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THERMOANALYTICAL STUDIES ON COMPLEXES OF KETOCONAZOLE WITH CYCLODEXTRIN DERIVATIVES

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Abstract

Inclusion complexation between cyclodextrin derivatives (hydroxypropyl-β-cyclodextrin and methyl-β-cyclodextrin) and a very poorly water-soluble antifungal agent, ketoconazole, was studied. Solid products were prepared by physical mixing, kneading and spray-drying methods in four molecular ratios: 2:1, 1:1, 1:2 and 1:3. The possibility of complex formation between the drug and the cyclodextrins was studied by thermal analysis. Supplementary techniques, such as X-ray diffractometry and Fourier transformation-infrared spectroscopy, were also applied to interpret the results of the thermal study of the products.

Keywords: FT-IR spectroscopy, hydroxypropyl-β-cyclodextrin, ketoconazole, methyl-β-cyclodextrin, thermal analysis, X-ray diffractometry

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides which are able to form complexes with lipophilic drugs or lipophilic parts of drugs, thereby changing their physicochemical and biopharmaceutical properties [1–3]. Giordano *et al.* described the thermal properties of CDs [4]. The thermal analysis of various CDs and their inclusion complexes has been used to differentiate inclusion complexes from adsorbates, and to characterize the special thermal effects due to molecular entrapment during a well-defined, standard heating process [5, 6]. The interaction between ketoconazole (KET) and hydroxypropyl-β-cyclodextrin (HP-β-CD) in the solid-state has already been studied by X-ray diffractometry and differential scanning calorimetry by Esclusa-Diaz *et al.* [7, 8]. Many publications are dealing with thermoanalytical study of drug-CDs inclusion complexes [9–11]. Thermoanalytical methods can be used to

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determine the host-guest ratio, or the water or volatile component content (in *w*/*w*%) in the investigated product, and in the identification of products with a spherical appearance. X-ray diffractometry was utilized to characterize HP-β-CD [12, 13].

The aim of the present study was to examine the possibility of formation of complexes between the KET and CD derivatives by thermal analysis, X-ray diffractometry and FT-IR spectroscopy.

Materials and methods

Materials

Ketoconazole (Fig. 1) [14, 15], *cis*-1-acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-yl-methyl-1,3-dioxalan-4-ylmethoxy]phenyl}piperazine was kindly donated by Ilsan Iltas Pharmaceuticals Co., (Turkey). Hydroxypropyl-β-CD (HP-β-CD), DS: 5.5 was a generous gift from Cerestar, Inc. (USA); methyl-β-CD (MEB), DS: 1.8 was kindly supplied by Wacker-Chemie GmbH (Germany).

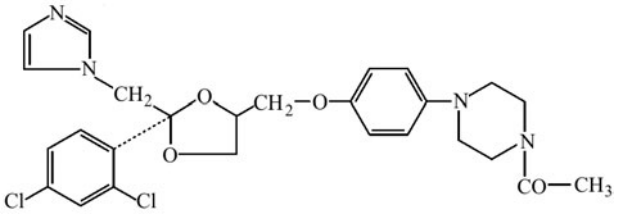

Fig. 1 Chemical structure of ketoconazole

Methods and apparatuses

Products were prepared in host:guest molar ratios of 2:1, 1:1, 1:2 and 1:3, as physical mixed products (PMs), kneaded products (KPs) and spray-dried (SDs). 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 STAR^e thermal analysis system, version 6.0, DSC 821^e (Switzerland), at a heating rate of 5°C min^{-1}, with argon as a 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 apparatus (Hungary). 50 mg of the sample to be investigated was placed in one chamber, and a thermally inert material, aluminium oxide, in another. The studies were carried out under a normal air flow, 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 con-

tained 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 manuplations were performed using GRAMS/386 (Galactic Ind.) running on a HP Vectra VL/50 computer.

Results and discussion

Both KET and the KET SDs melted at around 151°C. The mass loss was very small because of the high stability of KET. The active substance can easily be recognized by means of DSC, DTA, TG and DTG analysis (Fig. 2).

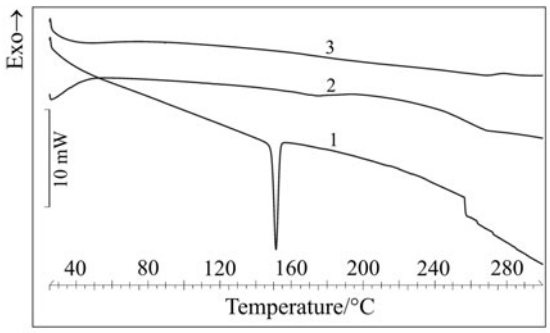

Fig. 2 DSC curves of 1 – KET, 2 – MEB and 3 – HP-β-CD

The CDs are generally marketed as hydrates with differing water contents; this crystal water is lost on heating up to a suitable temperature. The water losses for MEB and HP-β-CD were 2.4 and 6.3%, respectively. Thermal degradation started between 240 and 250°C. DSC analysis gave similar results. The DSC curves were flat at the temperature where KET gives a characteristic endothermic peak (Fig. 2).

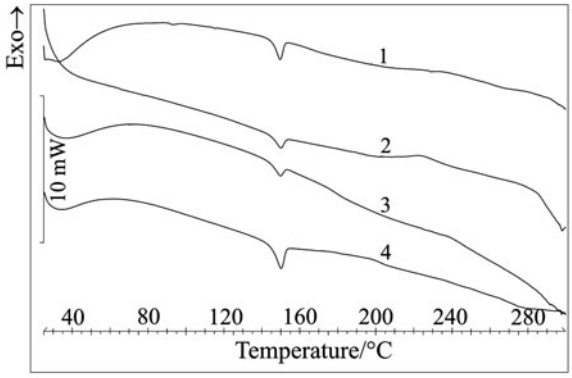

Fig. 3 DSC curves of 1 – KET:HP-β-CD 1:3 PM, 2 – KET:HP-β-CD 1:2 PM, 3 – KET:HP-β-CD 1:1 PM and 4 – KET:HP-β-CD 2:1 PM

The PMs of KET:HP-β-CD prepared in molecular ratios of 2:1, 1:1, 1:2 and 1:3 gave similar thermal results. From the DSC and DTA plots, the water loss ranged between 2.6 and 5.6% and the characteristic endothermic peak of KET could be recognized (Fig. 3). The DSC plots of the PMs were approximately the same as the superposition of those of the raw materials and the areas of the endothermic peaks decreased as the CD concentration was increased. Accordingly, no or at most partial complex formation is expected.

The KPs displayed a similar tendency to that for the PMs. The water losses from the 1:1 and 1:2 KPs prepared with HP-β-CD can be seen in the DSC plots (Fig. 4). The lowest water loss was detected for the 2:1 KP, this product containing the smallest proportion of the CD. The results paralleled the TG curves, where the water loss ranged between 2.2 and 6.3%. Degradation started at around 240°C. The peak area decreased with increasing quantity of CD. The disappearance of the endothermic peak for the 1:3 KP may be attributed to the inclusion of the drug in the HP-β-CD cavity.

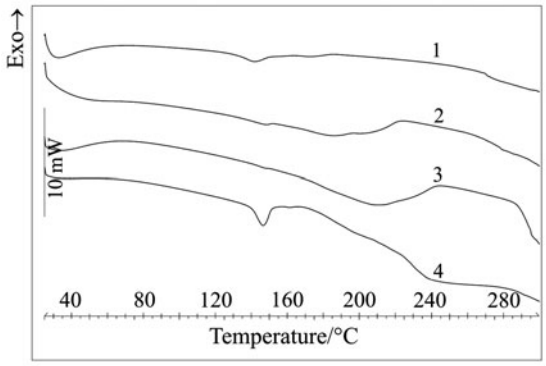

Fig. 4 DSC curves of 1 – KET:HP-β-CD 1:1 KP, 2 – KET:HP-β-CD 1:2 KP, 3 – KET:HP-β-CD 1:3 KP and 4 – KET:HP-β-CD 2:1 KP

Total complex formation may be assumed for the 1:1 and 1:2 SDs as these have amorphous structures. The view that the SDs may be inclusion compounds and not simple PMs, was based upon the result that the endothermic peak due to the phase transition profile of KET is not observed for products thought to involve inclusion compounds. The water losses from these SDs were 5.2 and 4.8%, respectively. In the case of KET, an amorphous structure was formed only with the spray-drying technique. The melting enthalpy decreased from 144 to 100 J g^{-1}, following spray-drying.

The PMs and KPs with ratios of 1:1 and 1:2 prepared with MEB gave similar results to those for the products prepared with HP-β-CD (Fig. 5). Complex formation could not be recognized from the DSC curves, which supports the idea that a proportion of the KET molecule is free and out of the CD cavity.

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

$$\text{Uncomplexed–guest\%} = \frac{\Delta H_i}{\Delta H_0 c} 10^4$$

where ΔH_i – normalized integral data on the product, ΔH_0=normalized integral data on the active ingredient and c – percentage active ingredient in the product.

Table 1 Percentage assumed uncomplexed guest in the products

Product	Uncomplexed–guest%
KET:HP-β-CD (2:1) PM	11.8
KET:HP-β-CD (1:1) PM	76.0
KET:HP-β-CD (1:2) PM	43.0
KET:HP-β-CD (1:3) PM	85.2
KET:HP-β-CD (2:1) KP	80.8
KET:HP-β-CD (1:1) KP	66.5
KET:HP-β-CD (1:2) KP	11.5
KET:HP-β-CD (1:3) KP	7.60
KET:HP-β-CD (1:1) SD	0
KET:HP-β-CD (1:2) SD	0
KET:MEB (1:1) PM	5.44
KET:MEB (1:2) PM	49.7
KET:MEB (1:1) KP	60.6
KET:MEB (1:2) KP	11.2

More evidence of complex formation was obtained by FT-IR spectroscopic investigation of the bands of the functional groups of KET involved in the complexation. The spectrum of the KET:HP-β-CD (1:3) KP prepared by using pharmaceutical grade

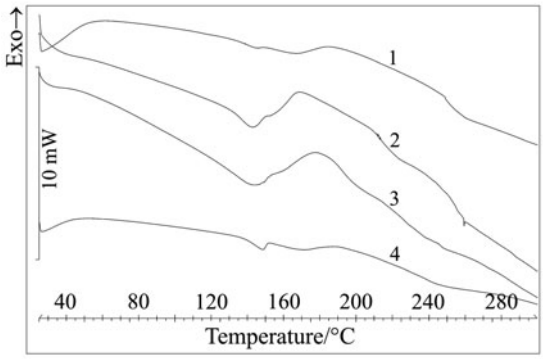

Fig. 5 DSC curves of 1 – KET:MEB 1:2 KP, 2 – KET:MEB 1:1 KP, 3 – KET:MEB 1:1 PM and 4 – KET:MEB 1: 2 PM

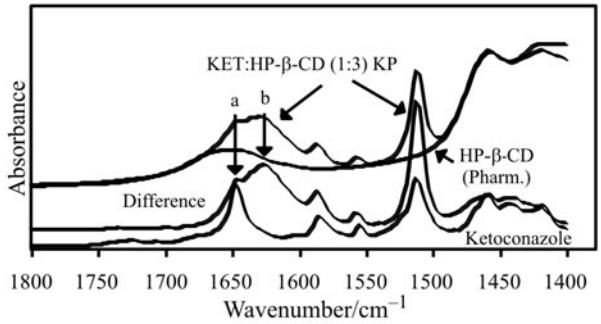

Fig. 6 Infra-red spectra of KET:HP-β-CD 1:3 KP

HP-β-CD is presented in Fig. 6. The amide-I band at 1646 cm^{-1}, in the spectrum of KET diminished considerably and a new broadened band was observed at 1626 cm^{-1}.

This was clear indication of the interaction through the C=O part of the amide group, since the C=O stretching vibration made a higher contribution to the amide-I normal mode besides the N–H bending. The other modes of the amide group were influenced to a lesser extent. The amide-II band at 1554 shifted only to 1557 cm^{-1}, while the amide-III band at 1291 cm^{-1} did not shift at all, like all the other bands of KET. These changes provided further evidence in support of bonding through the C=O group (the amide-II band is dominated by N–H bending and amide-III band by C–N stretching of the group).

The changes in the KET bonding caused an increase in intensity of the amide-I band on the higher wavenumber side when HP-β-CD of industrial origin was used (Fig. 7). On the other hand, the peak of non-bonded KET was found at a much lower KET concentration (Fig. 8).

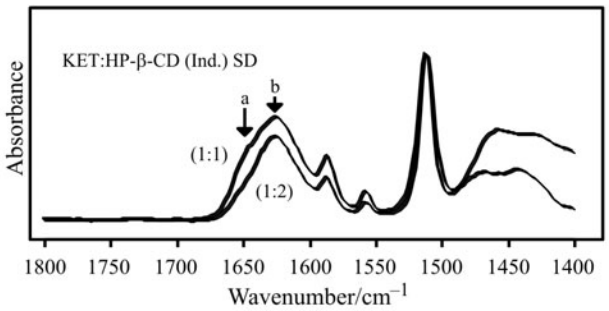

Fig. 7 Infra-red spectra of KET:HP-β-CD 1:1 SD and KET:HP-β-CD 1:2 SD

The above differences can be explained by differences between the HP-β-CDs of various origins in the region of the glycopyranose rings as depicted in Fig. 9. The higher intensities of the peaks in the interval 1200–1000 cm^{-1} indicated that the HP-β-CD of pharmaceutical origin was in a more crystalline state than the other one. The bonding sites were much better defined, but lower in number than those of the industrial grade HP-β-CD. The less crystalline HP-β-CD had bonding sites with vari-

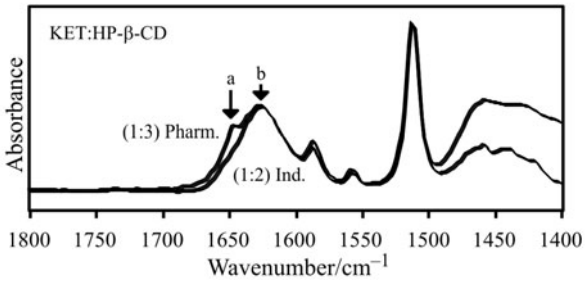

Fig. 8 Infra-red spectra of KET:HP-β-CD 1:3 KP and KET:HP-β-CD 1:2 KP

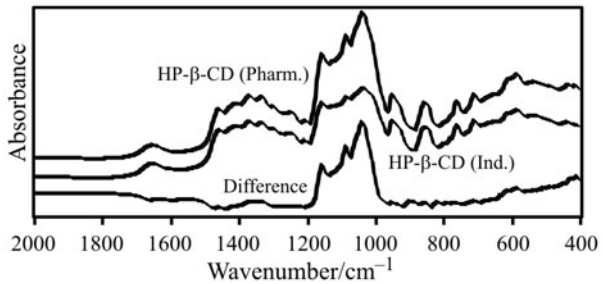

Fig. 9 Comparison of the infra-red spectra of HP-β-CDs of industrial and pharmaceutical grade

ous bonding abilities so that amide-I band gradually shifted to higher wavenumbers while the more or less uniform sites of the pharmaceutical grade HP-β-CD led to bands with the same shift and the excess appeared in the same state as for pure KET.

X-ray powder diffraction can elucidate the nature of the host-guest interactions in crystalline CD inclusion compounds. The changes in the powder crystallinity of the samples were studied by comparing their diffraction patterns.

The XRD patterns of KET, HP-β-CD and the KET:HP-β-CD (1:2) system are presented in Fig. 10. The diffractogram of KET (1) exhibited a series of intense

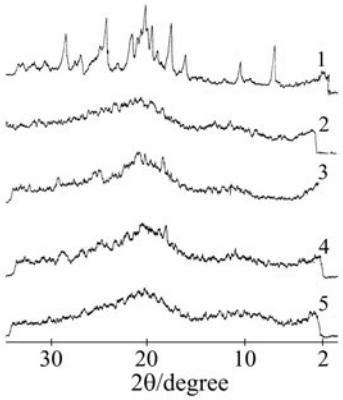

Fig. 10 X-ray diffraction patterns of 1 – KET, 2 – HP-β-CD, 3 – KET: HP-β-CD 1:2 PM, 4 – KET: HP-β-CD 1:2 KP and 5 – KET: HP-β-CD 1:2 SD

peaks, which is indicative of its crystalline character. HP-β-CD hardly displayed characteristic peaks (2).

The X-ray diffraction pattern of the KET:HP-β-CD PM (3) was practically identical to the superposition of the spectra of the individual components, indicating that no new structure was formed. When the pattern of the PM was compared with that of the KP (4), a very small modification in crystallinity was observed. The crystallinity of KET was nearly the same in the KP and PM. This crystallinity phenomenon may be due to the formation of KET:HP-β-CD mixed crystalline particles. The absence of any peak in the HP-β-CD diffractograms revealed the amorphous nature of this compound.

The KP presented a diffraction pattern quite similar to that of the PM, whereas the SD displayed fewer and less intense peaks (5). This reduction in crystallinity was obvious in the amorphous SD.

These results may point to an interaction between KET and HP-β-CD in the SD products, suggesting the presence of a new solid phase with lower crystallinity than that of the drug with the possible complexation of KET inside the HP-β-CD cavity.

Conclusions

KET and HP-β-CD or MEB may form inclusion complex(es). To study this phenomenon, different products in molecular ratios of 2:1, 1:1, 1:2 and 1:3 were prepared by physical mixing, kneading and spray-drying. The possibility of interaction (inclusion complex formation) between the components was studied by using thermoanalytical methods, X-ray diffractometry and FT-IR spectrometry.

In the case of KET, an amorphous structure was formed only with the spray-drying technique. The melting enthalpy decreased from 144 to 100 J g^{-1}, following spray-drying.

As concerns the KET:HP-β-CD 1:1 and 1:2 SDs, we are not sure whether inclusion complexes are formed or not, as the spray-drying procedure leads to an amorphous structure. However, as the solutions before spray-drying are clear, and the spray-drying procedure is fast (>0.01 s), there is no time for crystallization and we assume complex formation by spray-drying.

The X-ray diffractometric pattern (5) of the SD product shows an amorphous structure. In contrast, the characteristic peak can still be recognized at 2θ=18° for the PMs and KPs.

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References

1 R. A. Rajewski and V. J. Stella, J. Pharm. Sci., 85 (1996) 1142.
2 T. Loftsson and M. Brewster, J. Pharm. Sci., 85 (1996) 1017.
3 K. Uekama, F. Hirayama and T. Irie, Chem. Rev., 98 (1998) 2045.

4 F. Giordano, Cs. Novák and J. R. Moyano, Thermochim. Acta, 380 (2001) 123.
5 B. Pose-Vilarnovo, C. Rodríguez-Tereiro Sánchez, M. B. Pérez-Marcos and J. J. Torres-Labandeira, J. Therm. Anal. Cal., 68 (2002) 657.
6 N. Morin, A. Chilouet, J. Millet and J. C. Rouland, J. Therm. Anal. Cal., 62 (2000) 187.
7 M. T. Esclusa-Díaz, M. Guimaraens-Méndez, M. B. Pérez-Marcos, J. L. Vila-Jato and J. J. Torres-Labandeira, Int. J. Pharm., 143 (1996) 203.
8 M. T. Esclusa-Díaz, J. J. Torres-Labandeira, M. Kata and J. L. Vila-Jato, Eur. J. Pharm. Sci., 1 (1994) 291.
9 J. Szejtli, Cyclodextrin Technology. Kluwer Academic Publ., Dordrecht–Boston–London 1988.
10 K.-H. Frömming and J. Szejtli, Cyclodextrins in Pharmacy. Kluwer Academic Publ., Dordrecht 1994.
11 M. D. Veiga, M. Merino, D. Fernandéz and R. Lozano, J. Therm. Anal. Cal., 68 (2002) 511.
12 C. M. Fernandes, M. T. Vieira and F. J. B. Veiga, Eur. J. Pharm. Sci., 15 (2002) 79.
13 G. Bettinetti, Cs. Novák and M. Sorrenti, J. Therm. Anal. Cal., 68 (2002) 517.
14 Martindale, The Extra Pharmacopoeia, 32nd Ed., London, The Pharmaceutical Press, 1999.
15 The Merck Index, 11th Ed., Merck & Co., Inc., Rathway, NJ, USA, 1989.