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Influence of Cyclodextrin Complexation on the Physicochemical and Biopharmaceutical Properties of Ketoconazole

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Abstract

The effects of hydroxypropyl-β-cyclodextrin and methyl-β-cyclodextrin on the solubility of ketoconazole were studied. Products were prepared by physical mixing, kneading and spray-drying methods in four molecular ratios. Kneaded products in a ratio of drug: cyclodextrin (1:2) and spray-dried products showed the highest dissolution rate. Phase solubility diagrams of ketoconazole with these cyclodextrins at 25 °C in water and simulated intestinal medium were constructed. A solubility diagram of A_L type was obtained with hydroxypropyl-β-cyclodextrin, and A_P type with methyl-β-cyclodextrin. 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. The particle size of ketoconazole (70 $\sim$ μm) is reduced to 12 μm by the preparation of spray-dried products. As the solubilty in water increased, the partition coefficient, surface tension and wetting angle values decreased. Ketoconazole needed more energy for dissolution compared to the products. In order to examine complex formation thermal methods were used.

Introduction

Ketoconazole (KET) is a broad-spectrum antifungal imidazole derivative which interferes with the synthesis of ergosterol and therefore alters the permeability of the cell membrane of sensitive fungi [1]. It is administered topically or orally and practically as insoluble in water. The major drawback in the therapeutic application of KET as an oral dosage form is its low aqueous solubility because of its hydrophobic structure, especially in patients with an increased gastric pH [2].

Cyclodextrins (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].

Several papers have been published concerning the improvement of the solubility and the bioavailability of KET by inclusion complexation with CDs [6, 7], Esclusa-Díaz *et al.* recently reported on the use of hydroxypropyl-β-cyclodextrin to increase the water solubility of KET [8]. Similar studies were also carried out with different imidazole derivatives [9, 10]. Derivatization of CDs frequently transforms the crystalline structures into amorphous mixtures of isomeric CD derivatives so that the aqueous solubility of the derivatives is usually much higher than that of the parent CD [11]. Utilization of this property has led to many studies being performed with these types of CD derivatives [12, 13].

The aim of the present study is to check whether the aqueous solubility of KET can be increased by inclusion complexation with different CD derivatives, and examine their effects on the physicochemical and biopharmaceutical properties of KET. Physical mixing, kneading, spray-drying methods were applied for the preparation of the products in different molar ratios. Furthermore, we investigated the interactions between the CDs and KET by thermal methods.

Experimental

Materials

Ketoconazole (KET), cis-1-acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxalan-4-ylmethoxy]-phenyl}piperazine (Figure 1) (Ilsan Iltas Pharmaceuticals Ltd., Istanbul, Turkey) . *Hydroxypropyl-β-CD* (HP-β-CD, DS: 5.5, Cerestar, USA, Inc.); *methyl-β-CD* (MEB, DS: 1.7–1.9, Wacker-Chemie GmbH); *citric acid* (CA); *tartaric acid* (TA, pharmacopoeial grade); *malic acid* (MA, Reanal Ltd., Budapest, Hungary); *sodium carboxy methylcellulose* (Na-CMC, Company for Supply and Provision of Pharmaceutical Industry, Budapest, Hungary);

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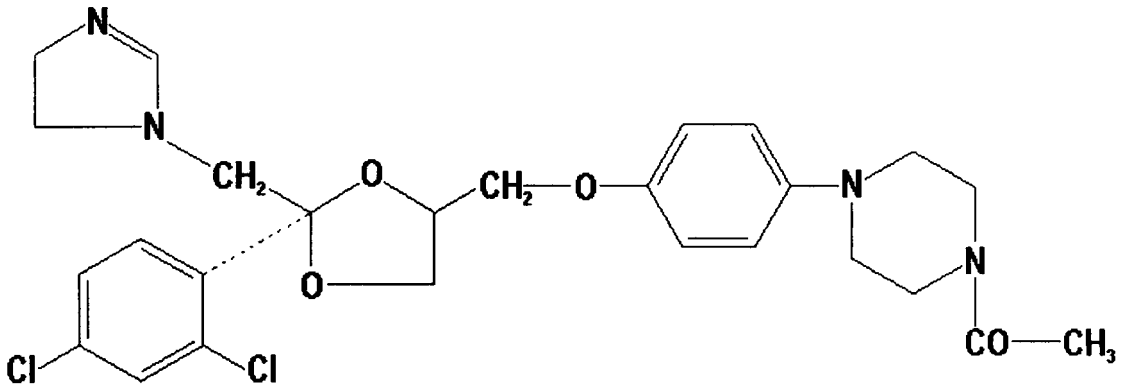

Figure 1. Structural formula of ketoconazole.

hydroxypropyl-methylcellulose (HPMC, The Dow Chemical Company, Canada).

The solvents used (methanol, etc.) are official in Pharmacopoeia Hungarica VII [14].

Apparatus

USP dissolution apparatus (modified paddle), type DT (Heusenstamm Kr. Offenbach/Main, Germany); Unicam UV/Vis spectrometer with Vision software V3.40 (Unicam Limited, Cambridge, UK); Krüss tensiometer (Hamburg, Germany); Leica Q500 MC image analysis system (Leica Cambridge Ltd., Cambridge, UK); Niro atomizer (Copenhagen, Denmark); Mettler Toledo type STAR^e Thermal Analysis System, version 6.0 (Schwerzenbach, Switzerland); and Derivatograph-C, MOM (Budapest, Hungary).

Preliminary experiments

Preliminary experiments were carried out to ascertain which CD derivative increases the solubility of the active ingredient most. A mixture of 0.10 g KET and 0.90 g of the CD tested was diluted to 25.0 g with distilled water and then stirred for 2 h with a magnetic stirrer. Suspension systems were filtered through filter papers and the UV spectra were recorded (Unicam UV-Vis). KET without CD was used as a control (Table 1).

HP-β-CD and MEB were used for further examinations on the basis of their appropriate effects and acceptable costs. The maximum absorption of the active ingredient in water was 280 nm, which shifted to 288 and 292 nm with HP-β-CD and MEB, respectively. The calibration curve of KET was produced in the concentration interval 37.5–300 (g/mL, where the equation was found to be $A = 0.0027 \cdot c$ (r^2 = 0.9996).

Preparation of products

Products were prepared in four molar ratios (drug:CD molar ratio = 2:1, 1:1, 1:2 or 1:3).

Physical mixtures (PMs): the ground components were mixed in a mortar and sieved through a 100 μm (Feinstkornprüfsieb) sieve.

Table 1. Aqueous solubility enhancement of 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
	(Abs.)
1. Ketoconazole (KET)	0.052
2. KET + α-CD	0.800
3. KET + β-CD	1.861
4. KET + γ-CD	1.069
5. KET + HP-β-CD	**2.114**
6. KET + MEB	**4.049**
7. KET + RAMEB	4.219
8. KET + TA	4.642
9. KET + DIMEB	6.569
10. KET + TA + HP-β-CD	5.775
11. KET + TA + MEB	7.064

Kneaded products (KPs): PMs of KET and CDs (HP-β-CD and MEB) were mixed in the same quantity of a methanol+water (1:1, V/V) mixture. They were kneaded until the bulk of the solvent mixture evaporated. After this, they were dried at room temperature and then at 105 °C. Next, they were pulverized and sieved (100 μm).

Spray-dried products (SDs): KET/methanol and CD/water solutions were mixed and heated (64 °C) to obtain clear solutions. The SDs were obtained by using a Niro atomizer at 90 °C inlet temperature with gas heating and a rotation rate of 25 000 rpm. Both chamber and cyclone products were collected. The products were stored under normal conditions at room temperature in closed glass containers.

Studies in aqueous phase

Determination of the effects of different hydroxy acids and water-soluble polymers on the aqueous solubility of KET

Different α-hydroxy acids (CA, TA and MA) were each dissolved in 25.0 g of water containing 0.10 g KET. After filtration, the absorbances were determined spectrophotometrically, which the references are the solutions of the hydroxy acids.

0.10 g KET and different water-soluble polymers (PVP, Na-CMC and HPMC) in a concentration of 0.25% were added to 25.0 g of distilled water. The suspensions were heated for 1 h in a water-bath at 70 °C. After equilibration at room temperature (23 °C) for 3 days, the suspensions were filtered through a 0.45 μm Sartorius membrane filter and the absorbances were determined spectrophotometrically.

Phase solubility studies

Solubility diagrams were obtained according to Higuchi and Connors [15] with HP-β-CD and MEB in water and SIM. Excess KET was added to aqueous solutions containing various concentrations of HP-β-CD and MEB (0–160 mM). The suspensions were stirred at room temperature until equilibrium was reached (approx. 7 days). The suspensions were next filtered and the concentrations of solubilized KET were measured spectrophotometrically at 288 and 292 nm.

The apparent stability constants of KET:HP-β-CD and KET:MEB complexes were calculated from the initial straight portion of the phase solubility diagrams.

Partition coefficient and surface tension measurements

The partition coefficient (K_p) measurements were carried out in two separate solutions of n-octanol saturated with water and in water saturated with n-octanol. 0.10 g KET and products containing 0.10 g KET, and further HP-β-CD and MEB, were suspended in 5 mL of each solution. The suspensions were stirred at 25 $\pm$ 2 °C until equilibrium was reached (approx. 6 days), and then filtered and the concentrations of solubilized KET were determined spectrophotometrically. K_p values were calculated according to the Nernst distribution law [16].

For the determination of surface tension, 0.01 g KET, HP-β-CD, MEB or products containing 0.10 g KET were dissolved in 30 mL of distilled water and the solutions were stirred for 20 min. After filtration, the surface tensions of the solutions were investigated by a modified tensiometric ring method, with a Krüss tensiometer [17].

Determination of the heat of dissolution in different temperature intervals

0.10 g KET and the KET:HP-β-CD (1:2) KP containing 0.10 g KET were suspended in 50 g of distilled water. The suspensions were placed in water-baths at 20, 40 or 60 °C and stirred for approximately 6 h, samples being taken after 3 and 6 h. After filtration and suitable dilution, the absorbances were examined spectrophotometrically. The energies of dissolution in the temperature intervals of 20–60 °C and 40–60 °C were calculated via the Clausius–Clapeyron equation.

Studies in solid phase

Particle size distribution study and determination of particle surface areas

The particle size determination was carried out on SDs of KET:HP-β-CD with molar ratios of 1:1 and 1:2. The study was carried out by means of a LEICA Q500 MC image processing and analysis system. The surface areas of the particles were also calculated.

Wettability studies

Two methods were used. (1) 0.50 g powder was placed on the glass filter (G_3) of an Enslin apparatus and the amount of water absorbed by the powder was determined with a calibrated pipet. (2) For Leica Q500 MC Analyzer measurements, 0.15 g powder was compressed under a pressure of 2 tons by a Perkin-Elmer hydraulic press [18]. The diameter and the height of the pressings were 8 mm and 2 mm, respectively. The wetting angles were determined after placing 2 μl of dilute methylene blue solution on to the surface of the pressing. The measurements were carried out in duplicate, using a microscope and a Leica Q500 MC Analyzer.

Thermoanalytical studies

The thermal behavior of KET, CD derivatives and each inclusion complex was examined by using a Mettler Toledo STAR^e Thermal Analysis System, DSC 821^e. Argon was used as carrier gas and the DSC analysis was carried out at a heating rate of 5 °C min^{-1} and an argon flow rate of 10 L^{-1}. The sample size was in the range 2–5 mg and examinations were made in the temperature intervals between 25–300 °C. TG, DTG and DTA studies were carried out with a Derivatograph-C apparatus. A normal air flow was used and the heating rate was 5 °C min^{-1}. 50 mg samples of materials and products were examined, the inert material being 50 mg of aluminum oxide.

In vitro dissolution studies

The dissolution studies were carried out on the products by using the USP dissolution apparatus, with a modified paddle method in simulated intestinal medium (SIM: contains 14.4 g $Na_2HPO_4 \cdot 2H_2O$, 7.1 g KH_2PO_4 and water to 1000 mL; pH= 7.0 $\pm$ 0.1) at 37 $\pm$ 1 °C during 120 min. Sampling was performed after 5, 10, 15, 30, 60, 90 and 120 min. The KET contents were determined spectrophotometrically at 292 nm (Unicam UV/Vis spectrometer). All the studies were carried out at least in triplicate.

Results and discussion

Results of the studies in aqueous phase

Determination of the effects of different hydroxy acid and water-soluble polymers on the aqueous solubility of KET

The combination effect of an acid and CD showed a synergistic effect and was always clearly more effective in enhancing the solubility of KET in comparison with either salt

formation or binary complexation. Multicomponent complex formation between a base type of drug such as KET, CD and a hydroxy acid as third component, proved to be an optimal tool for enhancing the drug solubility [19].

Of the studied acids (TA, MA and CA), TA caused the best increase in the solubility of KET. The highest aqueous solubility enhancement was obtained with the KET:TA:MEB (1:1:1) ternary system (Table 1).

In previous studies it has been observed that the addition of a small amount of 0.1–0.25% (w/v) polymer, results in a significant enhancement of the aqueous solubility of water-insoluble drugs or drugs with limited aqueous solubility [20].

In our work, the effects of PVP, Na-CMC and HPMC on the aqueous solubility of KET were examined. Na-CMC had a much greater solubilizing effect than the others. The addition of 0.25% Na-CMC resulted in an increase of about 1.5-fold in the solubility of KET.

Phase solubility studies

According to the classification introduced by Higuchi and Connors (1965), type A solubility curves are obtained when the apparent solubility of the substrate increases with ligand concentration throughout the entire concentration range. A linear relationship is designated as of A_L type, whereas A_P and A_N curves exhibit positive and negative curvature, respectively. The initial linear ascending part of a solubility diagram is generally ascribed to the formation of a 1:1 complex when the slope is less than 1. Figure 2 shows the phase solubility diagrams of KET with HP-β-CD and MEB in water and SIM. KET gave an A_L-type diagram with HP-β-CD and MEB. The apparent stability constant $K_{1:1}$ can be calculated from the solubility data through the use of Equation 1:

$$K_{1:1} = \frac{slope}{S_o(1 - slope)},$$

where S_o is the intrinsic solubility of KET, and the slope is the slope of the linear initial part of the solubility curves.

The intrinsic solubilities, the types of the solubility diagrams and the apparent complex stability constants $K_{1:1}$ are given in Table 2.

Partition coefficient and surface tension (γ) measurements

K_p was calculated according to the Nernst distribution law, using Equation 2:

$$K_p = \frac{a_1}{a_2}$$

where a_1 = concentration of drug in n-octanol, and a_2 = concentration of drug in water.

The K_p of KET in an n-octanol/water system is considerably reduced when it forms an inclusion complex with the host, and it is easily transferred into the aqueous phase, displaying better water solubility than that of the drug. Depending on the preparation method, the K_p values may differ due to the increased surface and amorphous structure of a SD, the smallest K_p value was found with KET:HP-β-CD (1:2) SD (Table 3).

The surface tension of distilled water is 76.5 mN/m. No significant difference was seen between the surface tension values of the materials and products but the smallest surface tension was found with the KET:HP-β-CD (1:1) PM, and the highest value was seen with the KET:HP-β-CD (1:2) SD (Table 3).

Determination of heat of dissolution in different temperature intervals

The determination of the heat of dissolution is accomplished by using the Clausius-Clapeyron equation:

$$\log\frac{c_1}{c_2} = \frac{\delta Q_{sol}}{4.573} \cdot \frac{T_1 - T_2}{T_1 \cdot T_2},$$

where (δQ_{sol} = heat of dissolution; c_1, and c_2 = solubilities at temperatures T_1 and T_2; and T_1, and T_2 = absolute temperatures (°K).

The experimentally determined energies of KET and the KET:HP-β-CD (1:2) KP; i.e., the heats of dissolution in the intervals between 20–60 °C and 40–60 °C were found as 27.4 and 27.6 kJ/mol for KET and 16.3 and 18.9 kJ/mol for KET:HP-β-CD (1:2) KP, respectively.

According to these results the energy needed for the active substance to dissolve is considerably higher than that for the complex. This clearly supports the fact of inclusion complex formation. It is also observed that the temperature increase did not affect the solubility of KET significantly.

Results of the studies in solid phase

Particle size distribution study and determination of surface area

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 50.0% of the same particles had a surface area of 500 μm^2, respectively (Figure 3). The size of the most frequent KET particles is 70 μm and its frequency is 70–80%.

Wettability studies

The Enslin numbers of KET (0.13 mL), KET SD (0.31 mL), HP-β-CD (0.02 mL), and the KET:HP-β-CD (1:1) SD (0.04 mL) were found while the others showed no absorption. The KET:HP-β-CD (2:1) KP had a high wetting angle value depending on the high content of KET. As MEB has a high wetting angle, the products containing MEB also displayed larger wetting angles on average (Table 3).

Thermoanalytical studies

Both KET and the KET SDs melted at around 151 °C. The mass loss is very small because of the high stability of KET. The active substance can be recognized easily by means of DSC, DTA, TG and DTG analysis (Figures 4 and 5).

Since CDs are generally marketed as hydrates with differing water contents, this crystal water will evaporate until a suitable temperature is reached. The water loss is 2.4 and 6.2% for MEB and HP-β-CD, respectively. Thermal degradation starts between 240 and 250 °C. DSC analysis gave similar results. The DSC curves are flat at the temperature where KET gives a characteristic endothermic peak.

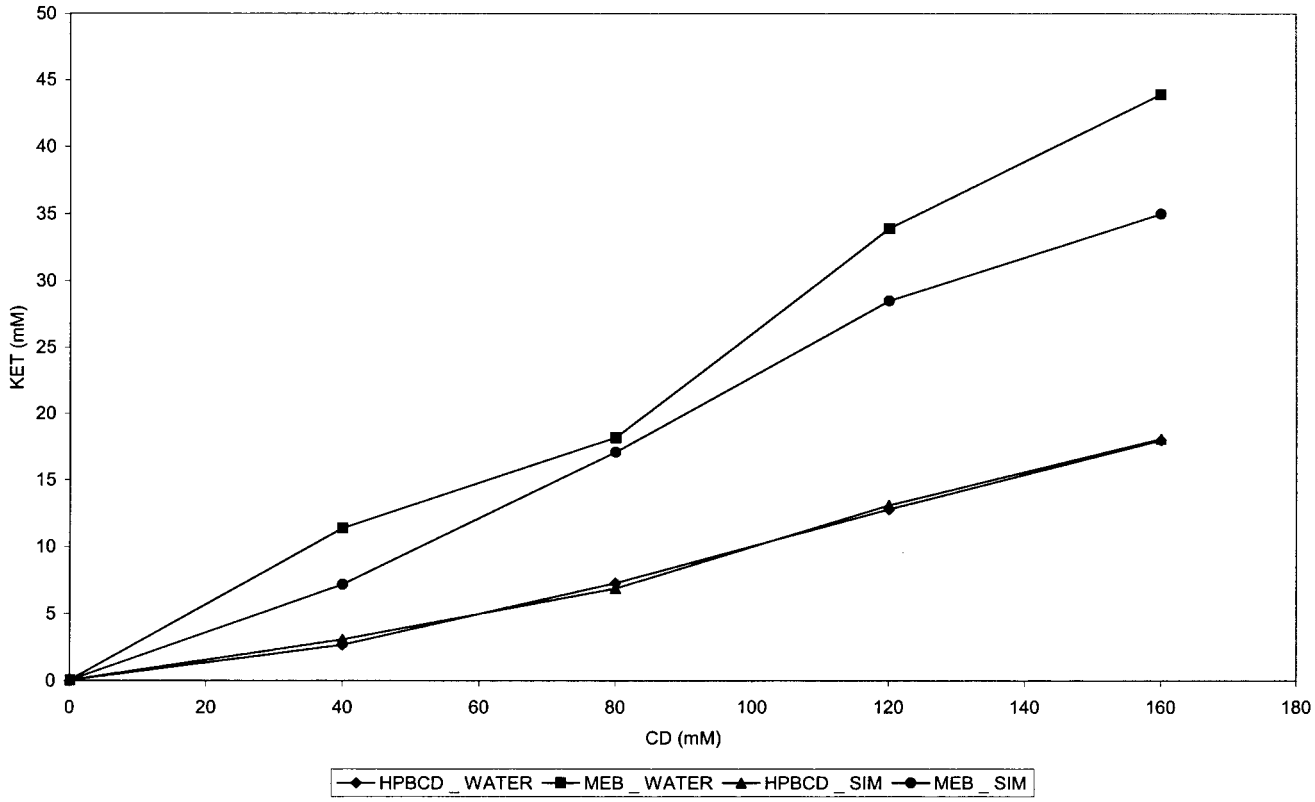

Figure 2. Phase solubility diagrams of KET with HP-β-CD and MEB in water and SIM. –♦– HP-β-CD _ water; –■– MEB _ water; –▲– HP-β-CD _ SIM; –●– MEB _ SIM.

Table 2. Intrinsic solubilities, apparent stability constants and types of solubility diagrams of KET

Substrate	Ligand	Solvent	Solubility (S_o) (M)	Stability constant (M^{-1})	Type of diagram
KET	HP-β-CD	water	4.9×10^{-5}	2652	A_L
KET	HP-β-CD	SIM	5.3×10^{-5}	2456	A_L
KET	MEB	water	5.0×10^{-5}	7605	A_L
KET	MEB	SIM	5.2×10^{-5}	5680	A_L

PMs prepared in different KET:HP-β-CD molar ratios (2:1, 1:1, 1:2 and 1:3) gave similar thermal results. From the DSC and DTA plots, water loss (from 2.58 to 5.61%) and the characteristic endothermic peak of KET can be recognized. Accordingly no or only partially complex formation is expected (Figure 6).

Water loss from the 1:1 and 1:2 ratio KPs (with HP-β-CD) can be seen in the DSC plots. The minimum water loss is detected for the 2:1 KP. The results were parallel with the TG curves where the water loss ranged between 2.2 and 6.3%. The peak area decreased with increasing quantity of CD and complex formation can be recognized for the 1:3 KP. Water loss and the start of degradation at around 240 °C can also be seen from the DTA curves.

Total complex formation is observed with 1:1 and 1:2 SD products by all thermal methods. The water loss from these SDs were 5.2 and 4.8%, respectively. For the products including MEB, complex formation could not be recognized from the thermal curves. The lowest amount of water loss was measured for the 1:1 KP:1.9%.

In vitro dissolution studies

The physical mixtures prepared with HP-β-CD yielded a dissolution profile that was higher as compared to that of KET. Increase of the HP-β-CD concentration did not change the results significantly. KPs with HP-β-CD yielded better results than those with PMs. Figure 7 reveals that the rate of dissolution of KET was most improved by the KET:HP-β-CD (1:2) KP. Also spray-drying significantly improved the rate of dissolution of KET from the products including HP-β-CD. SD KET exhibited similar results to those for the active substance itself. The dissolution profiles of PMs and KPs prepared with MEB, as compared to the PMs and KPs of HP-β-CD, were nearly the same, except that KET:MEB (1:2) KP yielded the highest rate of dissolution.

Table 3. 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 angles (°) ±SD	Surface tension (mN/m)
Ketoconazole	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 SD	15.70	0.057	275.4	–*	62.5
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).

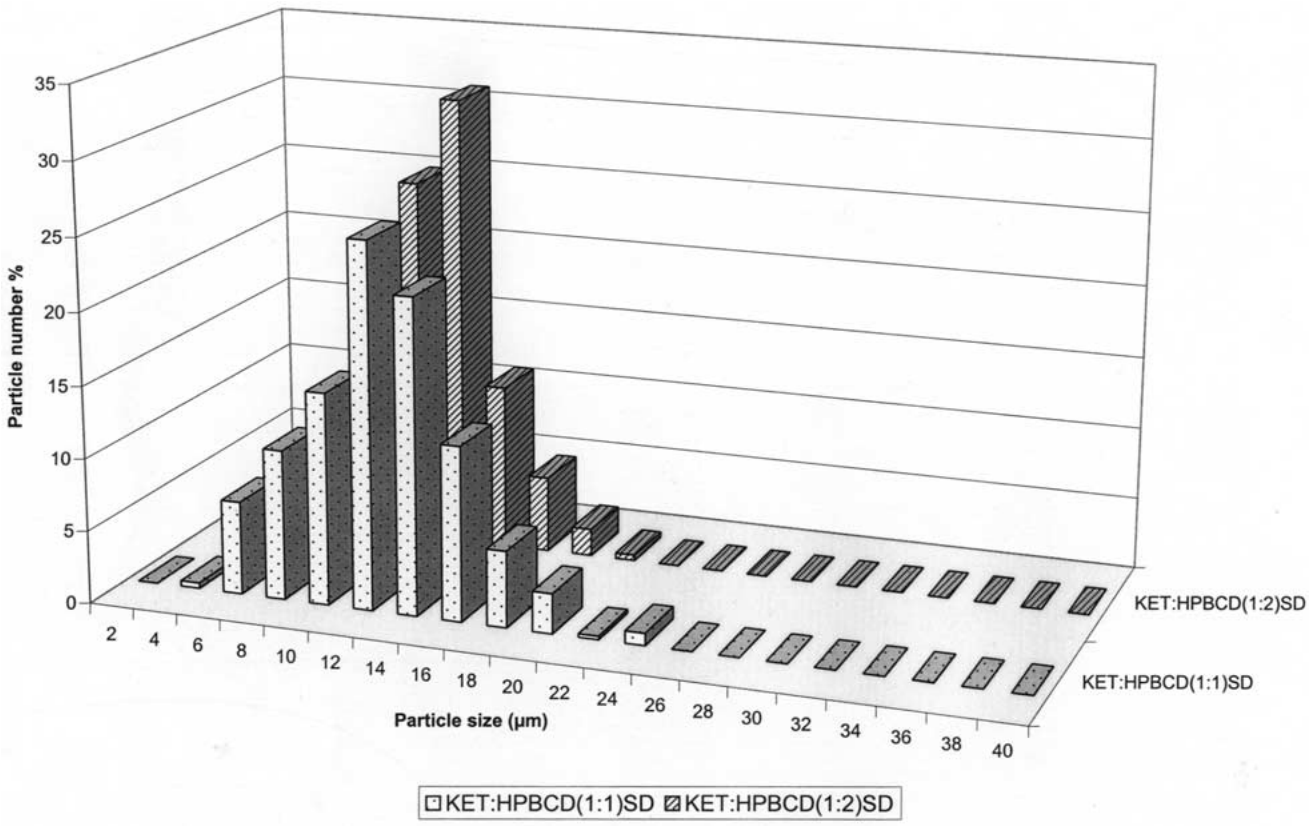

Figure 3. Particle size distribution of KET:HP-β-CD SDs.

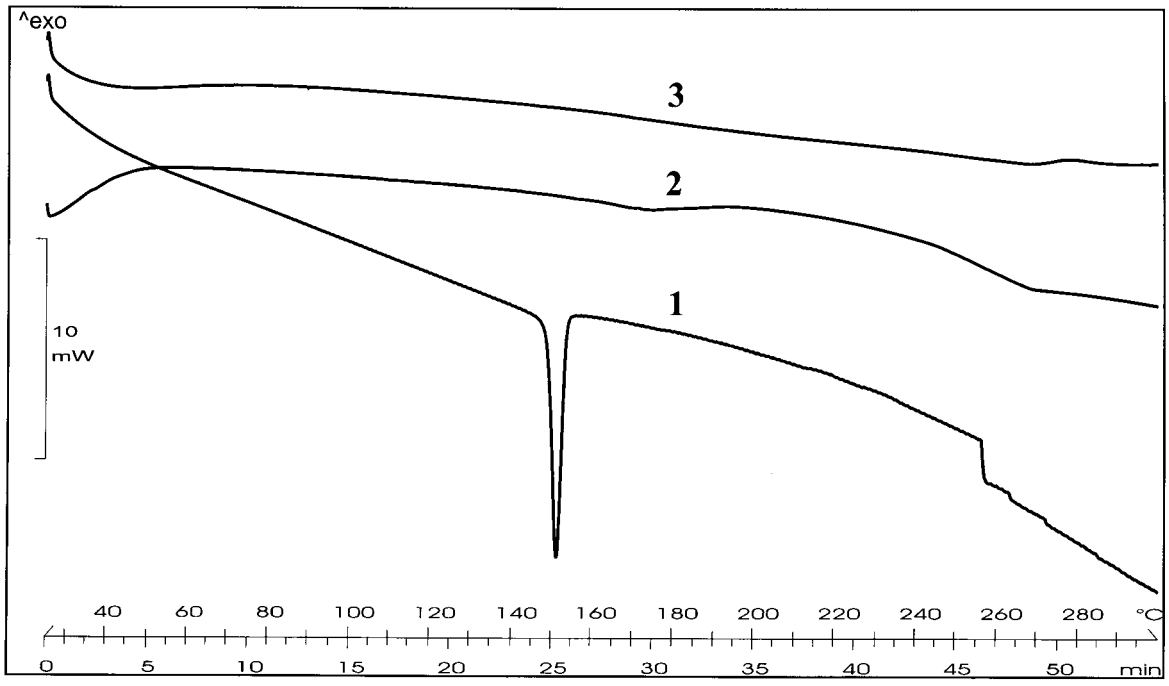

Figure 4. DSC curves of (1) KET, (2) MEB and (3) HP-β-CD.

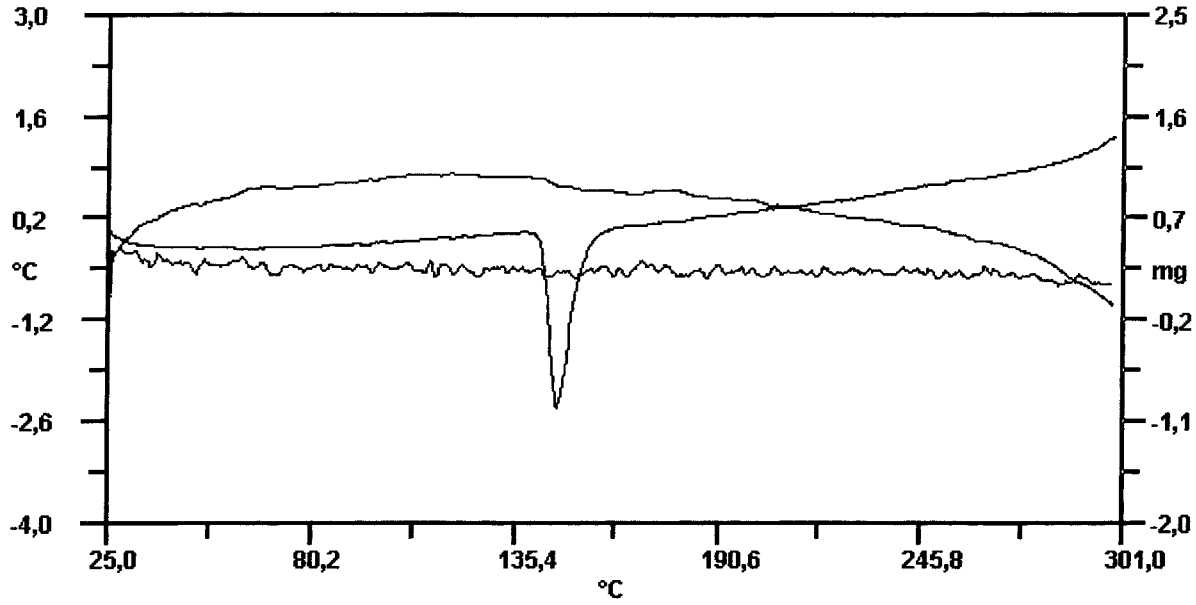

Figure 5. TG, DTG and DTA curves of KET.

Conclusions

- Two CD derivatives (HP-β-CD and MEB) were used during the experiments as they increased the solubility of KET significantly. The solubility of KET in SIM was higher than in water with both HP-β-CD and MEB. In parallel the stability constants were smaller in SIM.
- Products were prepared in molecular ratios of 2:1, 1:1, 1:2 and 1:3 with HP-β-CD and in 1:1 and 1:2 ratios with MEB by using physical mixing, kneading and spray-drying methods.
- Ternary systems containing TA and Na-CMC, enhanced the solubility.
- Phase solubility diagrams of type A_L were observed for MEB and HP-β-CD, respectively. The highest stability constant $K_{1:1}$ was found for MEB in water: 7605 M^{-1}.
- As the solubility in water increased, the partition coefficient, surface tension and wetting angle values decreased. The partition coefficients as absolute values are the quotients of the solubility data of KET in n-octanol and in water. K_p is considerably reduced when KET forms inclusion complexes with the CD derivatives (es-

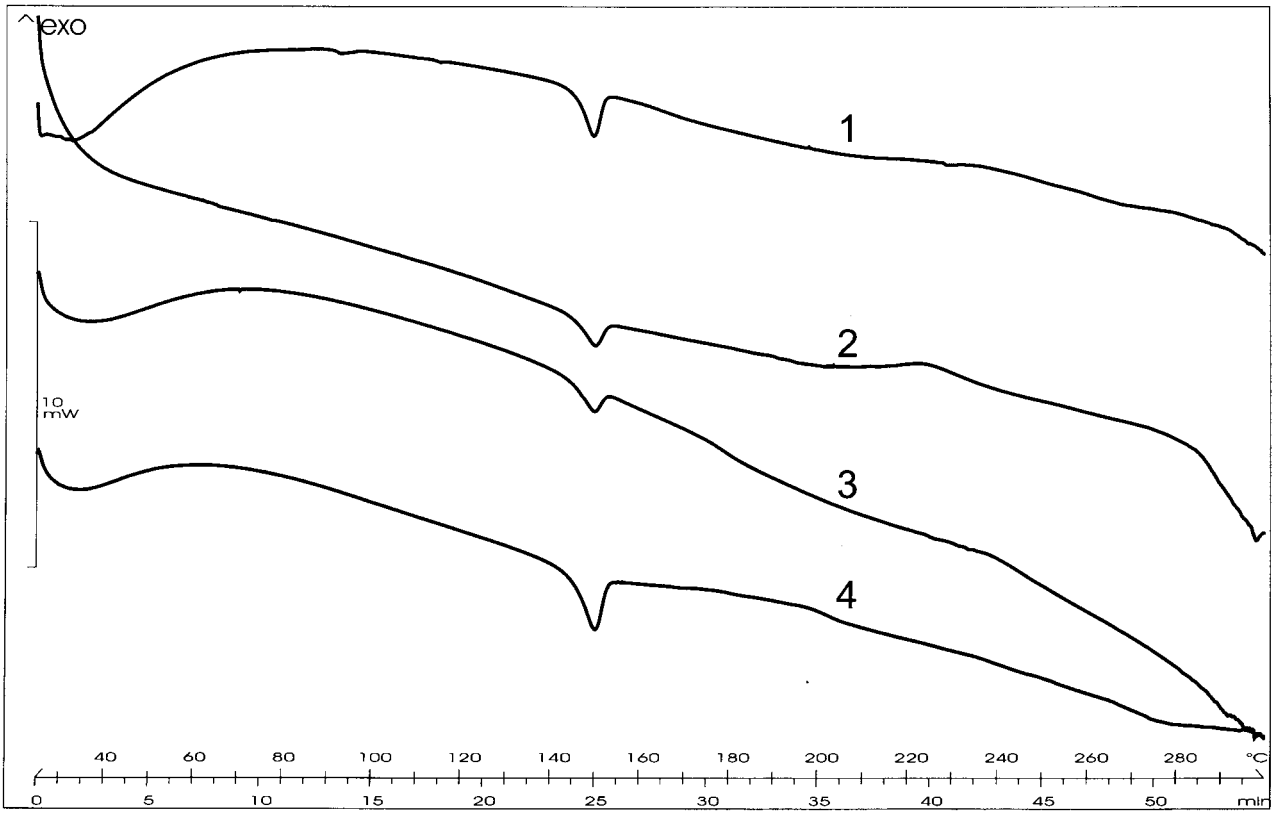

Figure 6. DSC curves of (1) KET:HP-β-CD (1:3) PM, (2) KET:HP-β-CD (1:2) PM, (3) KET:HP-β-CD (1:1) PM and (4) KET:HP-β-CD (2:1) PM.

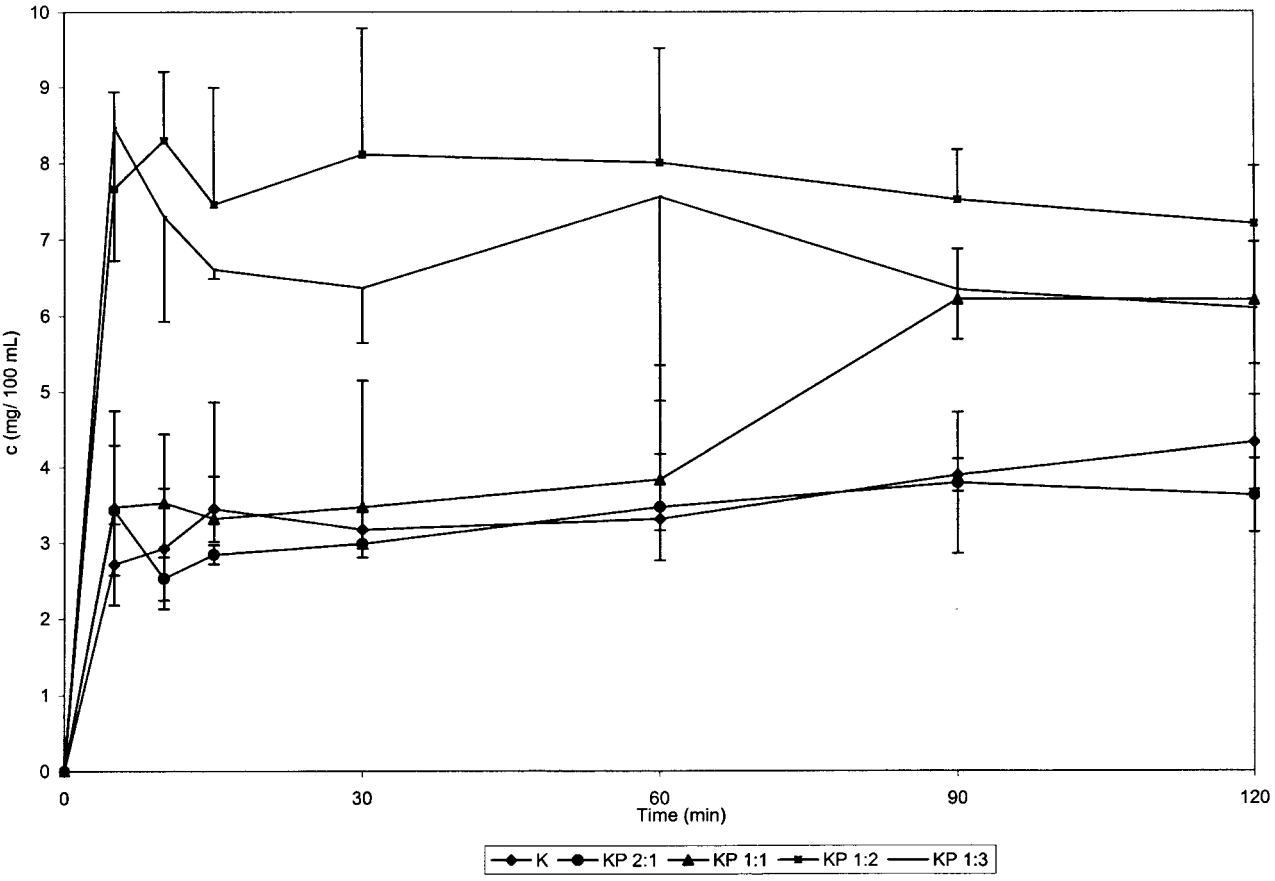

Figure 7. Dissolution profiles of KET and KET:HP-β-CD KPs in SIM at 37 °C. –♦– Ketoconazole; –●– KP 2:1; –▲– KP 1:1; –■– KP 1:2; —— KP 1:3.

pecially at a molecular ratio of 1:2). In practically all of the dissolution studies the products with a ratio of 1:2 gave improved results. Except for the PMs (where no inclusion complex could be seen), the partition coefficients of the KPs and SDs decreased in parallel with the decrease in the KET content.

- The particle size of the drug decreased approximately 6-fold by spray-drying tecnique. The surface tension was higher in the products with a molecular ratio of 1:2 containing HP-β-CD.
- During the wettability study, two widely applied methods were used. The results showed no correlation: with the Enslin apparatus, powder heaps were used in which the particles were covered with air while with Leica analyzer well-compressed compacts were used for investigation. Consequently, the results are not similar, but depend on the two different procedures. Products furnishing good dissolution results had smaller wetting angles.
- 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 occurence of inclusion complex formation.
- Formation of inclusion complexes has been proven by thermoanalytical studies. Thermal methods confirmed the presence of inclusion complexes for the spray-dried products.
- The dissolution in SIM with the USP modified paddle method revealed that spray drying significantly improved the rate of dissolution and the kneaded products also exhibited improved results (especially at a molecular ratio of 1:2).

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