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Improvement of the Physicochemical Properties of Clotrimazole by Cyclodextrin Complexation

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Abstract

Complex formation between CDs and a very poorly water-soluble antifungal agent, clotrimazole (CLT), was studied. Products containing γ-CD were prepared in two molecular ratios by four methods. The rates of dissolution of the 1 : 1 drug/CD combinations revealed better dissolution properties than those of the 1 : 2 products. Drug/CD interactions in both aqueous solution and the solid state were studied by phase solubility and thermal analysis. The effects of different auxiliary materials (polymers, hydroxy acids and surfactants) on the aqueous solubility of CLT were investigated. The aqueous solubility of CLT was increased significantly by the addition of the auxiliary materials. Particle size distribution, partition coefficient, surface tension, heat of dissolution and wettability studies were also carried out.

Introduction

Clotrimazole (CLT, Figure 1), a lipophilic, imidazole derivative, is an antimycotic agent with a broad spectrum [1] which is practically insoluble in water [2]. The preparations of the drug are used in the topical treatment of dermal infections and to combat vulvovaginal candidiasis [3].

Some antifungals are not administered by the oral route due to the slow dissolution and erratic and unpredictable bioavailability. Low solubility presents a problem in the treatment of cutaneous diseases by topical application of the drug. The drug must be delivered to the site of infection from the topical dosage form in sufficient concentration for effective treatment. Accordingly, a better oral, parenteral or topical formulation can be developed by increasing the water solubility of the antifungal [4].

Cyclodextrins (CDs) are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose units containing a relatively hydrophobic central cavity and with a hydrophilic outer surface [5]. As a result of the free rotation about the bonds connecting the glucopyranose units, the CDs are cone-shaped rather than perfectly cylindrical molecules. The most common naturally occurring CDs are α-CD, β-CD and γ-CD, consisting of 6, 7 and 8 glucopyranose units, respectively [6–8].

Depending on their hydrophobic interior cavity, the CDs can serve as hosts for a range of organic molecules. They are able to form complexes with lipophilic drugs or lipophilic moieties of drugs, thereby changing the physicochemical and biopharmaceutical properties of the drugs in a desirable manner. Complex formation may result in increased water solubility, increased chemical or physical stability, or increased bioavailability of the drug molecule [9–11].

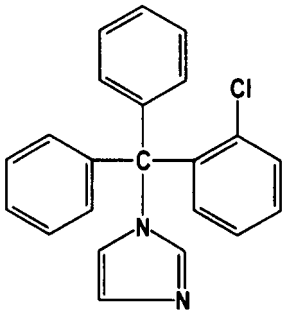

Figure 1. Chemical structure of clotrimazole.

The formation and antimycotic activity of inclusion complexes of CDs and imidazole derivatives were studied earlier [12]. Studies on the complexation of CLT with γ-CD have also been reported [13]. Improvement of the solubility and rate of release of CLT is essential for rapid antimycotic activity. Attempts have been made to increase the solubility properties of CLT by complexation with CDs.

The aims of this study were to establish whether the aqueous solubility of CLT can be increased by complexation with CDs and to gain an insight into the effects of CDs on the physicochemical properties of CLT.

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Table 1. Influence of CD derivatives on the solubility of clotrimazole

1. Clotrimazole (CLT)	1.00
2. CLT + α-CD	2.92
3. CLT + β-CD	3.84
4. CLT + HP-β-CD	5.94
5. CLT + RAMEB	11.16
6. CLT + γ-CD	14.47
7. CLT + DIMEB	18.82

Experimental

Materials

Clotrimazole (CLT), 1-(o-chloro-α, α-diphenylbenzyl)imidazole (Orva Pharmaceuticals Ltd., Izmir, Turkey) [1]. *γ-CD* (Cerestar, USA, Inc.); *dimethyl-β-CD* (DIMEB) (Cyclolab Ltd., Budapest, Hungary); *tartaric acid* (TA), *citric acid* (CA), *polyvinylpyrrolidone* (PVP) (pharmacopoeial grade), *malic acid* (MA) (Reanal Ltd., Budapest, Hungary); *hydroxypropyl-methylcellulose* (HPMC) (The Dow Chemical Company, Canada); *sodium carboxy methylcellulose* (Na-CMC) (Company for Supply and Provision of Pharmaceutical Industry, Budapest, Hungary).

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

Apparatus

USP rotating-basket dissolution apparatus, type DT (Heusenstamm Kr. Offenbach/Main, Germany); Unicam UV/Vis spectrometer $\sim$ 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 STAR^e Thermal Analysis System, version 6.0 (Schwerzenbach, Switzerland).

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 CLT and 0.90 g of different CDs 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). A system without CD was used as a control. DIMEB and γ-CD exerted the highest solubility-increasing effects on the solubility of the active ingredient (Table 1).

γ-CD was used for further examinations.

The absorption maximum of the active ingredient was at 260 nm. The calibration curve was obtained in the concentration interval 50–400 μg/ml, where the equation was found to be $A = 0.0021c$ for both of the calibration curves, prepared either with or without γ-CD.

Preparation of products

Products were prepared in two molecular ratios (drug : CD molecular ratio = 1 : 1 or 1 : 2).

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

Kneaded products (KP): physical mixtures of CLT and γ-CD were mixed in the same quantity of a methanol + water (1 : 1) mixture. They were kneaded until the bulk of the solvent mixture had evaporated. After this, they were dried at room temperature and then at 105 °C. Next, they were pulverized and sieved (100 μm).

Precipitated products (PP): a hot ($\sim$64 °C) saturated methanol solution of CLT and the appropriate aqueous CD solution were mixed and the clear solution was cooled, first spontaneously, and then with ice to 4 °C with continuous stirring. The precipitated product was filtered off under vacuum, then dried, ground, sieved (100 μm) and homogenized.

Spray-dried products (SD): CLT/methanol and CD/water solutions were mixed and heated (64 °C) to obtain clear solutions. The spray-dried products 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.

Dissolution studies

The dissolution studies were carried out by using the USP rotating-basket method. 0.10 g of pure CLT and products containing 0.10 g CLT were examined in 900 mL of distilled water with a rotation speed of 100 rpm. at 37 $\pm$1 °C during 90 min. Sampling was performed after 5, 10, 15, 30, 60 and 90 min. The CLT contents were determined spectrophotometrically at 260 nm (Unicam UV/Vis Spectrometer). All the studies were carried out at least in triplicate.

Phase solubility studies

Solubility measurements were carried out according to the method described by Higuchi and Connors [15]. Excess CLT was added to aqueous solutions containing various concentrations of γ-CD (0–150 mM), which were then stirred at room temperature until equilibrium was reached (approx. 8 days). The suspensions were next filtered and the concentrations of solubilized CLT were measured spectrophometrically at 260 nm. The stability constant (K_s) was determined from the initial straight part of the phase solubility diagram by using the equation of Higuchi and Connors, on the assumption that a complex with a stoichiometric ratio of 1 : 1 was formed in the initial step.

Particle size distribution study and determination of particle surface areas

The particle size determination was carried out on spray-dried products; CLT : γ-CD 1 : 1 and 1 : 2 and CLT : DIMEB

1 : 1. Approximately 300 particles were analysed by means of a LEICA Q500 MC image processing and analysis system. The surface areas of the particles were also calculated.

Determination of the effects of different hydroxy acids, water-soluble polymers and surfactants on the aqueous solubility of CLT

With consideration of the specific capacities of the carboxylic acid groups, 0.02 g of different α-hydroxy acids (CA, TA and MA) were each dissolved in 25.0 g of water containing 0.10 g CLT. After filtration, the absorbances were determined spectrophotometrically, the references containing only the hydroxy acids.

0.10 g CLT 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.

0.10 g CLT and 1.0 g of 1% solutions of different surfactants (each containing 0.01 g Tween 20, 40, 60 or 80) were added to 25.0 g distilled water. After filtration, the absorbances were determined spectrophotometrically.

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 (500.0 g of *n*-octanol + 22.0 g of water) and in water saturated with *n*-octanol (500.0 g of water + 1.0 g *n*-octanol). 0.10 g CLT and products containing 0.10 g CLT, further γ-CD and DIMEB were suspended in 5 mL of each solution. The suspensions were stirred at 25 ± 2 °C until equilibrium was reached (approximately 6 days). The suspensions were filtered and the concentrations of solubilized CLT were determined spectrophotometrically and by weight. K_p values were calculated according to the Nernst distribution law [16].

For the determination of surface tension, 0.01 g CLT, γ-CD, DIMEB or products containing 0.01 g CLT 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].

Wettability studies

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. For Leica Q500 MC Analyzer measurements, 0.20 g powder was compressed under a pressure of 3 tons by a Perkin–Elmer hydraulic press. The diameter and the height of the pressings were 7 mm and 3.5 mm, respectively. The wetting angles were determined after placing 3 μl of diluted methylene blue solution on the surface of the pressing. The study was carried out in duplicate, using a microscope and Leica Q500 MC Analyzer.

Determination of heat of dissolution in different temperature intervals

0.10 g CLT and the CLT : DIMEB 1 : 1 SD product containing 0.10 g CLT were suspended in 50 g of distilled water. The suspensions were placed in water baths at 20 °C, 40 °C 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 20–40 °C and 20–60 °C were calculated via the Clausius–Clapeyron equation.

Thermoanalytical studies

Differential scanning calorimetry (DSC) was used as the thermoanalytical method to confirm the presence of inclusion complexes. CDs generally lose water below 100 °C, and decompose above 250 °C. The DSC method can therefore be used if the crystallized drug melts in the temperature range between the temperature of water loss from the CD and the temperature of its decomposition (120–250 °C).

A distinction can be made between surface adsorption and inclusion complex formation by means of thermoanalytical methods. The presence of an inclusion complex is shown indirectly by changes (e.g., in evaporation, thermal decomposition, oxidation, melting or polymorphism) relative to the non-complexed free drug.

Approximately 2–5 mg of active material or product containing 2–5 mg of clotrimazole was examined between 25 °C and 300 °C. The heating rate was 5 °C min^{-1}. The argon flow rate was 10 L h^{-1}.

Results and discussion

Phase solubility studies

A knowledge of the abilities of guest molecules to undergo complexation with CDs is necessary to decide whether or not a host–guest complexation is useful in a particular application. Experimental determination of the complexation constant is often difficult, mainly because of the low solubility of the guest molecules [18].

According to the classification introduced by Higuchi and Connors (1965), phase diagrams, i.e., solubility curves, can be divided into two major categories. 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. A plateau region in the solubility curve is designated B_S if an initial increase in the apparent solubility is observed before the plateau region is reached [12].

Figure 2 shows a B_S-type phase-solubility equilibrium diagram for the CLT/γ-CD system in water at 25 °C. The

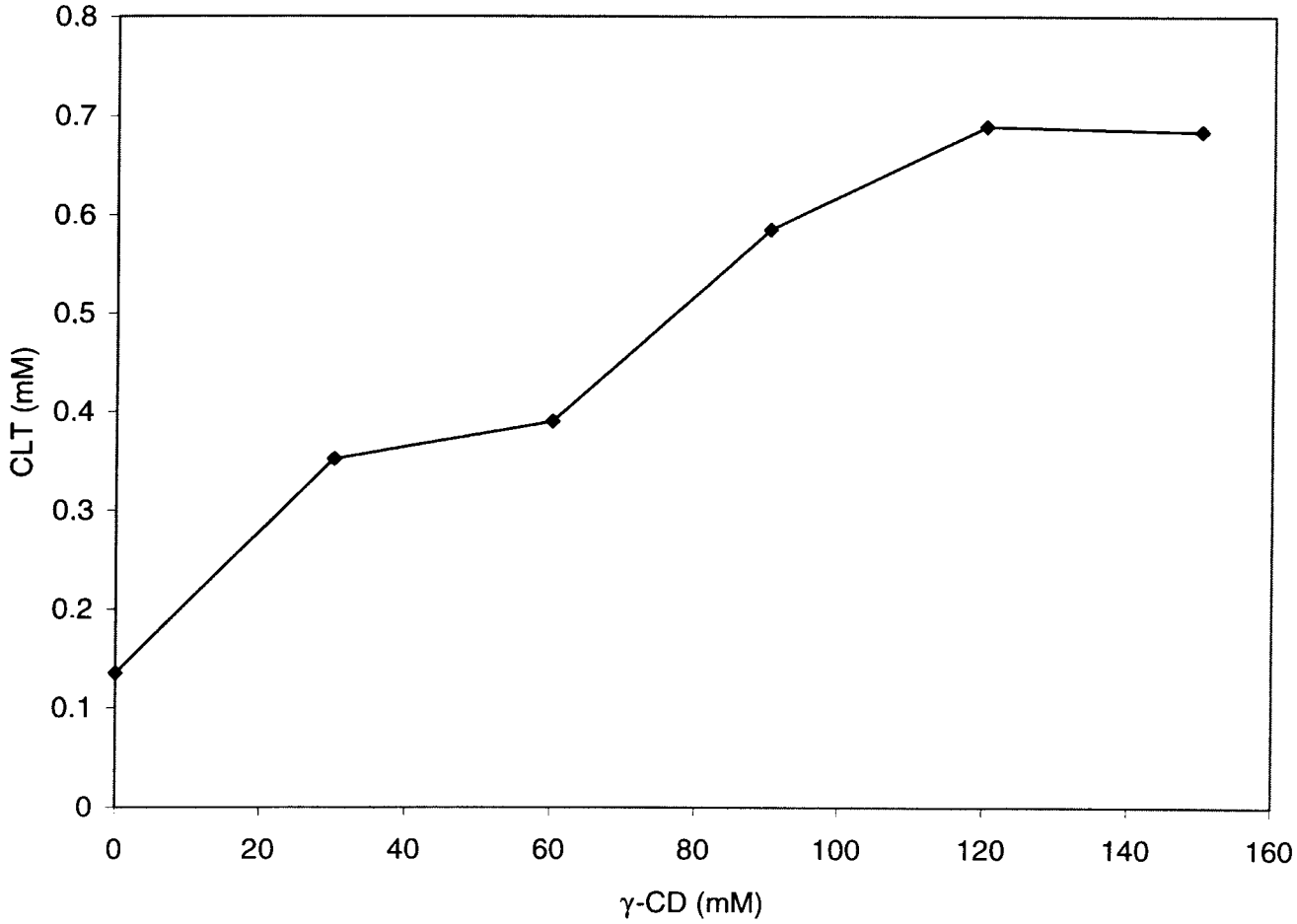

Figure 2. Phase solubility diagram of CLT with γ-CD in water at 25 °C.

aqueous drug solubility increased linearly in the presence of γ-CD at 25 °C (about 6-fold).

The apparent complex constant $K_{1:1}$ can be calculated from the solubility data through use of Equation (1):

$$K_{1:1} = \frac{\text{slope}}{S_0(1 - \text{slope})}, \quad (1)$$

where S_0 is the intrinsic solubility of CLT, the initial slope of the solubility diagram in Figure 1 is 3.8×10^{-3}, and the correlation coefficient is 0.9312. $K_{1:1}$ was calculated to be $28.3 \pm 2.18\ \text{M}^{-1}$.

Dissolution studies

Figure 3 reveals that the rate of dissolution of CLT was improved by the CLT : γ-CD (1 : 1) KP and CLT : γ-CD (1 : 1) SD products. The maximum dissolution was reached at approximately 30 min and did not change later. The 1 : 2 products prepared by different methods did not exert significant effects on the rate of dissolution of CLT (Figure 4). The SD products prepared with the use of different auxiliary materials displayed the highest dissolution profile. Nearly twice as much active ingredient was released from the product as for CLT alone. A similar result was obtained with the CLT : DIMEB (1 : 1) SD product. The rate of dissolution was low for the CLT SD product, probably as a result of the very large specific surface area and the air adsorbed on its surface (Figure 5).

Table 2. Particle size and surface area of spray-dried products

Products	Analysed particle %	Particle size (μm)	Analysed particle %	Surface area (μm^2)
CLT : γ-CD (1 : 1)	72	5–9	83	50–250
CLT : γ-CD (1 : 2)	88.2	4–8	93	50–200
CLT : DIMEB (1 : 1)	69.3	8–11	85	150–400

Particle size distribution study and determination of surface area

The solubility and rate of dissolution of a drug depend not only on its fundamental chemical properties, but also on its crystal structure and particle size. If the drug is poorly soluble in water, i.e., $K_d < K_a$, the dissolution is the rate-determining step and K_d has to be increased by micronized particles [16, 19, 20], where K_d = dissolution rate constant and K_a = absorption rate constant.

The particle size of the spray-dried products varied in the range 4–11 μm; the surface areas of the particles were also calculated as $4\pi r^2$, and are given in Table 2.

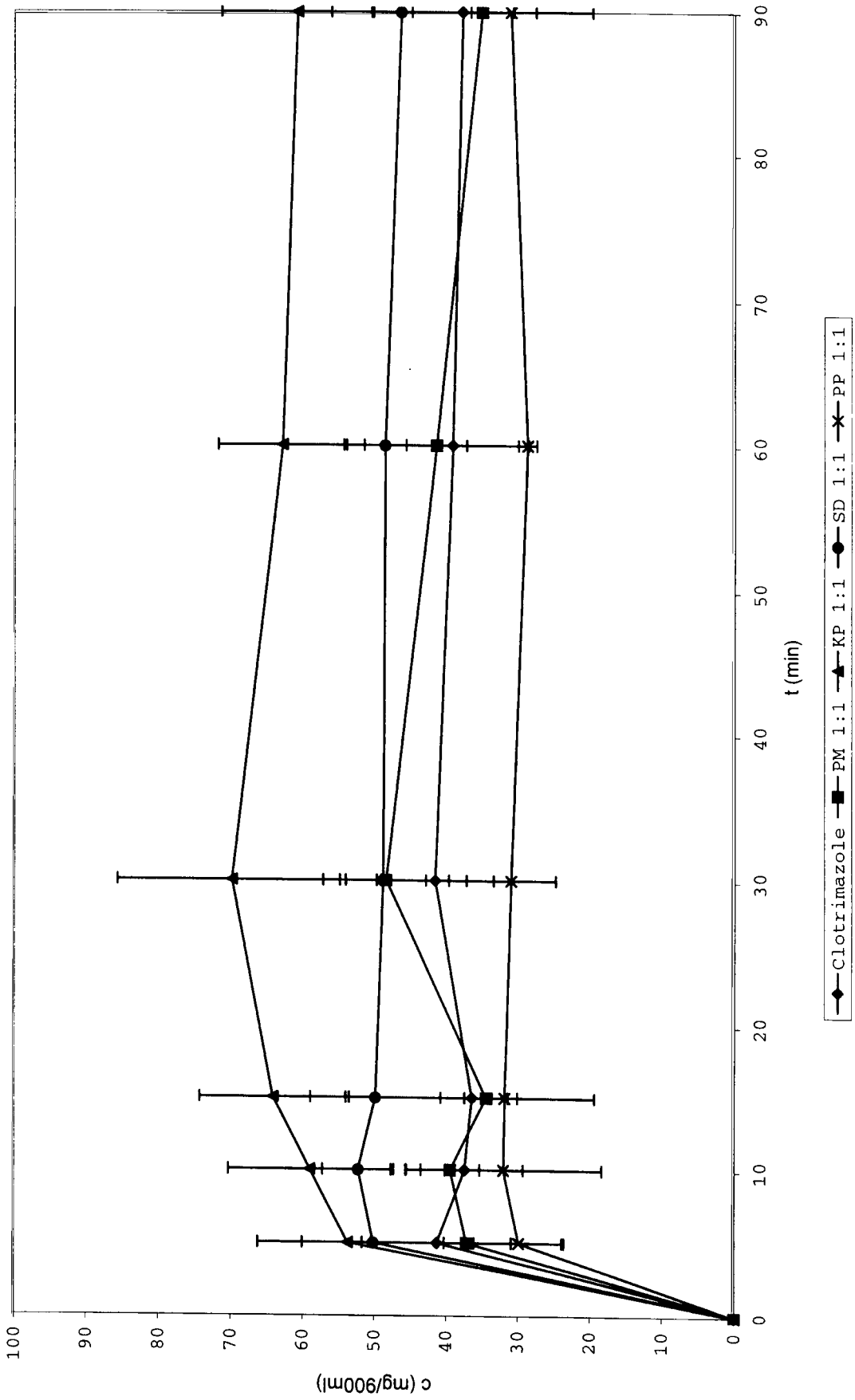

Figure 3. Dissolution profiles of CLT and CLT: γ-CD 1 : 1 products in water at 37 °. ♦, Clotrimazole; ■, PM 1 : 1; ▲, KP 1 : 1; ●, SD 1 : 1; ×, PP 1 : 1.

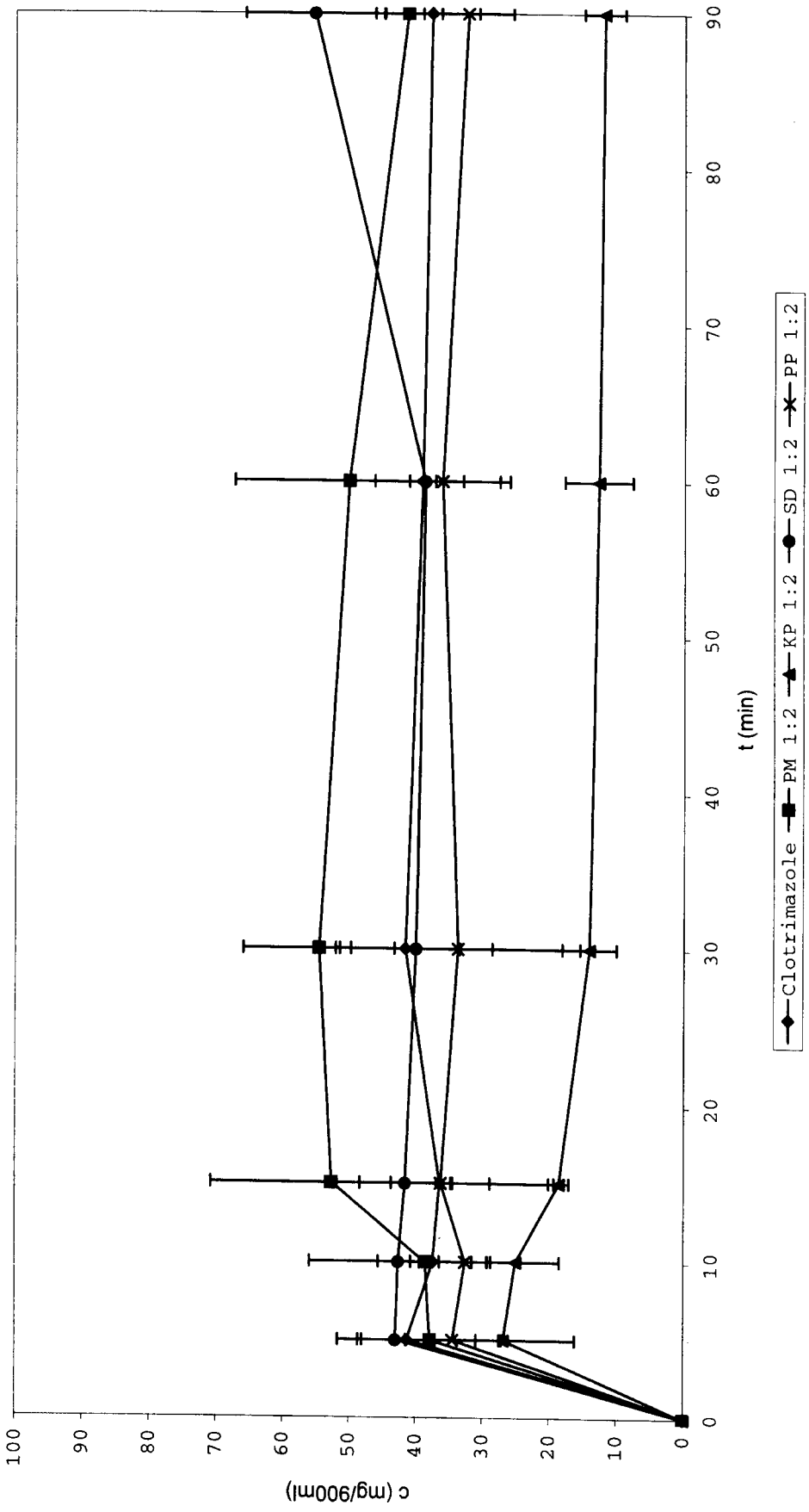

Figure 4. Dissolution profiles of CLT and CLT: γ-CD 1:2 products in water at 37 °. ♦, Clotrimazole; ■, PM 1:2; ▲, KP 1:2; ●, SD 1:2; ×, PP 1:2.

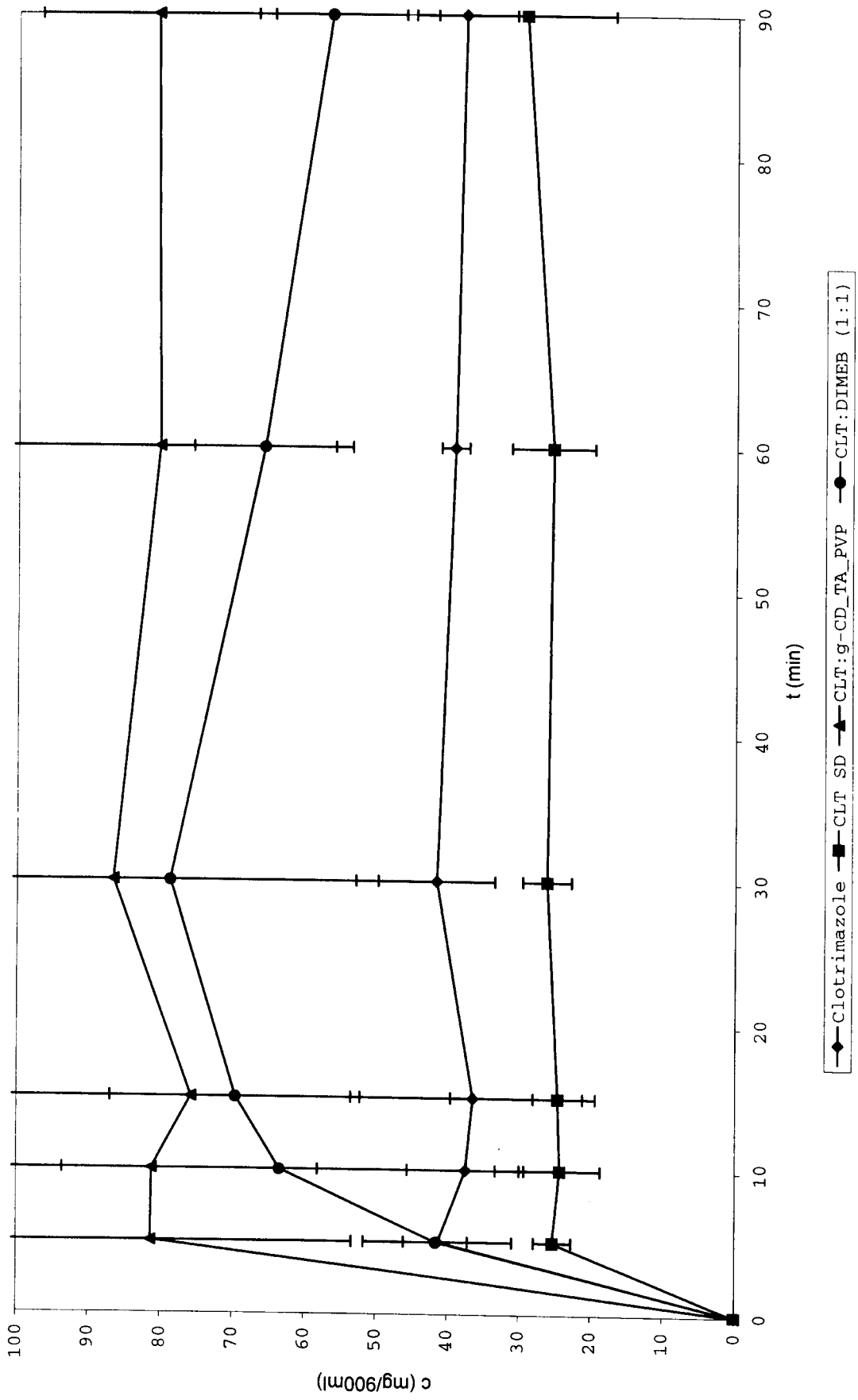

Figure 5. Dissolution profiles of CLT and different SD products in water at 37 °. ♦, Clotrimazole; ■, CLT SD; ▲,CLT:γ-CD + PVP + TA; ●, CLT:DIMEB (1:1).

Effects of different hydroxy acids, water-soluble polymers and surfactants on the solubility of clotrimazole in water

The combined effects of different acids (nitric, citric, lactic and malic) and CDs, both natural and derivative, in enhancing the aqueous solubility of the drug were investigated. Multicomponent complex formation was always more effective than salt formation or binary complexation in enhancing the aqueous solubility of the drug [21].

The highest absorbance among the acids was obtained with TA, which caused the greatest increase in the solubility of CLT.

It has been observed that the addition of a very small amount of polymer can increase the CD complexation of drugs in aqueous solution. Polymers have a synergistic effect on the solubilizing power of CDs and surfactants. Addition of a small amount (0.10–0.25%) (w/v) of polymer results in a significant enhancement of aqueous solubility of water-insoluble drugs or drugs with limited aqueous solubility [22].

They mainly interact with drug molecules via electrostatic bonds, i.e., ion-to-ion (in the case of CMC), ion-to-dipole or dipole-to-dipole bonds, but other types of forces, such as van der Waals forces and hydrogen bonds, are frequently involved in complex formation .

The complexation efficacy is usually enhanced and the drug availability in CD solutions is usually increased when aqueous solutions containing a water-soluble polymer are heated. Simple addition of the polymers to the solutions without heating does not enhance the complexation or drug bioavailability [23].

In our study, the highest absorbance for an auxiliary material was that for PVP which exerted the highest solubility-increasing effect on CLT.

Use of surfactants in pharmaceutical formulations is a very common practice. The simultaneous presence of a drug and a surfactant in a formulation containing CD can modify the pattern of release of the drug from drug-CD inclusion compounds.

The effects of surfactants on drug release have been found to depend both on the type of drug and on the CD applied. Certain pharmaceutical additives (i.e., surfactants) can act as complexants, and thus destroy the positive effects of inclusion complexation. It has been found that the dissolution of a drug can be increased by both the surfactant (sodium lauryl-sulphate) and the CD when they are added separately to the dissolution medium (binary systems). A decreased dissolution rate was observed, however, when both additives were present (ternary systems). The results of some studies have shown that the drug and the surfactant can be competitors and the dissolution of the drug depends on both the drug/CD and surfactant/CD interactions (and probably also on the drug/surfactant interactions) [24].

Among the binary systems that we prepared containing only the active substance and the surfactant, Tween 40 and Tween 80 exhibited the highest solubility-increasing effect. The solubility of CLT increased 30-fold when PVP, TA and γ-CD were used together.

Table 3. Results of partition coefficient and surface tension (γ) measurements

Active material and products	C_{octanol} (mg/ml)	C_{water} (mg/ml)	Partition coefficient [CLT] in octanol/ [CLT] in water	Surface tension (mN/m)
Clotrimazole	39.20	0.056	704.5	70.1
γ-CD	>20	803.3	0.025	79.7
DIMEB	>30	970.0	0.031	67.3
CLT : γ-CD(1 : 1) PM	18.50	0.223	82.6	65.8
CLT : γ-CD(1 : 2) PM	19.90	0.214	92.7	67.6
CLT : γ-CD(1 : 1) KP	13.00	0.111	115.7	69.0
CLT : γ-CD(1 : 2) KP	4.38	0.116	37.5	63.5
CLT : γ-CD(1 : 2) SD	1.26	0.211	5.9	70.0
CLT SD	56.20	0.218	257.3	70.1
CLT : DIMEB (1 : 1) SD	14.60	1.640	8.9	60.6
CLT : γ-CD(1 : 1) PP	22.00	0.058	375.4	67.8
CLT : γ-CD(1 : 2) PP	12.80	0.059	214.5	64.5
CLT : γ-CD + PVP + TA (1 : 1) SD	11.70	2.430	4.8	59.8

Partition coefficient and surface tension (γ) measurements

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

$$K_P = \frac{a_1}{a_2}, \tag{2}$$

where K_p = partition coefficient, a_1 = concentration of drug in *n*-octanol, and a_2 = concentration of drug in water.

K_p represents the oil-water partitioning of a drug. Drugs that are more lipid-soluble will have a larger K_p, which may influence the rate of diffusion according to Fick's law of diffusion. The values of K_P calculated according to the Nernst distribution law are influenced by both the concentration and the nature of the CD.

The K_p values of CLT, CLT : γ-CD (1 : 1) PP and CLT SD product are the highest, depending on their low aqueous solubility. In contrast, γ-CD and DIMEB are highly water-soluble materials and therefore their partition coefficient values are the lowest. The products of SD DIMEB or auxiliary materials have the best aqueous solubility (where their solubilities are nearly the same in *n*-octanol). This is an expected result of the increased surface and amorphous structure of a SD product. K_p also depends on the preparation method. This can be seen for the PP, PM, KP and SD 1 : 2 products, where the K_p values are 214.5, 92.7, 37.5 and 5.9, respectively. The spray-drying method significantly decreased the K_p value of CLT.

The surface tension values of CLT and the CLT SD product are the same, ~70 mN/m. γ-CD has the greatest surface tension, and the CLT : auxiliary material SD products the lowest. The surface tension is also affected by the preparation method and the molecular ratio of the products. The surface tension of distilled water is 73.5 mN/m (Table 3).

Table 4. Amounts of absorbed water by CLT and CLT : γ-CD products

Theoretical Enslin numbers	ν_{15}	ν_{30}	ν_{60}	ν_{120}
CLT SD	0.17	0.23	0.32	0.44
CLT : γ-CD (1 : 2) KP	0.20	0.29	0.40	0.55
CLT : γ-CD (1 : 2) PP	0.35	0.48	0.67	0.93

Table 5. Wetting angles and Enslin numbers of materials and products

Active material and products	Wetting angles	Enslin numbers
Clotrimazole	34°	0.02
γ-CD	33°	0.07
CLT : γ-CD (1 : 1) PM	71°	0.02
CLT : γ-CD (1 : 2) PM	54°	0.02
CLT : γ-CD (1 : 1) KP	56°	0.22
CLT : γ-CD (1 : 2) KP	43°	0.51
CLT : γ-CD (1 : 2) SD	63°	0.08
CLT SD	69°	0.42
CLT : DIMEB (1 : 1) SD	48°	0.02
CLT : γ-CD (1 : 1) PP	34°	0.04
CLT : γ-CD (1 : 2) PP	54°	0.92
CLT : γ-CD + PVP + TA (1 : 1) SD	37°	0.08

Wettability studies

The Enslin number is the water-absorbing capacity of 1.00 g of active substance in a certain period of time. The Enslin apparatus is used for the determination [25]. The amount of water absorbed can be calculated via Equation (3):

$$\nu = \nu_0 + m\sqrt{t}, \tag{3}$$

where ν_0 = the amount of water absorbed at 0 sec, m = the velocity constant of the process and t = time (sec). The amounts of water absorbed by products, as determined theoretically, are given in Table 4.

The practical results on the wetting angles and the Enslin numbers are also given in Table 5. γ-CD has the smallest wetting angle value, depending on its good wetting properties. The value increases for the products containing CLT. The CLT SD product has a wetting angle of 69°. This is probably a result of its very large specific surface area and the air adsorbed on its surface.

The Enslin numbers of the 1 : 2 products are generally higher than those of the 1 : 1 products. A direct relation could not be observed between the wetting angle and the Enslin number.

Determination of the heat of dissolution in different temperature intervals

The rates of dissolution and diffusion of CLT from different products depend on the energy relations of the formation of the products and on the stability constants of the complexes. The energy needed for the formation of inclusion complexes is not the same for different preparation methods. The experimentally determined energies of CLT and the CLT : DIMEB (1 : 1) SD product solubility, i.e., the heats of dissolution in the intervals 20–40 °C and 20–60 °C, were calculated by using the Clausius–Clapeyron equation [26, 27]:

$$\log \frac{c_1}{c_2} = \frac{\Delta Q_{\text{sol}}}{4.573} \cdot \frac{T_1 - T_2}{T_1 T_2}, \tag{4}$$

where ΔQ_{sol} = heat of dissolution; c_1, c_2 = solubilities at temperatures T_1 and T_2; T_1, T_2 = absolute temperatures (K). The results of the study are given in Table 6.

Thermoanalytical studies

The thermoanalytical curves of clotrimazole, spray-dried clotrimazole, γ-CD, DIMEB, tartaric acid, PVP, clotrimazole + γ-CD physical mixtures, kneaded products, spray-dried products, precipitated products with ratios of 1 : 1 and 1 : 2, clotrimazole + DIMEB spray-dried product with molecular ratio of 1 : 1 were investigated.

Clotrimazole and spray-dried clotrimazole melted at around 143 °C, as seen in the DSC plots (Figures 5 and 6). The active ingredient decomposed above 250 °C. No change can be seen in the DSC curve of γ-CD, DIMEB, tartaric acid and PVP in this temperature range. Tartaric acid has a characteristic melting point at 171 °C. The water content of γ-CD was lost until about 80 °C, and the degradation started at 260 °C. The water content of DIMEB is negligible and no decomposition can be seen until 300 °C (Figure 6).

The DSC curves of the physical mixtures are the sums of the curves of the two components containing both peaks representative of γ-CD and clotrimazole itself. There is no signal indicating a thermally induced interaction between the two components. The endothermic peak of clotrimazole decreases with increasing CD content (Figure 8).

The DSC curves of the kneaded, spray-dried and precipitated products have no endothermic peak of clotrimazole or the peak is smaller than for the physical mixtures. According to these results, partial or total complex formation is presumed. The clotrimazole + γ-CD + tartaric acid + PVP spray-dried product gave similar results (Figures 7 and 8).

Conclusions

- DIMEB and γ-CD exerted the highest solubility-increasing effects on the solubility of CLT, γ-CD was used for further experiments for its acceptable cost compared to DIMEB and depending on the similar dissolution results of CLT : γ-CD (1 : 1) SD and CLT : DIMEB (1 : 1) SD products.
- The products were prepared in 1 : 1 and 1 : 2 (CLT : γ-CD) molecular ratios, using physical mixing, kneading, spray-drying and precipitation methods.
- The effects of different auxiliary materials (polymers, hydroxy acids and surfactants) on the aqueous solubility of CLT were investigated. The best results were obtained with PVP, TA and Tween 40 or Tween 80.

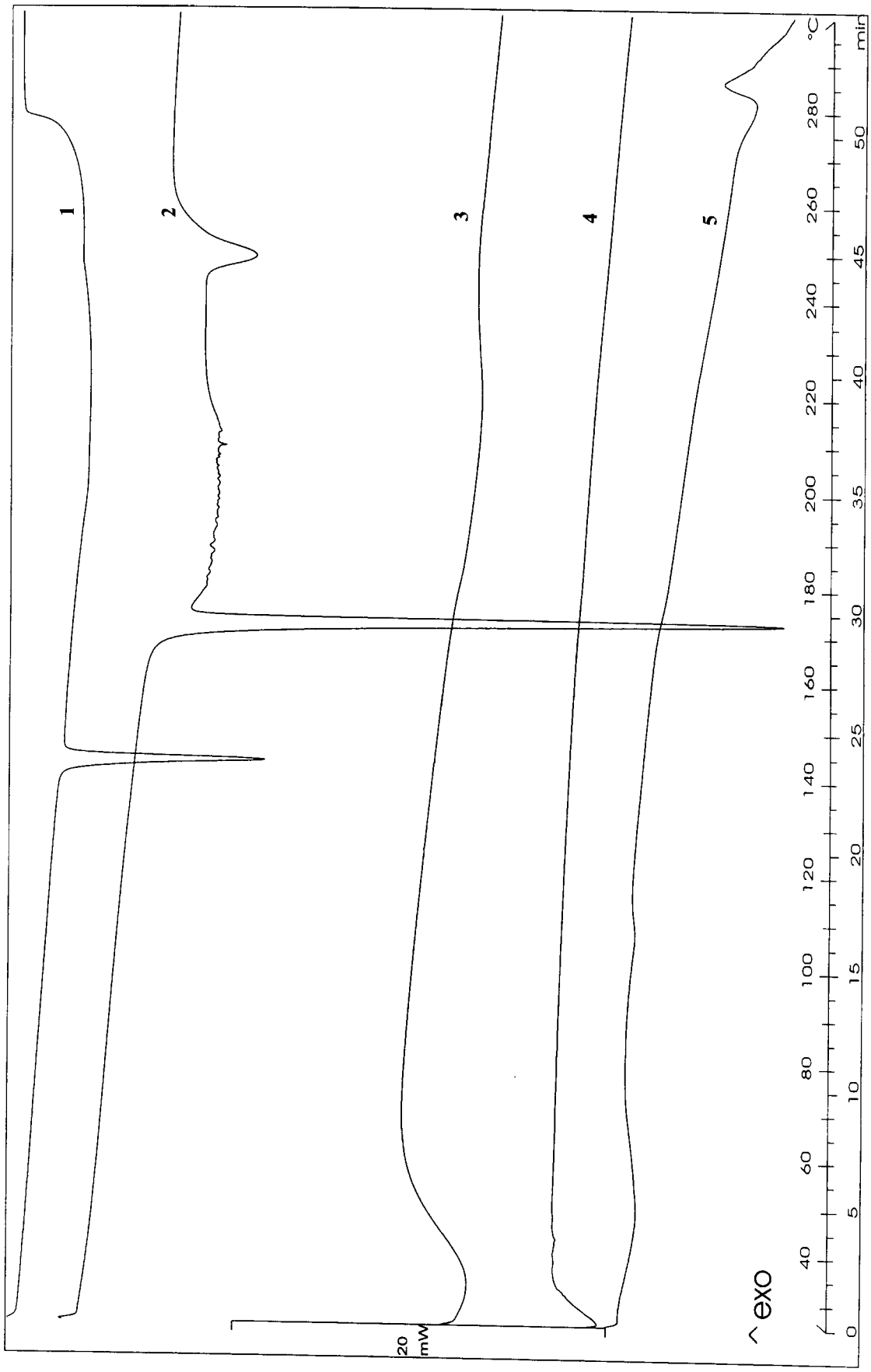

Figure 6. DSC curves of (1) CLT, (2) TA, (3) PVP, (4) DIMEB and (5) γ-CD.

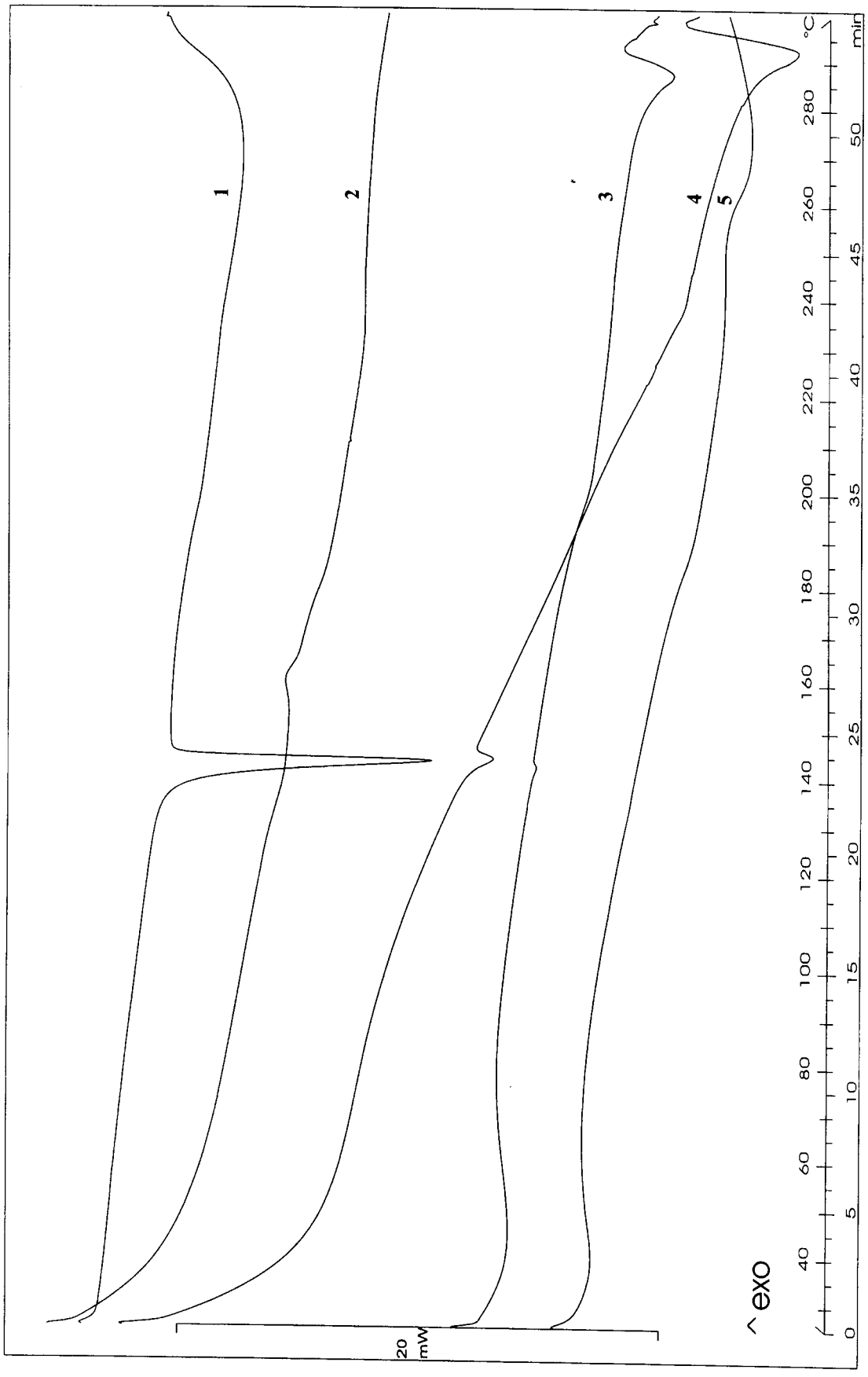

Figure 7. DSC curves of (1) CLT SD, (2) CLT : DIMEB 1 : 1 SD, (3) CLT : γ-CD 1 : 2, (4) CLT : γ-CD 1 : 1 SD and (5) CLT : γ-CD + PVP + TA 1 : 1 SD.

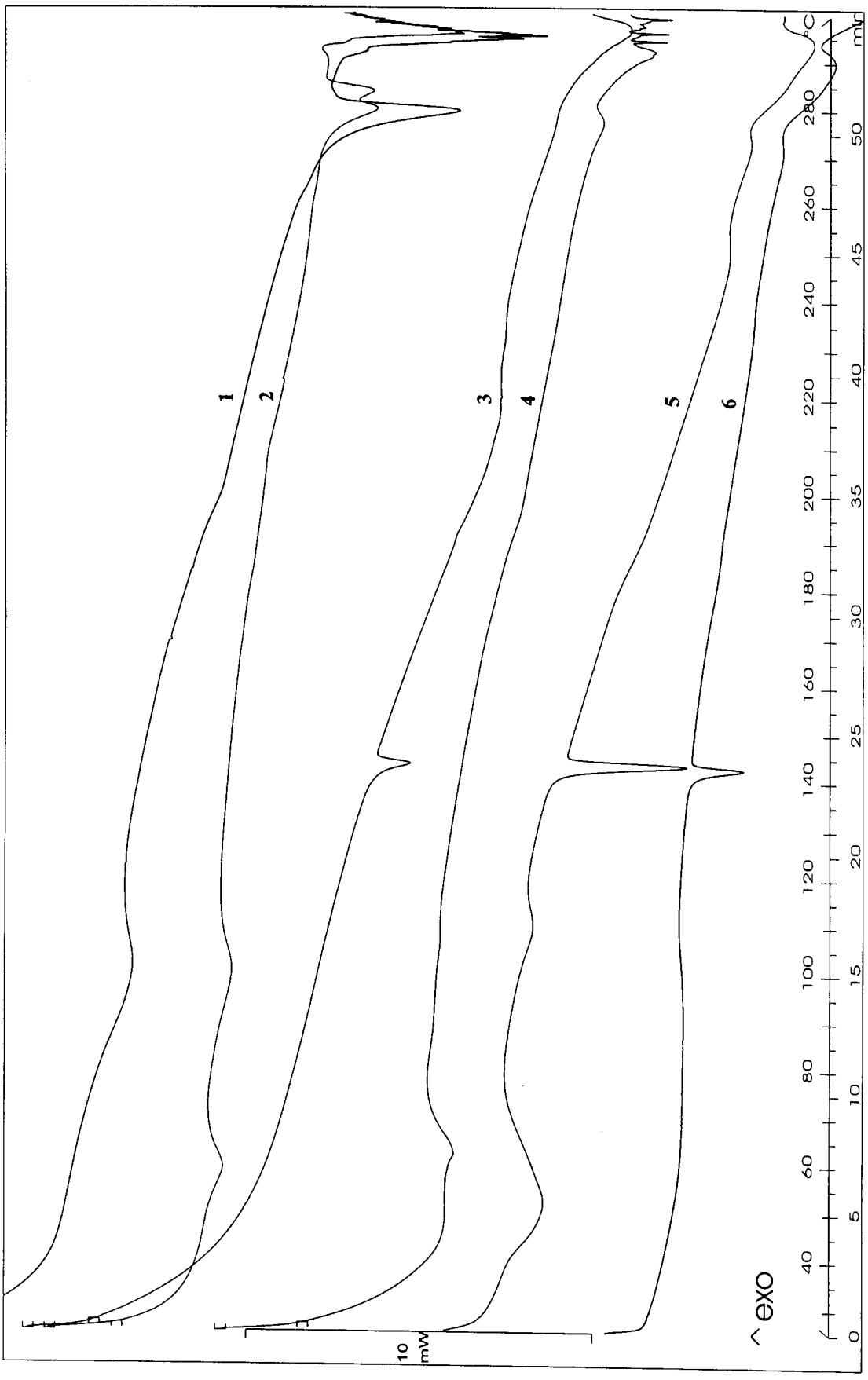

Figure 8. DSC curves of (1) CLT : γ-CD 1 : 1 PP, (2) CLT : γ-CD 1 : 2 PP, (3) CLT : γ-CD 1 : 1 KP, (4) CLT : γ-CD 1 : 2 KP, (5) CLT : γ-CD 1 : 1 PM and (6) CLT : γ-CD 1 : 2 PM.

Table 6. Heats of dissolution in the intervals 20–40 °C and 20–60 °C

	ΔQA_{sol} (kJ/mol)		
Temperature (°C)	Clotrimazole	CLT : DIMEB (1 : 1) SD	CLT : γ-CD (1 : 1) SD
20–40 °C	11.76	8.99	19.29
20–60 °C	11.61	9.86	10.85

- The dissolution rate was measured by using the USP XXII rotating-basket method, and the highest dissolution rate increase was obtained for the CLT : auxiliary material SD products. Considering the air absorbed on the surface of CLT and its products, besides the low wettability property of the active ingredient (Table 5), the dissolution behaviour may differ in each dissolution.
- Solubility studies were carried out by using γ-CD; a B_s-type phase solubility equilibrium diagram was observed with a stability constant of 28.3 M^{-1}.
- As the solubility in water increased, the partition coefficient, surface tension and wetting angle values decreased. The results depended on the preparation method.
- CLT needed more energy for dissolution at higher temperatures as compared to its products.
- Taking into consideration the chemical structure of CLT and the dissolution results, it may have establish that the *o*-chloro-phenyl ring or one of the phenyl rings of CLT forms inclusion complex with one molecule of CDs and not more because it is impossible sterically.
- Partial or total inclusion complex formation was observed by means of DSC studies for the ratios of 1 : 1 and 1 : 2 physical mixtures, kneaded, spray-dried, precipitated products and spray-dried product containing auxiliary materials.

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