Journal of Thermal Analysis and Calorimetry, Vol. 76 (2004) 471–479

THERMOANALYTICAL STUDIES ON COMPLEXES OF CLOTRIMAZOLE WITH CYCLODEXTRINS

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(Received July 4, 2003; in revised form February 6, 2004)

Abstract

γ-Cyclodextrin and dimethyl-β-cyclodextrin were used as solubilizing agents for a very poorly water-soluble drug, an imidazole derivative antifungal agent, clotrimazole; with the aim of improving the physicochemical properties of the drug. Solid products were prepared by physical mixing, kneading, precipitation and spray-drying methods in 1:1 and 1:2 drug:cyclodextrin molar ratios. Drug interactions were studied by thermoanalytical methods such as DSC, DTA, TG and DTG, X-ray diffractometry and Fourier transformation-infrared spectroscopy. The results demonstrated the formation of inclusion complexes in some products.

Keywords: clotrimazole, γ-cyclodextrin, dimethyl-β-cyclodextrin, FT-IR spectroscopy, thermal analysis, X-ray diffractometry

Introduction

Inclusion complexes between drugs and cyclodextrins (CDs) are a topic of current interest to the pharmaceutical research and industry as they may improve the solubility, stability and bioavailability of the guest molecules [1–4]. The guest inclusion gives rise to a new crystal lattice, and crystalline compounds can be identified by various physical methods. Different analytical techniques have been reported for the confirmation of inclusion, such as thermal analysis, X-ray diffractometry (XRD) and Fourier transform infrared (FT-IR) spectroscopy [5, 6]. Differential scanning calorimetry (DSC) allow establishment of the success of molecular encapsulation. Thermal analysis (DSC, TG, DTG and DTA) can also be used to characterize inclusion complexes. These methods show beyond doubt that the guest:host materials formed are truly complexes [7–9]. X-ray powder diffraction is utilized to characterize CD inclusion compounds. The changes in the powder crystallinity of the samples are studied by comparing their diffraction patterns. To

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1388–6150/2004/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

characterize clotrimazole (CLT) and its CLT:γ-CD inclusion complexes, DSC and XRD studies were carried out previously by Pedersen *et al.* to characterize the physical mixture of CLT:γ-CD in 1:1 molar ratio [10]. In the present study, our aim was to confirm and investigate the presence of inclusion complexes of CLT and -CD in 1:1 and 1:2 molar ratios prepared by physical mixing, kneading, spray-drying and precipitation methods by thermal analysis, X-ray diffraction and FT-IR studies.

Materials and methods

Materials

Clotrimazole (CLT, Fig. 1), 1-(*o*-chloro-α,α-diphenylbenzyl)imidazole [11, 12], was kindly donated by Orva Pharmaceuticals Co., (Turkey). Dimethyl-β-cyclodextrin (DIMEB) was purchased from Cyclolab Res. & Dev. Ltd., (Hungary). γ-Cyclodextrin (γ-CD) was a generous gift from Cerestar, Inc. (USA).

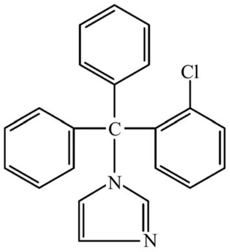

Fig. 1 Chemical structure of clotrimazole

Methods and apparatuses

Products were prepared in 1:1 and 1:2 guest:host molar ratios, as physical mixtures (PMs), kneaded products (KPs), spray-dried products (SDs) and precipitated products (PPs). The SDs were obtained by using a Niro Minor Atomizer apparatus (Denmark) with an inlet air temperature of 90°C, gas heating and a rotation speed of 25 000 rpm.

The DSC analysis was carried out with a Mettler Toledo type STAR^e thermal analysis system, version 6.0 software, DSC 821^e (Switzerland) at a heating rate of 5°C min^{-1} argon being used as carrier gas. The sample size was in the range 2–5 mg and examinations were made in the temperature interval 25–300°C.

TG, DTG and DTA studies were performed with a Derivatograph-C (Hungary) apparatus. 50 mg of the sample to be investigated was placed in one holder, and a thermally inert material, aluminium oxide, in another. The studies were carried out under air atmosphere at a heating rate of 5°C min^{-1}.

XRD spectra were recorded with a Dron UM-1 diffractometer (Russia), with scanning at 3° min^{-1} in terms of the angle 2θ.

The IR spectra of the complexes in KBr pellets were recorded with a Bio-Rad Digilab Division FTS-65A/896 Fourier transform FT-IR spectrometer (Japan) with a deuterated triglycyl sulphate detector, in the range of 4000–400 cm^{-1}. Pellets contained 300 mg KBr and 20 mg pure material, or 250 mg KBr and 100 mg product. The optical resolution was 4 cm^{-1}, and 256 scans were averaged to gain a good signal-to-noise ratio. All spectral manipulations were performed using GRAMS/386 software (Galactic Ind.) running on an HP Vectra VL/50 computer.

Results and discussion

CLT and CLT SD melted at around 143°C. The active ingredient did not contain any water, it decomposed at about 240–250°C and it could easily be recognized on DSC, TG, DTG and DTA analysis, where this exothermic process reflects an oxidative decomposition. The mass loss was very small, due to the high stability of CLT (Fig. 2).

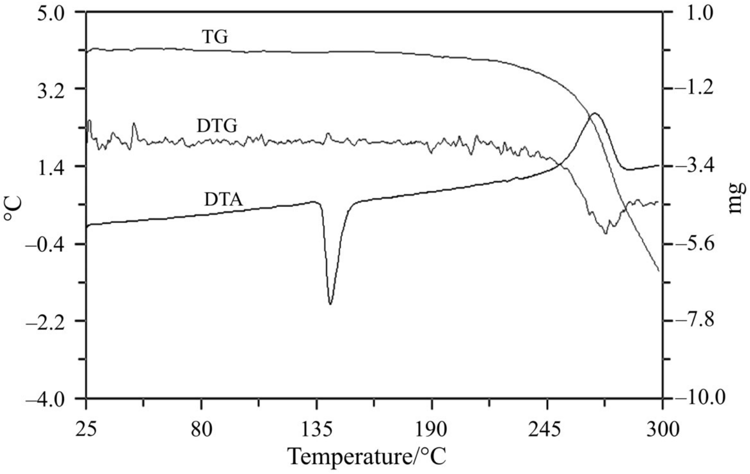

Fig. 2 TG, DTG and DTA curves of CLT

No change could be seen in the DSC curves of γ-CD in this temperature change. The thermal behaviour of γ-CD has been detailed by Giordano *et al.* [6]. The water contents of γ-CD and DIMEB were evaporated off until about 130°C, and the thermal decomposition started at 260°C. The water losses for γ-CD and DIMEB were 9.2 and 0.4%, respectively. The DTA curve of γ-CD revealed solid-state (oxidation), melting and liquid-phase processes, which were exothermic, endothermic and exothermic, respectively (Fig. 3).

The DSC curves of the PMs were the superpositions of the curves of the two individual components, containing peaks representative of both γ-CD and CLT alone (Fig. 4). There was no signal indicative of a thermally induced interaction between the two components. The endothermic peak of CLT decreased with increasing CD content and the characteristic peak of CLT could be recognized. The superposition of the two individual components could also be observed from the thermoanalytical curves (Fig. 5).

The water losses from 1:1 and 1:2 PMs were 7.2 and 8.0%, respectively. KPs with the same ratios gave similar results to those of the PMs. The water loss percentages from the 1:1 and 1:2 KPs were 5.8 and 7.5%, respectively.

The DSC curves of the CLT:γ-CD (1:2) SD did not reveal a melting peak (Fig. 6). This may be due to complex formation or to the formation of an amorphous structure, or both. As no endothermic peak could be observed, complex formation may be assumed for the CLT:γ-CD (1:1) PP (Fig. 7).

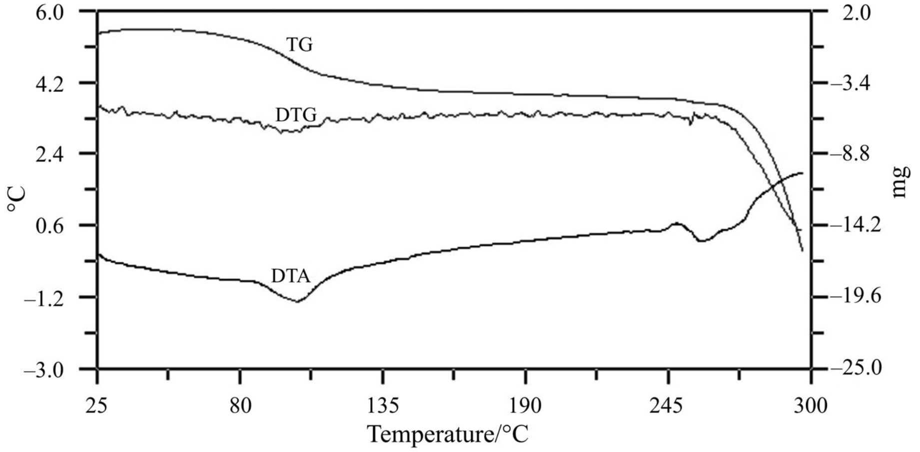

Fig. 3 TG, DTG and DTA curves of γ-CD

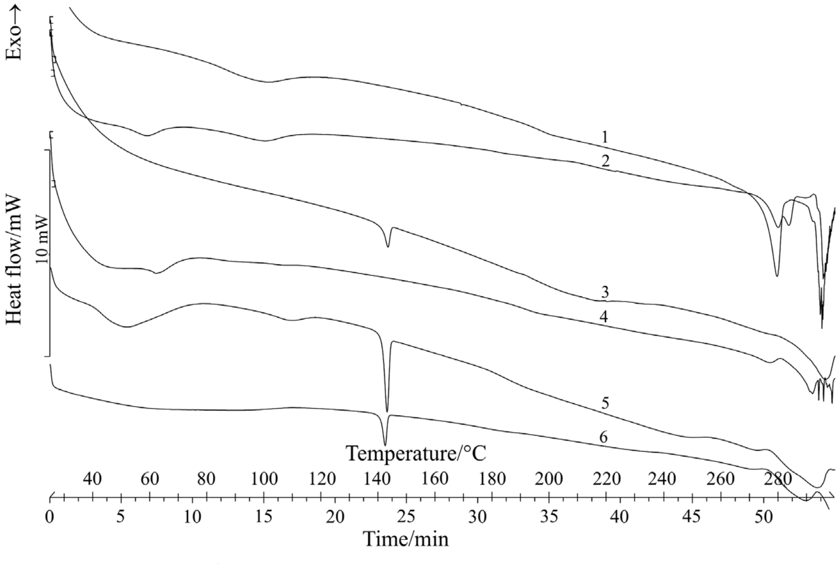

Fig. 4 DSC curves of 1 – CLT:γ-CD 1:1 PP, 2 – CLT:γ-CD 1:2 PP, 3 – CLT:γ-CD 1:1 KP, 4 – CLT:γ-CD 1:2 KP, 5 – CLT:γ-CD 1:1 PM and 6 – CLT:γ-CD 1:2 PM

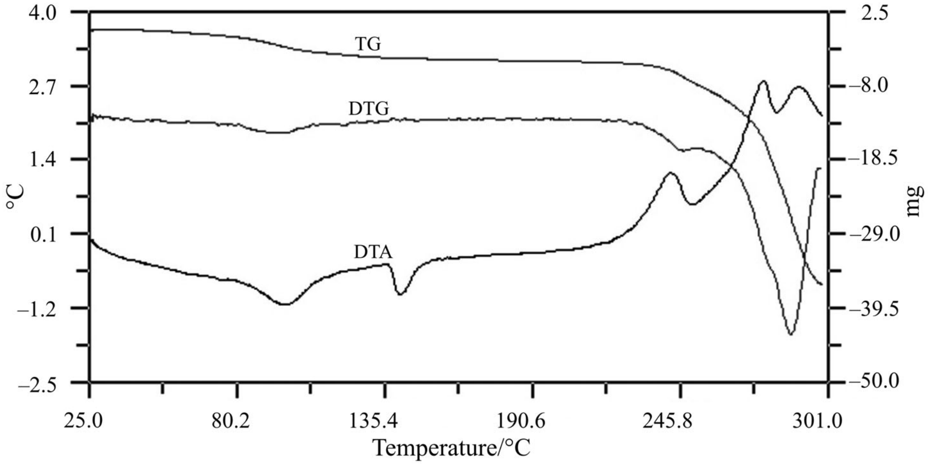

Fig. 5 TG, DTG and DTA curves of CLT:γ-CD 1:1 PM

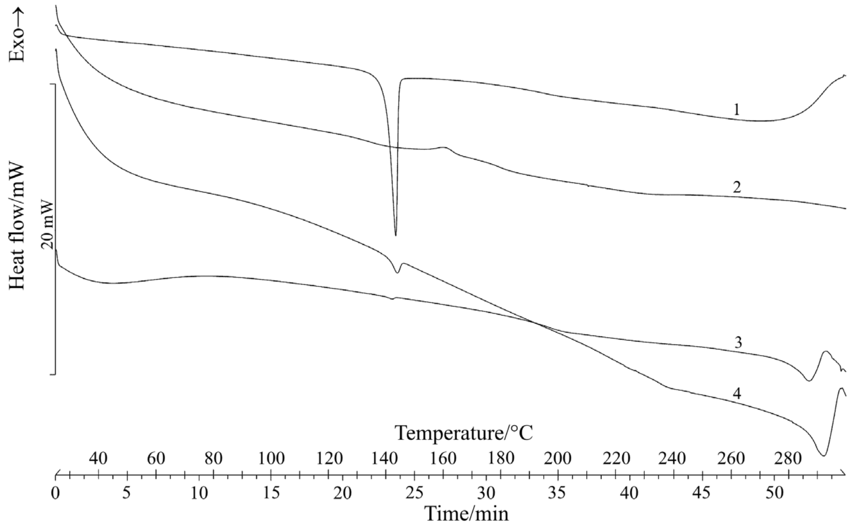

Fig. 6 DSC curves of 1 – CLT SD, 2 – CLT:DIMEB 1:1 SD, 3 – CLT:γ-CD 1:2 SD, 4 – CLT:γ-CD 1:1 SD

The assumed uncomplexed guest (active material) percentages were calculated semiquantitatively from the DSC curves by using the following equation (the results are given in Table 1):

$$(\text{uncomplexed} - \text{guest})\% = \frac{\Delta H_{\mathrm{i}}}{\Delta H_0 c} 10^4$$

where ΔH_{i} – normalized integral data on the product, ΔH_0 – normalized integral data on the active ingredient, c – percentage active ingredient in the product.

Table 1 The assumed uncomplexed guest content of the products

Product	Uncomplexed guest/%
CLT:γ-CD (1:1) PM	76.7
CLT:γ-CD (1:2) PM	66.7
CLT:γ-CD (1:1) KP	32.8
CLT:γ-CD (1:2) KP	0
CLT:γ-CD (1:1) SD	33.6
CLT:γ-CD (1:2) SD	8.7
CLT:γ-CD (1:1) PP	0
CLT:γ-CD (1:2) PP	0
CLT:DIMEB (1:1) SD	0

The XRD patterns of CLT, γ-CD and the CLT:γ-CD systems are presented in Fig. 8. The diffractograms of CLT (1) and γ-CD (2) exhibited a series of intense peaks, which are indicative of their specific crystalline character. The XRD patterns of the CLT:γ-CD PM (3) was practically a superposition of the spectra of the individual components, indicating no formation of a new structure. Comparison of the KPs with the PMs revealed a small modification in crystallinity. The crystallinity of CLT was nearly the same in the KP as in the corresponding PM. The small increment in crystallinity may be due to the formation of CLT:γ-CD mixed crystalline particles. The very similar patterns for the pure substances and their physically mixed counterparts indicate that the physical mixing process has no influence on the structure of any material.

The KPs presented a diffraction pattern quite similar to that of the PMs, while those obtained on the SDs exhibited fewer and less intense peaks (5). This reduction in crystallinity was obvious in the SDs, the diffraction pattern of which was completely diffuse, reflecting the amorphous nature of the substance.

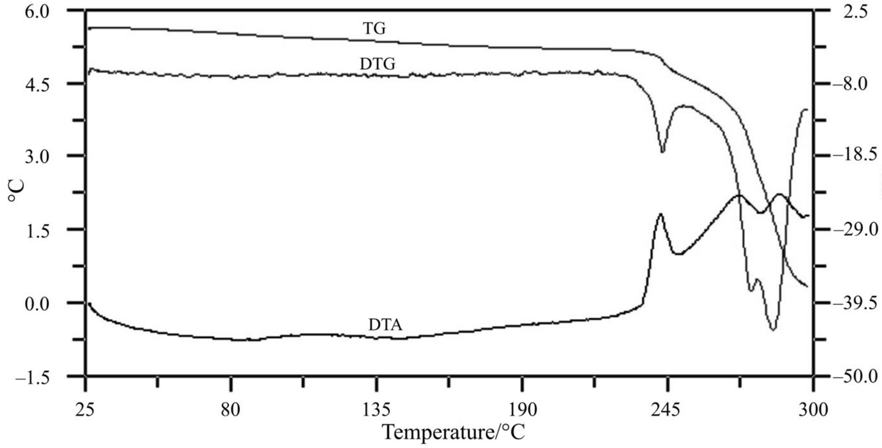

Fig. 7 TG, DTG and DTA curves of CLT:γ-CD 1:1 PP

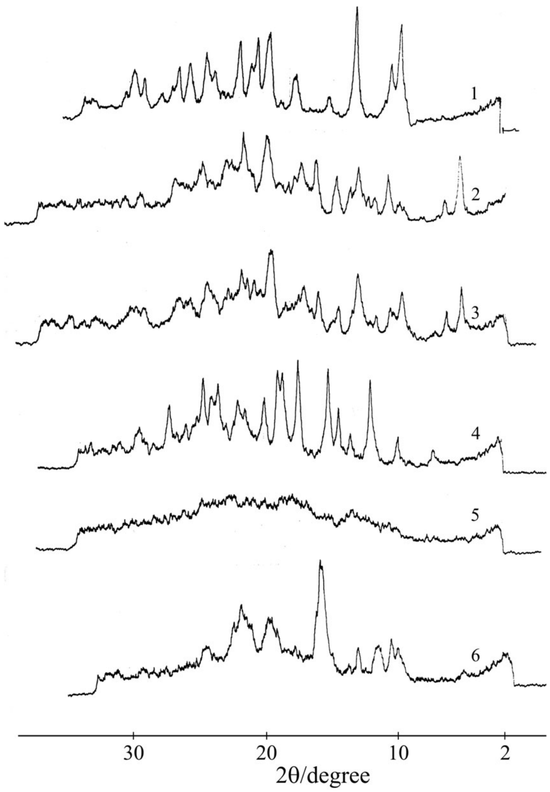

Fig. 8 X-ray diffraction patterns of 1 – CLT, 2 – γ-CD, 3 – CLT:γ-CD 1:1 PM, 4 – CLT:γ-CD 1:1 KP, 5 – CLT:γ-CD 1:1 SD and 6 – CLT:γ-CD 1:1 PP

These results may be attributed to an interaction between CLT and γ-CD in the SDs, suggesting the presence of a new solid phase with lower crystallinity (i.e. a practically amorphous structure) than that of the drug where possible complexation of CLT inside the γ-CD cavity was contemplated.

The FT-IR spectra of the CLT:DIMEB (1:1) SD and its pure components are presented in Fig. 9. The spectrum of DIMEB was subtracted from the spectrum of the product and the spectral difference, containing the changes due to the interaction is included. There were two regions in which essential changes occurred. The aromatic ring skelatal modes (framed region) showed that the ring structure was influenced by the interaction. Two peaks, on both sides of 1450 cm^{-1}, disappeared and a new broad band appeared at 1449 cm^{-1}. The peaks at 1305 and 1263 cm^{-1} also disappeared, indicating that the central non-π-bonded moiety of the substrate was also influenced.

Similar changes were observed in the spectrum of CLT:γ-CD (1:1) KP, with slight shifts in the positions of the peaks to lower wavenumbers. On the other hand, there were no essential changes in the positions of the bands in the spectrum of the CLT:γ-CD (1:1) SD; the peaks at 1305 and 1263 cm^{-1} can still be identified (Fig. 10).

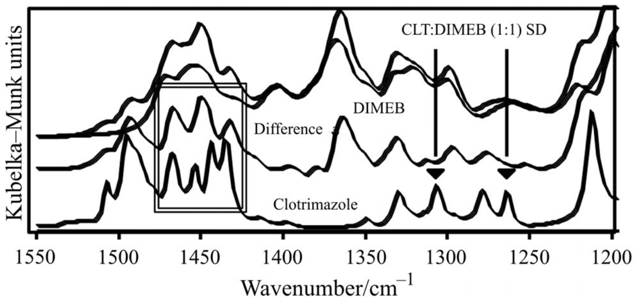

Fig. 9 Infra-red spectra of CLT:DIMEB 1:1 SD

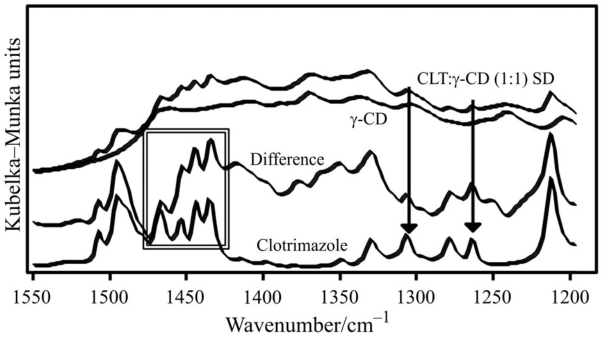

Fig. 10 Infra-red spectra of CLT:γ-CD 1:1 SD

Conclusions

CLT and its SD form melt at 143°C and do not contain any water. In contrast, both γ-CD and DIMEB contain physically bound water, which evaporates up to 130°C. CLT decomposes at 240–250°C, and the thermal decompositions of the CDs start at 260°C.

The PMs are simple powder mixtures (not complexes) which display the characteristic peaks of the two components. The areas of the endothermic peaks of CLT vary in proportion to its ratio in the products. In the PMs and KPs, the water loss varies linearly with the ratio of CD in the product.

The derivatograms of the SDs do not indicate the melting peak which may be a consequence of complex formation.

From the X-ray patterns, it is very clear that both CLT and γ-CD yield series of intensive characteristic peaks. These peaks can also be seen for the PMs and KPs. It is an expected result that the SD product is amorphous.

The FT-IR spectroscopic results are in accordance with the earlier results. The shifts observed by FT-IR spectroscopy also support the thermoanalytical and XRD results.

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This study was supported by the Hungarian National Science Fund (OTKA) (Project number: T 026579) and by the Health Science Council (Project number: T 03250/99). The authors would like to thank Dr. Cs. Novak for his kind contribution.

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