Solid-state Characterization of Bifonazole – beta-cyclodextrin Binary Systems. II

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Continuing our previous researches, this paper presents the studies regarding the solid state characterization of binary systems between antimycotic bifonazole and beta-cyclodextrin. The binary systems were prepared in two (bifonazole : beta-cyclodextrin) molar ratios, 1:2 and 1:3, using the physical mixture and the kneading method. In order to characterize the solid state interaction between the two components, hot-stage microscopy, differential scanning calorimetry, X-ray diffractometry and Fourier-transformed infrared spectroscopy were used. The analysis performed indicate a molecular interaction between the components due to a partially encapsulation of bifonazole into the cyclodextrin cavity.

Keywords: bifonazole, beta-cyclodextrin, inclusion complex

Cyclodextrins are torus-shaped cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic central cavity which can interact with appropriately sized molecules to form inclusion complexes [1]. Cyclodextrin complexation may improve some physicochemical properties of drugs and bioavailability [1-3]. Bifonazole (BIF) is an imidazole derivative with antimycotic activity [4], practically insoluble in water [5], which is a major drawback for obtaining pharmaceutical formulations of optimal bioavailability [2,3,6]. Beta-cyclodextrin (β-CD) is a natural cyclodextrin composed of 7α-(1,4) linked D-glucopyranose units [7]. Hydrophilic cyclodextrins, including beta-cyclodextrin, are able to improve the local drug release and delivery, by increasing the aqueous solubility of drug in the formulation and by increasing the availability of free drug molecules at the membrane surface [3,7]. The preparation of solid-state cyclodextrin inclusion complexes can be carried out by many simple procedures, two of them being the physical mixture and the kneading method [1]. The powder obtained by these methods may be a true homogenous inclusion complex, or a mixture of complex, uncomplexed guest and cyclodextrin [8, 9]. Different analytical techniques are used to characterize the host-guest interaction and the formation of inclusion complex: thermal analyses, X-ray diffractometry, and Fourier-transformed infrared spectroscopy, these techniques being able to provide the detection of inclusion complexes [10-13].

Continuing our previous researches, the complexation of bifonazole with beta-cyclodextrin was characterized in solid state, using the hot-stage microscopy (HSM), differential scanning calorimetry (DSC), X-ray diffractometry and Fourier-transformed infrared spectroscopy (FT-IR). The binary systems between bifonazole and beta-cyclodextrin were prepared in two molar ratios, 1:2 and 1:3 (bifonazole : cyclodextrin), using the physical mixture and the kneading method.

Experimental part

Materials and methods

Bifonazole (1-[(R,S)-biphenyl-4-yl)phenylmethyl]-1-H-imidazole) was kindly provided by Gedeon Richter S.A. (Târgu Mureş, Romănia). β-cyclodextrin was purchased from Cyclolab R&D (Budapest, Hungary). Other chemical reagents were of analytical grade purity requested by the European Pharmacopoeia 7th ed [5] and by the Romanian Pharmacopoeia 10th ed. [14].

Preparation of the binary systems. In order to prepare the physical mixtures (PM), the components were mixed in a mortar and sieved through a 100 μm sieve; for the kneaded products (KP) the physical mixtures of BIF and β-CD were mixed with the same quantity of a 50 % ethanolic solution. The obtained paste was kneaded until the bulk of the solvent had evaporated. After drying at room temperature and then in the oven at 105 °C, the KP were pulverized and sieved through a 100 μm sieve. The molecular ratio of the products were 1:2 and 1:3 BIF : β-CD. The products were stored at room conditions [15].

Thermal analysis

The temperature and enthalpy measurements were performed with a Mettler Toledo STAR Thermal Analysis system, version 6.0 (Schwerzenbach, Switzerland). Approximately 2-5 mg of active material or binary systems was examined between 25-300 °C in argon flow (10 L/h). The heating rate was 5 °C/min (and the Argon flow rate was 10 L/ h.)

The relative degree of crystallinity (RDC) of BIF in the PM and KP samples, as a percentage of the BIF mass fraction, was calculated according to the relation [16,17]:

$$BIF_{RDC} = 100 \cdot \frac{\Delta H_{binary\ system}}{\Delta H_{uncomplexed\ BIF}}$$

HSM analysis was performed with a hot-stage thermomicroscope LEICA MZ6, (LEICA Microsystems, Swiss).

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X-ray powder diffractometry. The X-ray spectra were recorded with a DRON UM-1 diffractometer (Russia) with $CuK_{\alpha 1}$ radiation (λ=1.54051A°) over the 2Ĉ within 2-44 degrees. The measurement conditions were : Cu target, Ni filter, as follows: target, Cu; filter, Ni; 35 kV acceleration potential, 20 mA current, 1 s time constant, angular range of $2° < 2\Theta < 44°$, and angular step of 0.030°.

Fourier-transformed infrared spectroscopy

The IR spectra of BIF, β-CD and their binary systems were recorded using a FT-IR 670 Plus, Able Jasco (Japan) spectrometer. The resolution was 4 cm^{-1},the wave number range was 2000-400 cm^{-1} and the scan number was 64. The samples were included in KBr pallet. Analyses were performed at room temperature.

Results and discussions

Differential scanning calorimetry

As shown in our previous research, BIF presents a sharp endothermic peak at 150 °C and the thermogram of β -CD reveals a dehydration process between 40-110°C, corresponding to a broad endothermic effect [15]. Table 1 presents the melting temperatures, the specific melting enthalpies and the RDC values determined from the DSC analysis of the binary systems.

All the binary systems reveal a very fine shifting of the melting temperatures, observed also in our previous research [15]. The values of the melting enthalpies and of the RDC decrease with increasing the amount of β-CD in the binary system. All these results may be an index of dispersion of the crystals of BIF in the matrix of β-CD [8,9,16,17].

Table 1
RESULTS OF DSC ANALYSIS OF BIF AND OF BINARY SYSTEMS WITH β-CD AND THE RDC OF BIF IN THE BINARY SYSTEMS

Sample	T_{peak} (°C)	ΔH (Jg^{-1})	BIF_{RDC} (%)
BIF	150.89	-118.2	100%
PM 1:2	150.38	-10.47	8.86
PM 1:3	149.81	-7.38	6.24
KP 1:2	150.26	-11.73	9.92
KP 1:3	150.15	-7.8	6.6

Hot-stage microscopy

The HSM analysis was used to compare the crystalline states of BIF and β-CD with the crystalline states of the binary systems. As mentioned in our previous research, BIF melts at 145 °C and the melting of β-CD takes place at 200°C [15]. The analysis was performed at 25°C and 145 °C. The results of HSM analysis for the binary systems are presented in figures 1 (A-D) for the PM and in figure 2 (A-D) for the KPs.

Analyzing the HSM photomicrographs of all binary systems, one can notice the presence of some free crystals of BIF, which melt at 145 °C.

The results of HSM analysis support the hypothesis of molecular interaction between BIF and β-CD in all types of binary systems.

X-ray analysis

Bifonazole and β-CD present a crystalline structure, revealed by many sharp characteristic peaks in their diffractograms [15]. In our previous research, we pointed that the most intense peaks of BIF in its diffractogram correspond to the following values of the 2Θ angle: 15.9682, 18.5322, 19.3698, 21.3330 [15].

The diffractograms of PM and KP are presented in figure 3 (A-D). Analyzing the diffractograms and the results of X-ray analysis of the binary systems, one can notice the disappearance or the reduction of the intensities of some characteristic peaks of BIF.

Analyzing the diffraction patterns of the binary systems, the X-ray analysis provided the detection of inclusion complexation.

FT-IR spectroscopy

As shown in our previous study, the FT-IR spectra of BIF reveal numerous absorbtion bands in the fingerprint region and the spectrum of β-CD reveals a wide absorbtion band attributed to the glucopyranosic ring, in the 1200- 1000 cm^{-1} region [13]. For the binary systems, to reveal the modification of spectra due to complexation the 1600-1800 cm^{-1} domain was chosen. The PM and KP spectra are presented in figure 4.

Similar observation with our previous research could be revealed by the IR spectra of the binary systems: the appearance of some new absorbtion bands and the shift of other absorbtion bands in the 1100-800 cm^{-1} region and the disappearance of the characteristic absorbtion bands of BIF in the 1600-1100 cm^{-1} region.

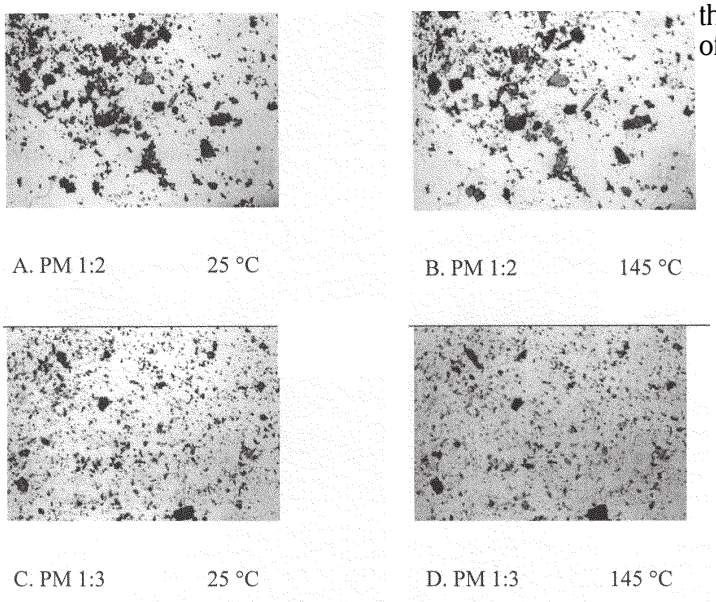
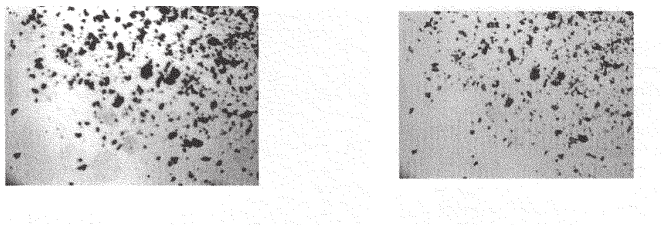


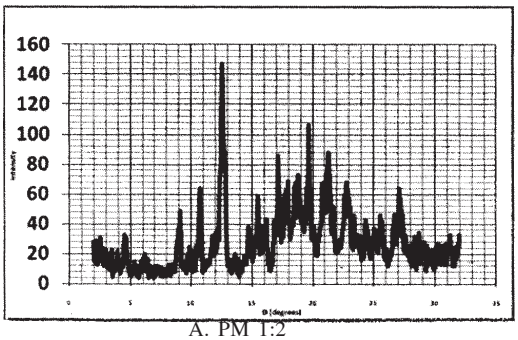
Fig. 1 (A-D). HSM photomicrographs of crystals of PM products



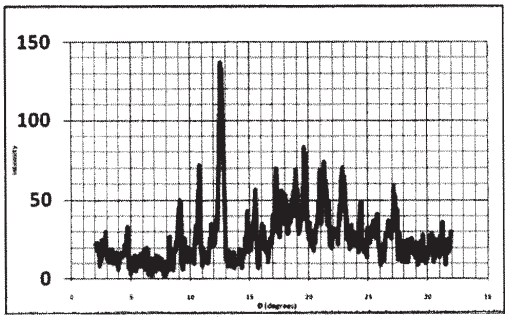
A. KP 1:2 25 °C B. KP 1:2 145 °C

C. KP 1:3 25 °C D. KP 1:3 145 °C

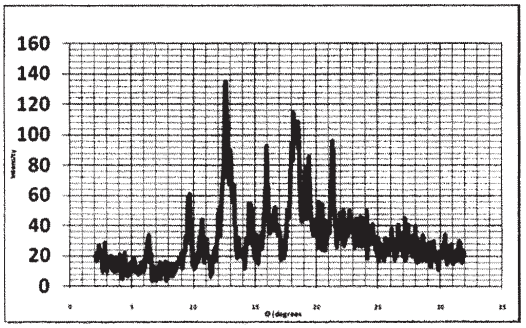
Fig. 2. (A-D). HSM photomicrographs of crystals of KP products



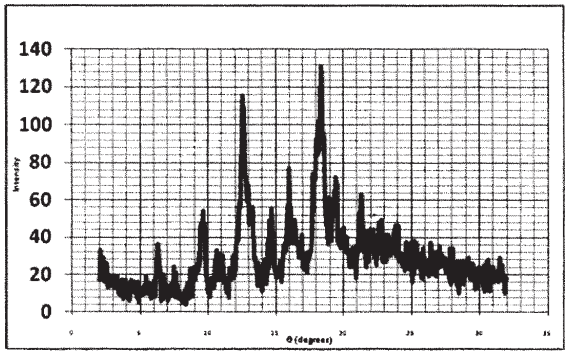
A. PM 1:2



B. PM 1:3

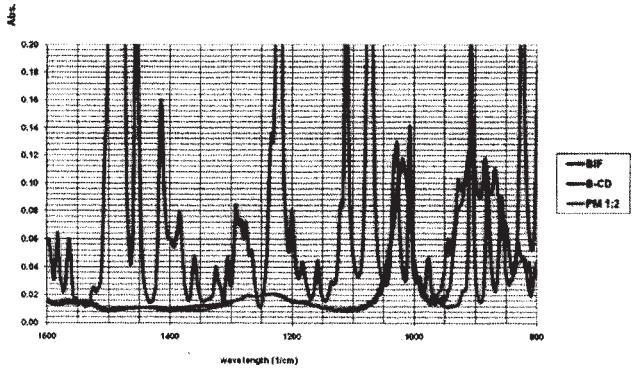


C. KP 1:2

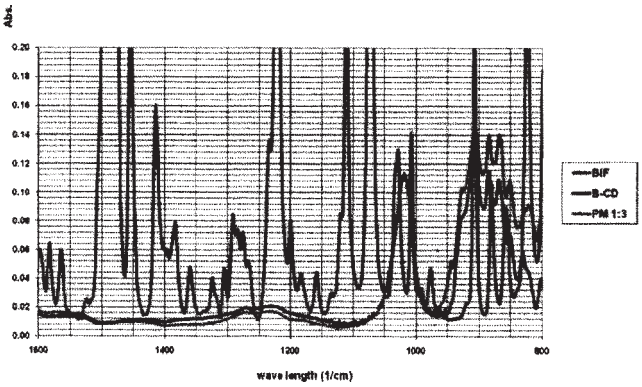


D. KP 1:3

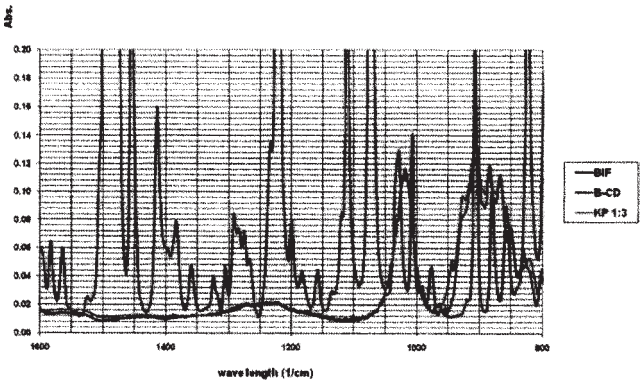
Fig. 3 (A-D). X-ray diffractograms of physical mixtures and kneaded products



A. PM 1:2

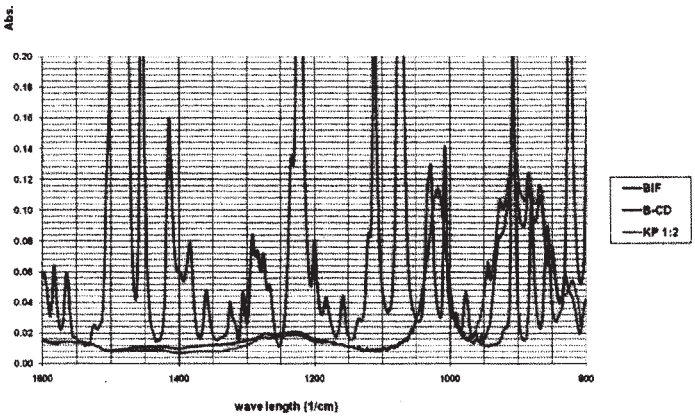


B. PM 1:3



C. KP 1:2

Fig. 4 (A-C). The FT-IR spectra of the PM and KP



D. KP 1:3

Fig. 4 (D). The FT-IR spectra of the KP

Conclusions

Binary systems between antimycotic bifonazole and β-CD were prepared in two molar ratios, using two simple laboratory methods. The formation of a true complex between the components was investigated by thermal and spectral methods.

The X-ray diffractometry and the FT-IR analysis provide the detection of the inclusion complexation, in terms that the diffraction and the IR spectra of the binary systems were not the superimposition of individual diffraction and IR spectra patterns.

The DSC analysis point at the formation of a new solid phase due to a molecular interaction between BIF and β-CD, suggested by the shifting of the melting peak of the guest and the reduction of the melting enthalpies values, observed in the thermograms of the binary systems.

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