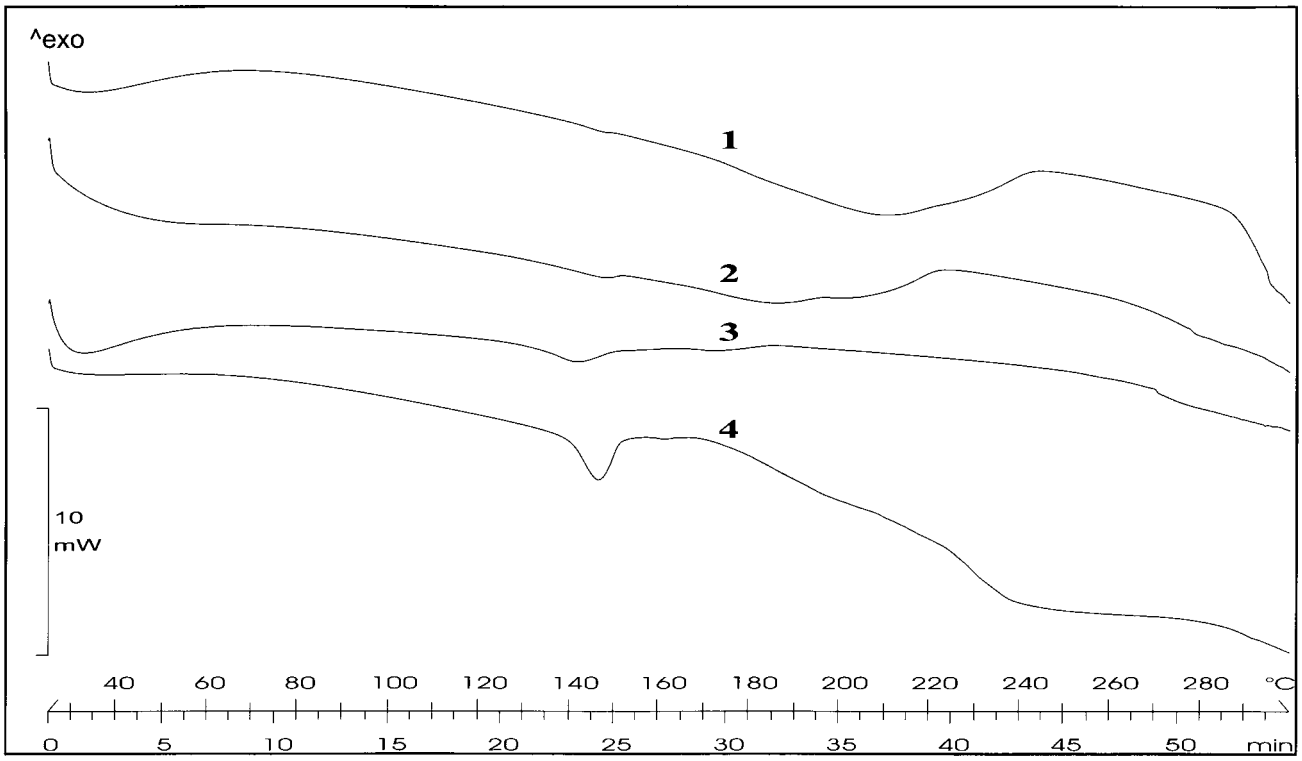

Figure 2. DSC curves of (1) KP 1:3, (2) KP 1:2, (3) KP 1:1 and (4) KP 2:1.

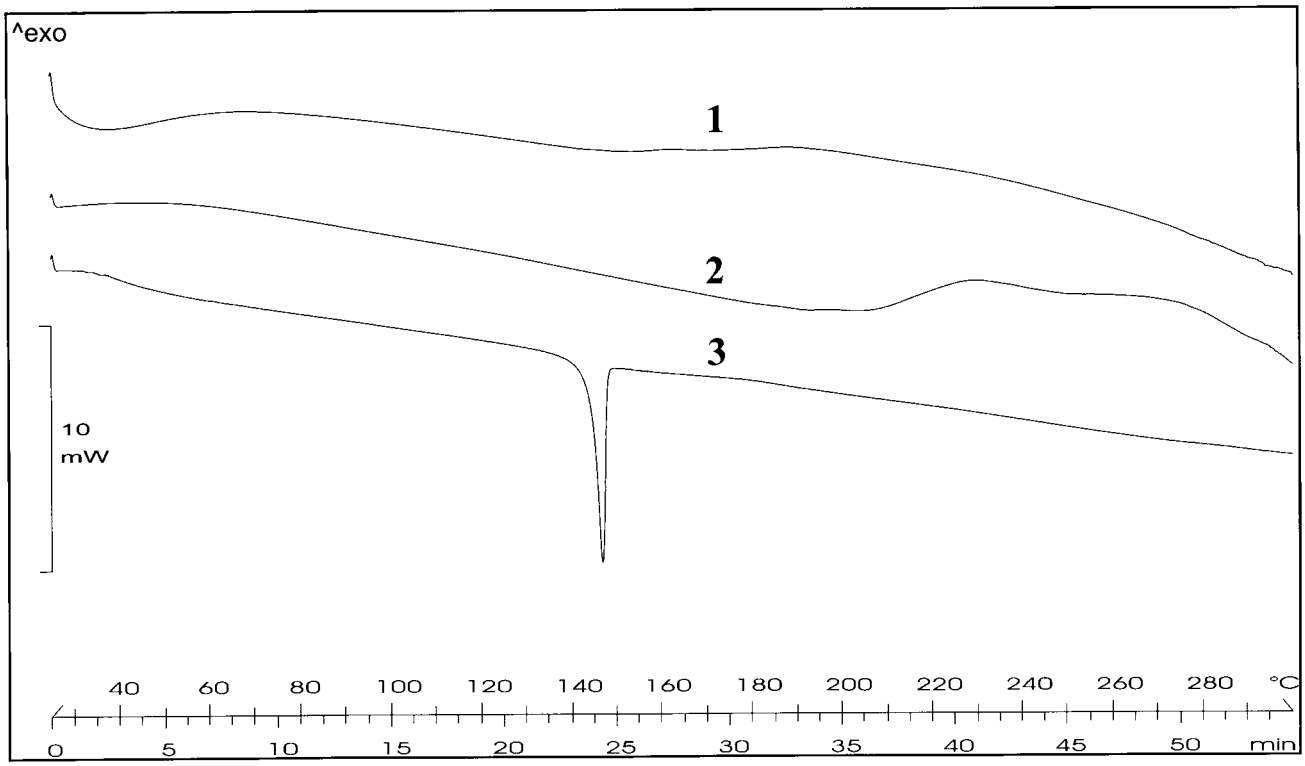

Figure 3. DSC curves of (1) SD 1:1, (2) SD 1:2 and SD KET.

paddle method in simulated intestinal medium (SIM)[1] at 37 ± 1 °C during 120 min. The KET contents were determined spectrophotometrically at 292 nm with a Unicam UV/Vis spectrophotometer.

Solubility diagrams were obtained according to Higuchi and Connors with various CDs in water and SIM. Particle size distribution studies were carried out on the spray-dried products by means of a LEICA Q500 MC image processing and analysis system. The surface areas of the particles were also calculated. The effects of different hydroxy acids (citric acid, tartaric acid and malic acid, CA, TA and MA) and water-soluble polymers (polyvinylpyrrolidone, hydroxypropyl-methylcellulose and sodium carboxy methyl-cellulose, PVP, Na-CMC and HPMC) on the aqueous solubility of KET were investigated. The partition coefficient (K_p) measurements were carried out in solutions of *n*-octanol saturated with water and in water saturated with *n*-octanol. K_p values were calculated according to the Nernst distribution law. The surface tensions of the solutions were investigated by a modified tensiometric ring method, with a Krüss tensiometer. Wettability studies were carried out with the Enslin apparatus and a Leica Q500 MC analyzer, by using powder heaps and pressings. The energies of dissolution in the temperature intervals 20–60 °C and 40–60 °C were calculated via the Clausius-Clapeyron equation. The thermal behavior of KET, the CD derivatives and each inclusion complex was examined with a Mettler Toledo STAR^e thermal analysis system, the DSC 821^e.

Results and discussion

Table 1 provides data on the solubility-enhancing effects of the various additives. HP-β-CD and MEB were used for further examinations on the basis of their appropriate effects and costs. As concerns the polymers and hydroxy acids, Na-CMC and TA exerted the highest solubility-increasing effects on the solubility of KET. Figure 1 reveals that spray-drying significantly improved the rate of dissolution of KET from the products containing HP-β-CD. KET gave an A_L-type diagram with HP-β-CD and an A_P-type diagram with MEB, with stability constants of 2652 and 7605 M^{-1}, respectively in water. 25.2% and 31.4% of the particles of the KET:HP-β-CD (1:1) and (1:2) SDs had a particle size of 12 μm while 40.5% and 50%, respectively, of the same particles had a surface area of 500 μm^2. The partition coefficients are the quotients of the solubility data for KET in *n*-octanol and in water. K_p is considerably reduced when KET forms inclusion complexes with the CD derivatives (especially at a molecular ratio of 1:2). Products furnishing good dissolution results had smaller wetting angles (Table 2). The experimentally determined energies of KET and the KET:HP-β-CD (1:2) KP, i.e., the heats of dissolution in the intervals 20–60 °C and 40–60 °C were found to be 27.4 and 27.6 kJ/mol for KET and 16.3 and 18.9 kJ/mol for the KET:HP-β-CD (1:2) KP, respectively. The heat of dissolution results supported the fact that the active substance needs more energy for dissolution as compared to the products, which proves the occurrence of inclusion complex formation. The formation of inclusion complexes was proven by thermoanalytical studies. Both KET and the KET SDs melted at around 151 °C. The active substance can be recognized easily by means of DSC. Thermal degradation starts between 240 and 250 °C for MEB and HP-β-CD. DSC analysis yielded similar results. The DSC curves are flat at the temperature where KET gives a characteristic endothermic peak. The peak area decreased with increasing quantity of CD and complex formation could be recognized for the 1:3 KP. Total complex formation was observed for the 1:1 and 1:2 SD products (Figures 2 and 3).

References

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[1] SIM contains 14.4 g $Na_2HPO_4.2H_2O$, 7.1 g KH_2PO_4 and water to 1000 mL; pH= 7.0 ± 0.1.