

INVESTIGATION OF THE BINARY SYSTEMS OF ALBENDAZOLE WITH HYDROXYPROPYL-BETA-CYCLODEXTRIN

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REZUMAT

A fost studiat efectul hidroxipropil- β -ciclodextrinei asupra solubilității antihelminticului albendazol. În acest scop, au fost preparate sisteme binare formate din albendazol și hidroxipropil- β -ciclodextrină, în două raporturi molare și au fost determinate profilele de solubilizare a acestora în suc gastric și suc intestinal artificial. Interacțiunea dintre albendazol și hidroxipropil- β -ciclodextrină în soluție și în stare solidă a fost studiată utilizând studiul solubilității de fază și analiza termică.

Cuvinte cheie: albendazol, hidroxipropil- β -ciclodextrină, solubilitate, calorimetrie cu scanare diferențială, studiul solubilității de fază

ABSTRACT

The effect of hydroxypropyl- β -cyclodextrin on the solubility of antihelminthic albendazole was studied. Binary systems containing albendazole and hydroxypropyl- β -cyclodextrin were prepared in two molar ratios and the solvation profiles of the binary systems in both simulated gastric medium and intestinal medium, were determined. Albendazole-hydroxypropyl- β -cyclodextrin interactions in both aqueous solution and in the solid state were studied by phase solubility study and thermal analysis.

Key Words: albendazole, hydroxypropyl- β -cyclodextrin, solubility, differential scanning calorimetry, phase solubility study

INTRODUCTION

Albendazole (ABZ) is a benzimidazole anti-helminthic drug with a broad spectrum of activity. (Fig. 1) Albendazole is practically insoluble in water, which limits its oral bioavailability for the treatment of systemic helminthiasis.^{1,2}

Cyclodextrins are cyclic (α -1,4)-linked oligo-saccharides formed of α -D-glucopyranose units, that are known to be able to form inclusion complexes with lipophilic drugs or lipophilic moieties of drugs, thereby changing the physicochemical and biopharmaceutical properties of drugs.^{3,4}

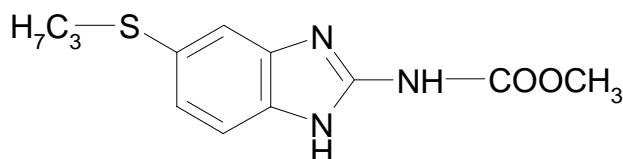


Figure 1. Structural formula of albendazole.

Complex formation between ABZ and hydroxypropyl- β -cyclodextrin (HP-BCD) may result in increased water solubility and bioavailability of the drug molecule.⁴⁻⁶

Binary systems containing ABZ and HP-BCD were prepared in 1:2 and 1:3 molar ratios and their solvation profiles in simulated gastric medium (SGM) and intestinal medium (SIM) were determined. The interaction between ABZ and HP-BCD was characterized by phase solubility study and by differential scanning calorimetry.^{4,7,8}

MATERIALS AND METHODS

- Albendazole, methyl[5-(propylsulphonyl)-1-H-benzimidazol-2-yl]carbamate (Biesterfeld Siemgluess, Hamburg, Germany);
- Hydroxypropyl- β -cyclodextrin (Cyclolab, Budapest, Hungary);

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- The solvents used are of analytical grade requested by the Romanian Pharmacopoeia 10th Ed., and by the European Pharmacopoeia 5th Ed;⁹

- ERWEKA solvation apparatus with modified paddle (Germany);

- UNICAM UV/VIS spectrophotometer with vision software V 3.40 (Unicam Limited, Cambridge, England);

- METTLER TOLEDO type STARe Thermal analysis system, version 6.0 (Schwerzenbach, Switzerland).

Preliminary experiments

The absorption maximum of ABZ was determined spectrophotometrically in SGM (292) and SIM (296) and they were not modified by the presence of HP-BCD. The calibration plot revealed that absorption obeys the Bouguer-Lambert-Beer law in the concentration interval 2-12 µg/ml. The transformation coefficients were 0.043 for SGM and 0.053 for SIM.

Preparation of binary systems

Binary systems were prepared in 1:2 and 1:3 molar ratios (drug : cyclodextrin).

Physical mixtures (PM): the components were homogenized in a mortar with a pestle and sieved through a 100 µm sieve.

Kneaded products (KP): physical mixtures of ABZ and HP-BCD were mixed with the same quantity of methanol-water (1:1) mixture and they were kneaded until the evaporation of the bulk of the solvent mixture. After drying at room temperature and in the oven at 105°C, the products were pulverized and sieved through 100 µm sieve.

Study of the solvation properties

The solvation studies were carried out using the Erweka solvation apparatus with modified paddle, with a rotation speed of 100 rpm, at 37±1°C. The study was performed in triplicate, in 100 ml simulated gastric medium and simulated intestinal medium.

0.5 g ABZ and the binary systems containing 0.5 g ABZ were added to 100 ml of SGM/SIM. Sampling was performed after 5, 10, 15, 30, 60, 90 and 120 min. The volume of each sample was 5 ml and after each sampling, the withdrawn volume of the sample was replaced with the same volume of medium. The ABZ concentration was determined spectrophotometrically, at 292 nm in case of SGM and at 296 nm in case of SIM.

The solvation profiles of the binary systems were compared with those of ABZ.

Thermal analysis

The thermal behaviors of ABZ, HP-BCD and each binary system were examined by using the differential scanning calorimetry. Approximately 2-5 mg of active material was examined between 25°C - 300°C. The heating rate was 5°C /min and the argon flow rate was 10 l/h.

Phase solubility study

Solubility diagrams were developed using the Higuchi and Connors method. An excess of ABZ was added to SGM and SIM containing various concentrations of the HP-BCD (0, 1, 25, 50, 100, 150 mM). The suspensions were shaken at room temperature for 7 days, then filtered through a Millipore cellulose acetate membrane filters. The concentration of the dissolved drug was measured by UV spectrophotometry. The phase solubility study was performed in triplicate.

The apparent solubility constant of the complex, $K_{1:1}$, was calculated from the initial straight-line portion of the solubility diagram, according to the following equation:

$$K_{1:1} = \frac{tga}{S_0} (1 - tga)$$

where S_0 represents the intrinsic solubility of ABZ, without cyclodextrin.^{2,9}

RESULTS AND DISCUSSIONS

Study of the solvation properties

The solvation profiles of ABZ and of the binary systems between ABZ and HP-BCD in SGM are presented in Figure 2 and in SIM are presented in Figures 3 and 4.

The concentration of dissolved ABZ in SGM is larger than the concentration in SIM, due to the basic character of the molecule of ABZ.

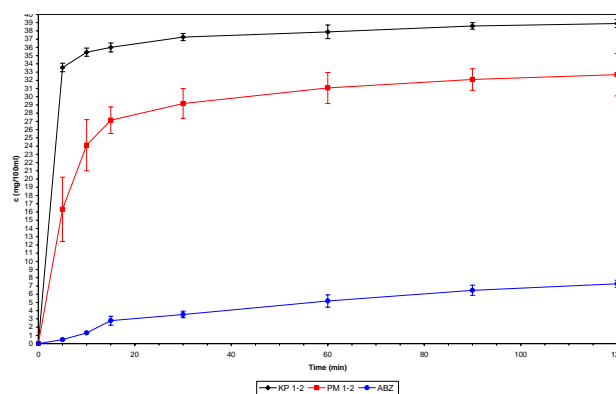


Figure 2. The solvation profiles of albendazole, the physical mixture products (PM) and the kneaded products (KP) in SGM.

As Figure 2 reveals, the preparative method improves the solubility of ABZ in SGM, the best results are achieved by KP. In case of 1:2 products, after 120 minutes, for PM, the quantity of dissolved ABZ is approximately four times higher and for KP, the quantity of solvated ABZ is approximately five times higher, as compared to the pure ABZ. In case of KP, the quantity of dissolved ABZ in the first 5 minutes, is two times higher as compared to PM.

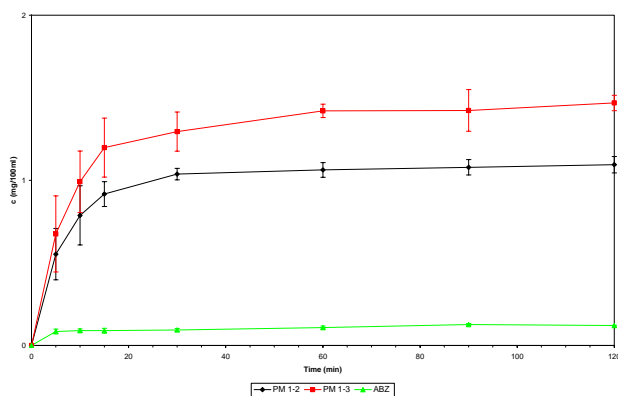


Figure 3. The solvation profiles of albendazole and the physical mixture products (PM) in SIM.

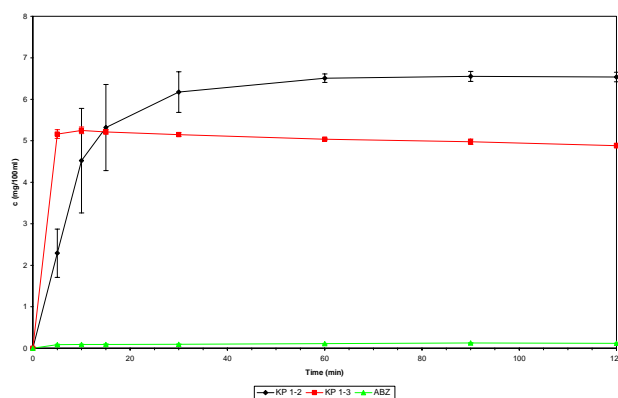


Figure 4. The solvation profiles of albendazole and the kneaded products (KP) in SIM.

In SIM the preparative method also influences the solvation properties of ABZ. (Figs. 3,4) For the same molar ratio, the best results are obtained for KPs. For PM 1:2, the quantity of dissolved ABZ is 9 times higher and for PM 1:3, the dissolved quantity of ABZ is 12 times higher, as compared to the pure ABZ. (Fig. 3) For KPs, the increase of the molar ratio at 1:3, does not improve the solvation of ABZ. The rate of solvation is higher in case of KP 1:3, in the first 5 minutes almost the entire quantity of ABZ is dissolved. For KP 1:2, the quantity of dissolved ABZ increases for approximately 55 times.

Thermal analysis

The DSC curve of ABZ reveals an endothermic peak at 195.93 °C, due to the melting of the substance.

(Fig. 5) The DSC curve of HP-BCD shows its thermal decomposition which begins around 280°C. (Fig. 6)

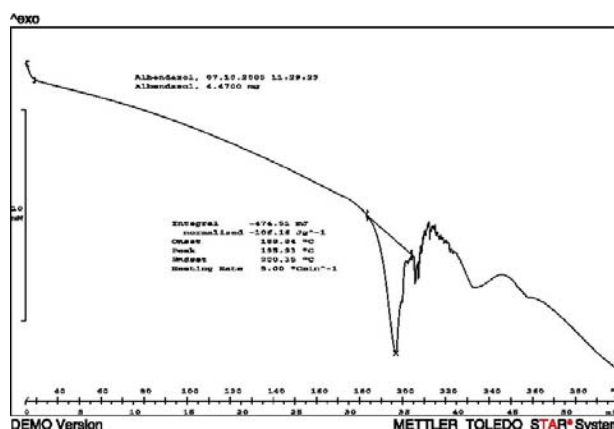


Figure 5. DSC of albendazole.

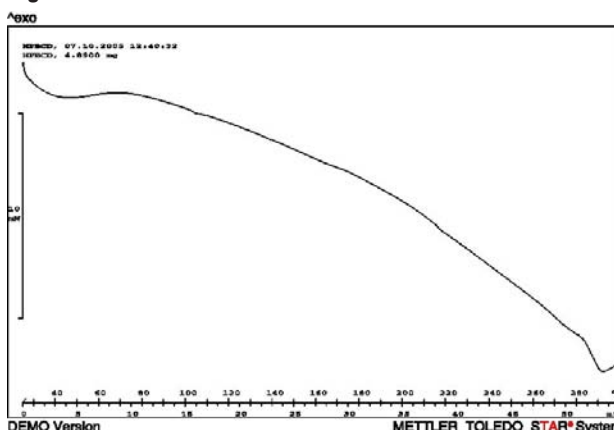


Figure 6. DSC of HP-BCD.

Thermal curves of the PMs show the typical ABZ melting endotherm peak, which shifts to lower temperature values. For PM 1:2 the peak temperature is 193.36°C and for PM 1:3, the peak temperature is 194.30°C. (Figs. 7,9)

Endothermic peaks appear in the DSC curves of KPs, and their characteristic temperature values are lower as compared to the peak temperature of pure ABZ. For KP 1:2 the characteristic peak temperature is 192.68°C and for KP 1:3 the peak temperature is 194.39°C. (Figs. 8,9)

The down-shift of the peak temperature can be considered as a consequence of an increasing interaction between the components. Marked reduction of area and broadening of the peak temperature of 1:2 products as compared with the 1:3 products, indicate a more evident loss of drug crystallinity.

Phase solubility studies

The phase solubility diagrams of ABZ in SGM and SIM are presented in Figures 10 and 11. In both cases, the diagrams are of type AL, according to the classification introduced by Higuchi and Connors.^{2,7}

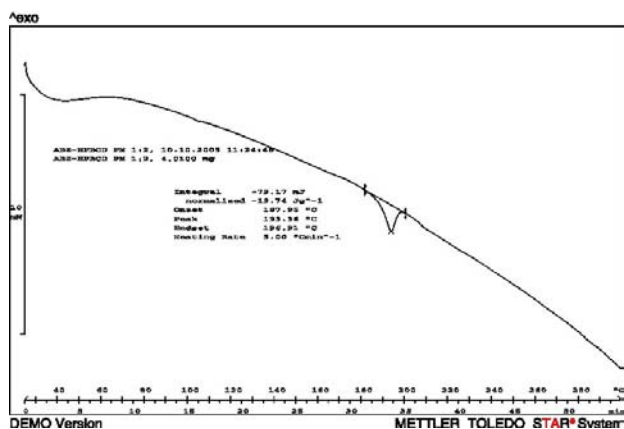


Figure 7. DSC of physical mixture 1:2.

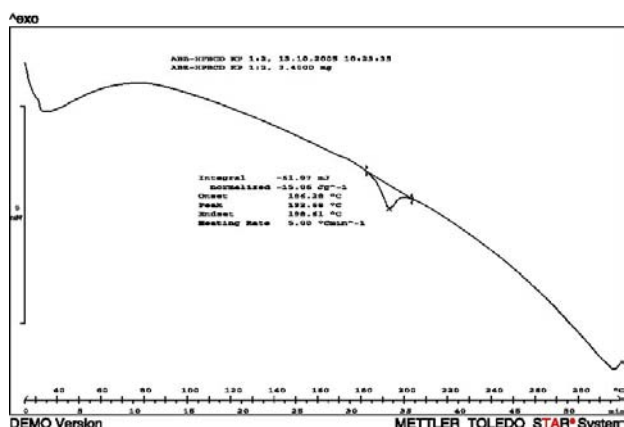


Figure 8. DSC of kneaded product 1:2.

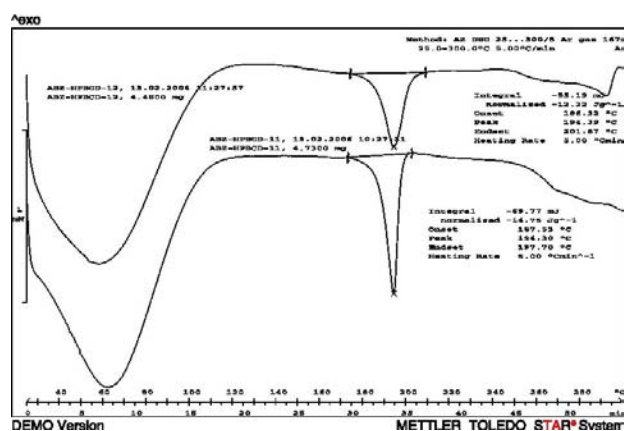


Figure 9. DSC of PM (ABZ-HPBCD-11) and of KP (ABZ-HPBCD-12) 1:3.

This indicates that, within the studied cyclodextrin concentration range, soluble ABZ-HP-BCD complexes are formed. The slope of the initial ascending part of the solubility diagram is less than one, indicating that the stoichiometry of the complex is 1:1. The values of S_0 and of the apparent stability constants are indicated in Table 1.

Table 1. The values of the intrinsic solubilities (S_0), of $tg\ \alpha$ and of the apparent stability constants of ABZ in SGM and in SIM.

Binary system	S_0	$tg\ \alpha$	$K_{1:1}$
ABZ-HP-BCD in SGM	2.54596	0.3104	176.805
ABZ-HP-BCD in SIM	0.01896	0.0051	270.37

The value of the apparent stability constant in SIM is higher than the value of the apparent stability constant of ABZ-HPBCD in SGM, indicating a better interaction between ABZ and HP-BCD in SIM.

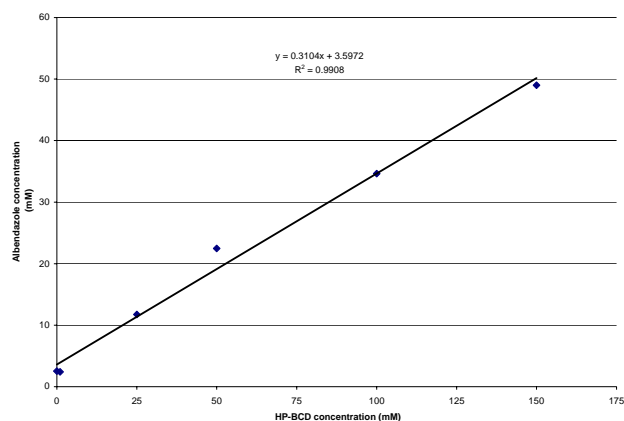


Figure 10. Phase solubility diagram of ABZ-HP-BCD in SGM.

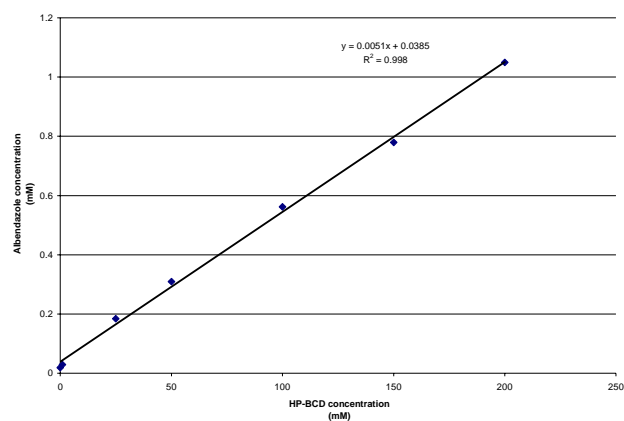


Figure 11. Phase solubility diagram of ABZ-HP-BCD in SIM.

CONCLUSIONS

On the basis of the obtained results, one can conclude:

- Hydroxypropyl- β -cyclodextrin exerts a favorable effect of improving the solubility properties of albendazole.
- The solubility of albendazole increases in simulated gastric medium and intestinal medium, in the presence of HP-BCD.
- The molar ratio and the preparative method of the binary systems, influences the solubility and solvation rate of albendazole.
- The differential scanning calorimetry confirmed a possible partial interaction between the two components, similarly to the case of a true inclusion complex.
- The phase solubility studies indicate the possibility of formation of soluble complexes, in the cyclodextrin concentration range taken into consideration.
- As a detail of the results, one may observe a descending part in the solvation curve presented

in Figure 4. A possible account for this unusual phenomenon seems to be related to the technique of adding a corresponding volume of pure solvent after each sampling. If theoretically, in a successive pure solvent addition variant, the curve should have a final horizontal plateau, practically the curve may show a descending evolution, because of successive dilutions of bulk solvation medium. One may expect that this phenomenon be more evident in the case of the samples with marked solubility.

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