

SOLID-STATE CHARACTERIZATION OF BIFONAZOLE - RANDOM METHYL-BETA-CYCLODEXTRIN BINARY SYSTEMS

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Abstract

The aim of this paper was to investigate the interaction in solid state between the antimycotic agent bifonazole with random methyl- β -cyclodextrin. The binary systems between bifonazole and random methyl- β cyclodextrin were prepared in four molar ratios, by two methods. The interaction between the components was characterized by thermal and spectral methods.

Rezumat

Scopul acestei lucrări a fost investigarea interacțiunii în stare solidă dintre agentul antimicotic bifonazol și β -ciclodextrina metilată aleator. Sistemele binare dintre bifonazol și această ciclodextrină au fost preparate în patru rapoarte molare, utilizând două metode. Interacțiunea dintre componente, în sistemele binare, a fost caracterizată prin metode termice și spectrale.

Keywords: bifonazole, random methyl- β -cyclodextrin, hot-stage microscopy, X-ray diffractometry

Introduction

The hydrophobic nature of bifonazole is a major drawback for its use to treat local fungal infections [3,4]. Cyclodextrins are cyclic oligosaccharides used in the pharmaceutical field to enhance the bioavailability of drugs, due to their property of forming inclusion complexes [2]. An important demand for the use of an inclusion complex in

practice, is the understanding of the interaction between the host molecule and the guest molecule in the complex [1,3].

The purpose of this work was to examine the interaction in solid state between the antimycotic agent bifonazole (BIF) and random methyl- β -cyclodextrin (RAMEB) using hot-stage microscopy analysis (HSM), which gives important data about the complexation, and X-ray analysis which is frequently used to clarify the nature of the new crystalline state obtained by complexation.

Heating-induced drug-cyclodextrin interaction during HSM and differential scanning calorimetry analysis may lead to a loss of drug crystallinity even in physical mixture products, but this phenomenon can not be seen during the X-ray analysis [5-7,10].

Materials and Methods

Bifonazole (BIF) (1-[(R,S)-biphenyl-4-yl]phenylmethyl]-1-H-imidazole) was kindly provided by Gedeon Richter S.A. (Târgu Mureș, România). Random methyl- β -cyclodextrin (RAMEB) (DS~12) was purchased from Cyclolab R&D (Budapest, Hungary). Other chemical reagents were of analytical grade purity requested by the Romanian Pharmacopoeia 10th Ed. [12] and by the European Pharmacopoeia 7th Ed [11]. HSM analysis was performed with a hot-stage thermomicroscope LEICA MZ6, (LEICA Microsystems, Swiss). The X-ray data were collected using a DRON UM-1 diffractometer (Russia).

The binary systems between BIF and RAMEB were obtained in four molar ratios 2:1, 1:1, 1:2 and 1:3, using the physical mixture method and the kneaded method, by techniques described in our previous publications [8,9].

Results and Discussion

Using the HSM analysis we compared the crystalline state of BIF and of RAMEB at the temperature of 25 °C and at 145 °C, with the crystalline state of the binary products.

In figures 1, 2 and 3, the results obtained by HSM analysis are presented. BIF melts at 145 °C, while at this temperature RAMEB does not exhibit any modification of its crystalline structure, its melting beginning at 180°C. For the physical mixture products (PM) 2:1 and 1:1, the presence of free crystals of BIF was observed, which melt at 145°C, while for the PM 1:2 and 1:3 this phenomenon was not observed. For the kneaded products (KP) with molar ratios 2:1 and 1:1, the melting of BIF was revealed at

145°C, while for the KP 1:2 and 1:3 no modification in the crystallinity of the binary system was revealed.

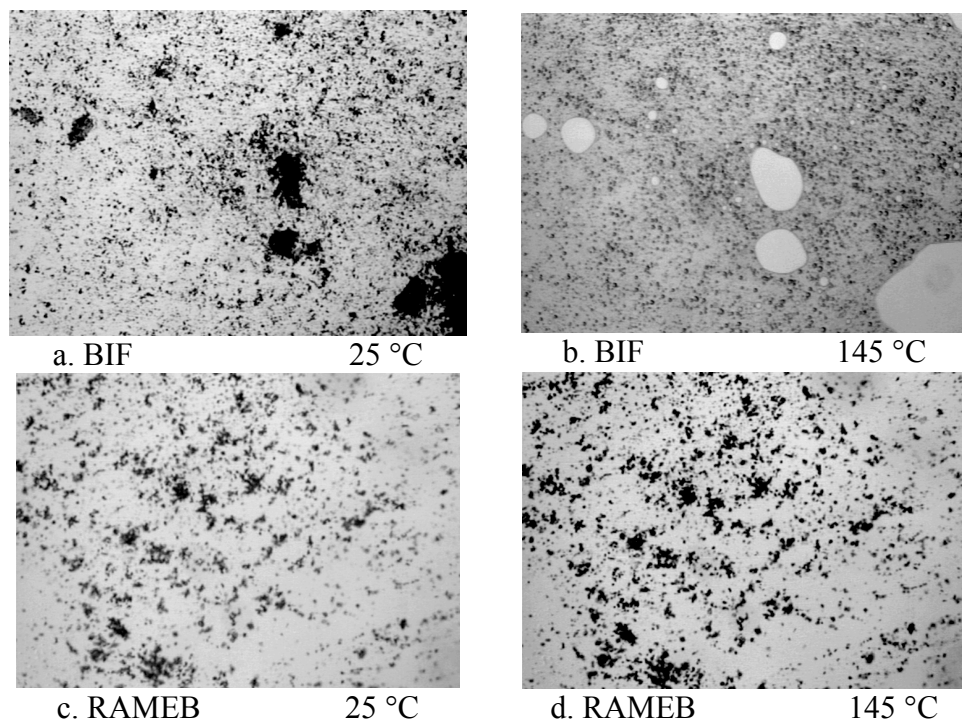


Figure 1 (a-d).
Photomicrographs of crystals of bifonazole and RAMEB
taken during the HSM analysis

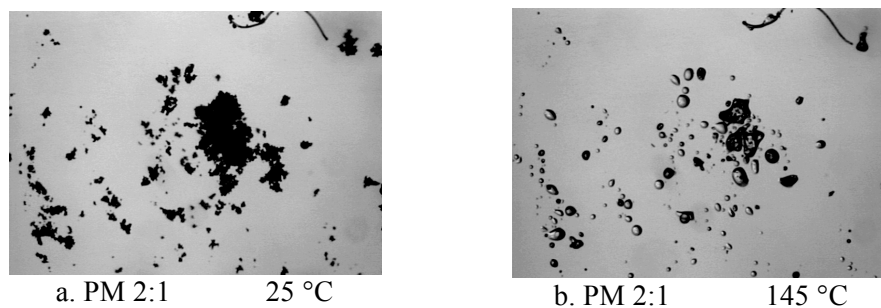
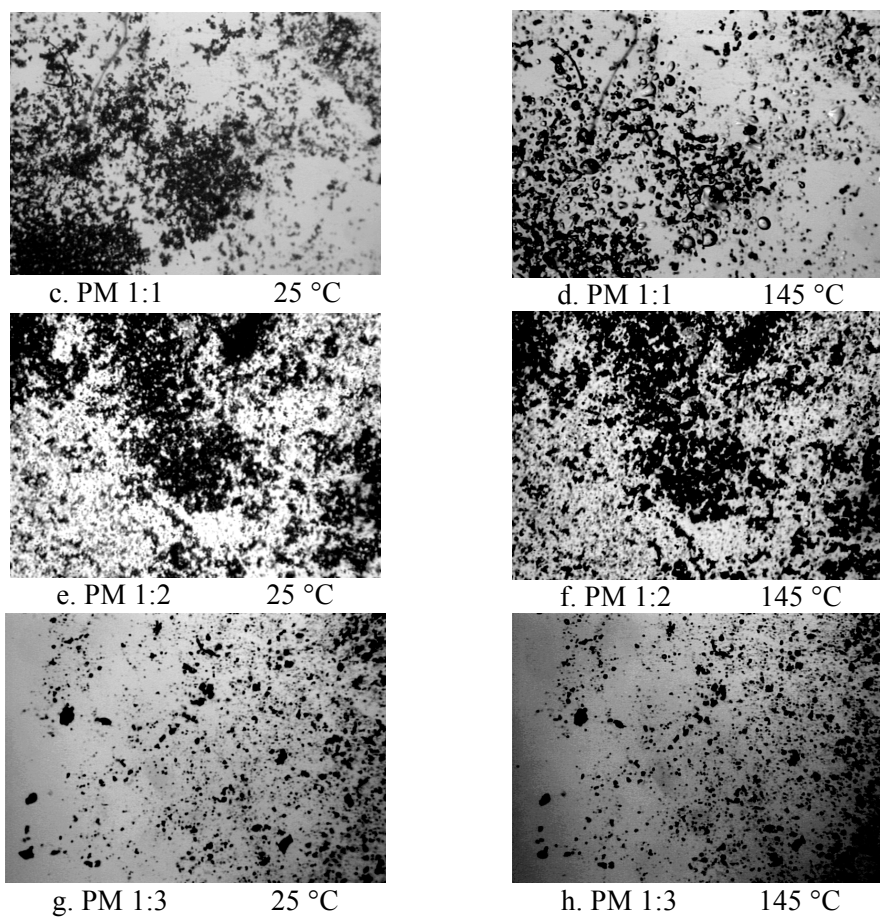
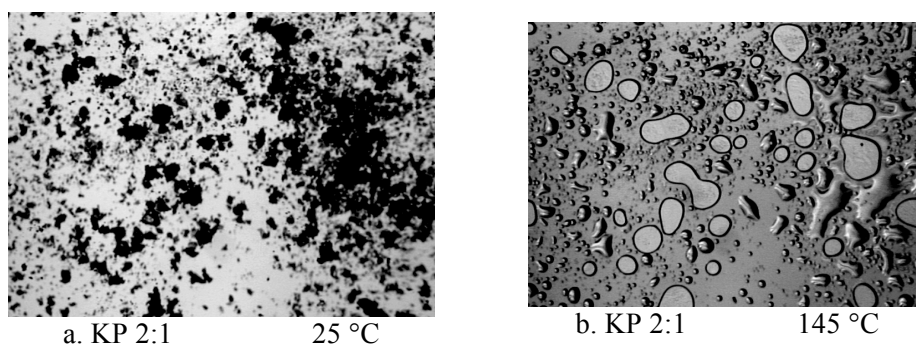
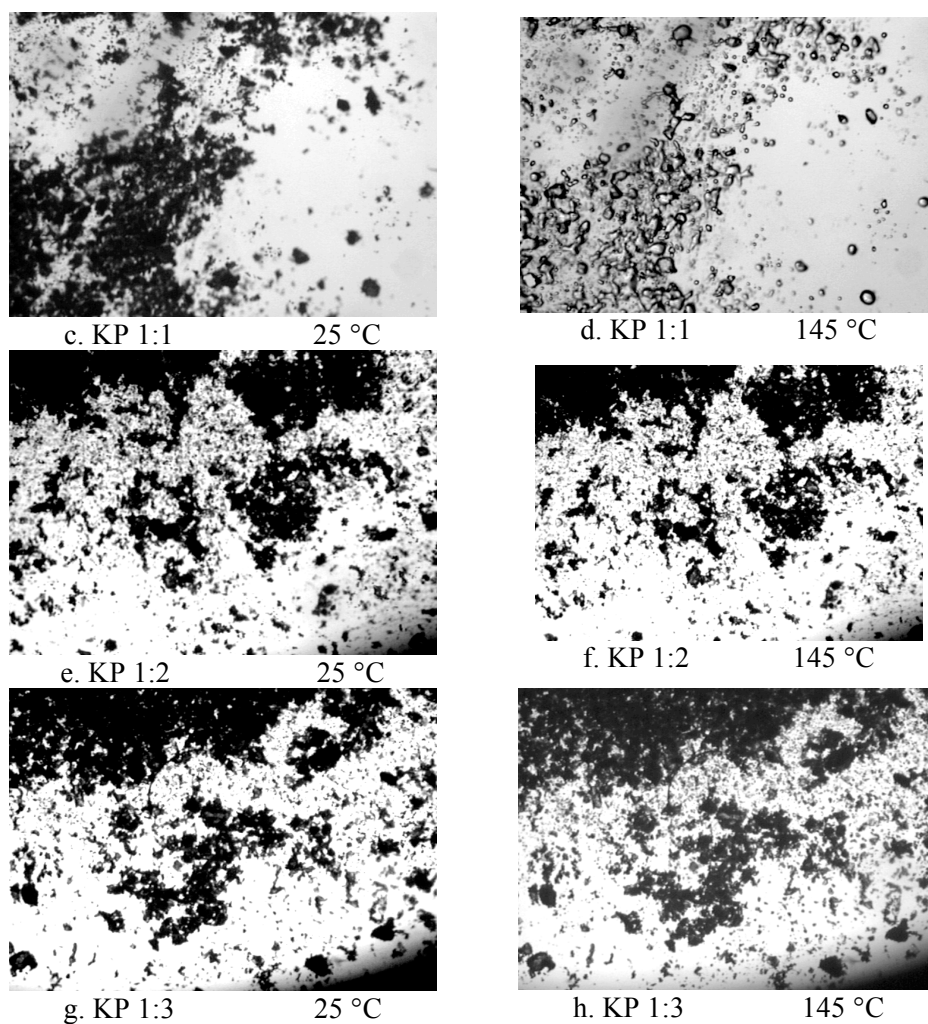


Figure 2 (a-b)
Photomicrographs of crystals of the PM mixture products taken during the HSM
analysis

**Figure 2 (c-h)**

Photomicrographs of crystals of the PM taken during the HSM analysis



**Figure 3 (c-h)**

Photomicrographs of crystals of the KP taken during the HSM analysis

The PM and the KP in 1:2 and 1:3 molar ratios, presented a different melting temperature as compared to pure BIF, indicating a molecular interaction between the components. These data are collected in Table I.

Table I

The melting temperatures of the PM and KP of BIF and RAMEB

Binary system	PM 1:2	PM 1:3	KP 1:2	KP 1:3
Melting temperature (°C)	165	160	160	165

In the figures 4 and 5 the X-ray diffractograms of binary systems are presented. Bifonazole has a crystalline structure, and the X-ray diffractogram reveals a series of characteristic peaks, while the X-ray diffractogram of RAMEB is characteristic for its amorphous structure [9].

For the PM 2:1 and 1:1 a strong decrease and the disappearance of some characteristic peaks of BIF was observed, while in case of the PM 1:2 and 1:3 products the amorphisation is of a higher degree [9].

For the KP 2:1 an evident loss of drug crystallinity is observed, and an almost complete amorphous state of the samples, for the KP 1:1, as well as for the 1:2 and 1:3 is observed [9].

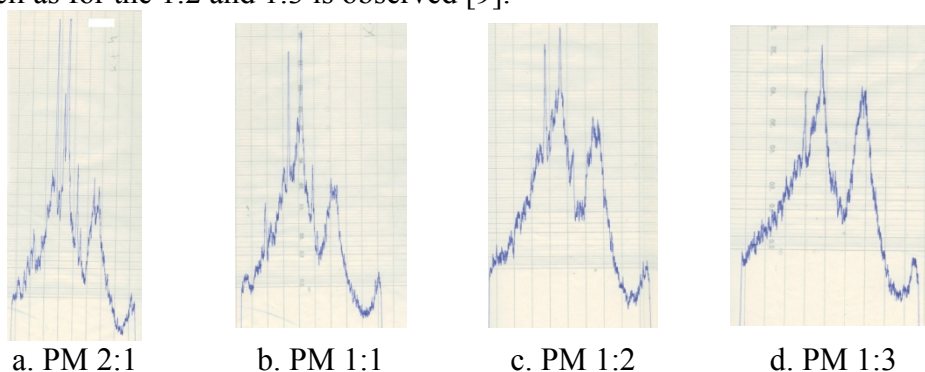


Figure 4 (a-d)
X-ray diffractograms of PM

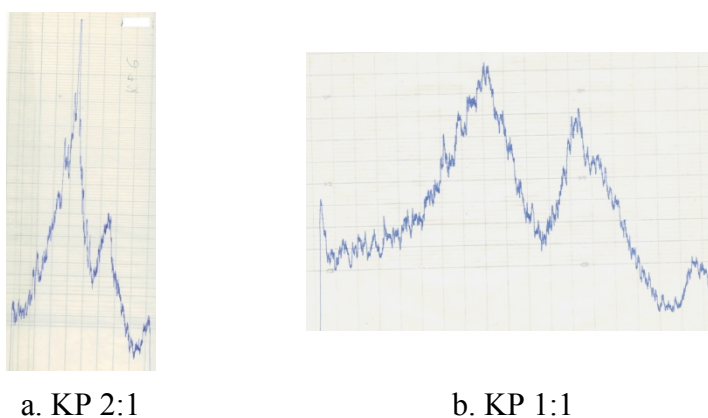
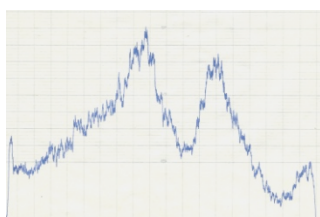
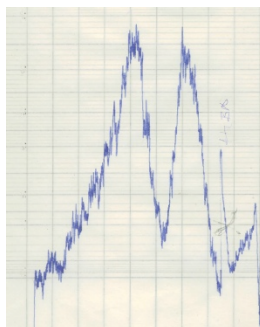


Figure 5 (a-b)
X-ray diffractograms of KP



c. KP 1:2



d. KP 1:3

Figure 5 (c-d)
X-ray diffractograms of KP

Conclusions

The hot-stage microscopy (HSM) of the binary systems of bifonazole (BIF) with random methyl- β -cyclodextrin revealed the remarkable ability of this cyclodextrin to establish molecular interactions in solid state with bifonazole, as seen in the case of PM (mixture products) and KP (kneaded products) 1:2 and 1:3, and the phenomenon of partial drug complexation in the case of PM and KP 2:1 and 1:1.

These results are strongly sustained by the X-ray spectra which revealed the important capacity of RAMEB in modifying the crystalline state of BIF and amorphisation, and support the hypothesis of forming molecular interactions between the components, in solid state.

The study also underlines the efficiency of the kneaded method, easily reproducible, in obtaining the products with the best results.

Acknowledgements

The Project named "TÁMOP-4.2.1/B-09/1/KONV-2010-0005 - Creating the Center of Excellence at the University of Szeged" is supported by the European Union and co-financed by the European Regional Fund.

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Manuscript received: March 20th 2011