ENHANCED WATER-SOLUBILITY OF ALBENDAZOLE BY HYDROXY-PROPYL-β-CYCLODEXTRIN COMPLEXATION

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ABSTRACT

The inclusion complexation of methyl (5-(propylthio)-1*H*-benzimidazol-2-yl) carbamate, albendazole (ABZ) with 2-hydroxypropyl-β-cyclodextrin (HPβCD) in water was investigated with a view to improving the low aqueous solubility of the drug. The combination of albendazole and HPβCD in a molar ratio of 1/10 resulted in a significant increase in the aqeous solublity of the drug, up to 3500 times. Albendazole/HPβCD complexes could be recommended as a parenterally administered formulation because of its good solubility properties and the safety of the cyclodextrin used.

1. INTRODUCTION

Albendazole (Figure 1) belongs to a group of benzimidazol derivatives with a broad spectrum of activity against human and animal helminthe parasites such as nematodes, metacestodes and hydatoses [1, 2]. These potential anthelmintic effects of ABZ, its relatively good tolerance and its low cost explain its wide use against veterinary and human parasites for more than two decades. However, the low water solubility of the drug (0.2 μg/ml at pH 7.4) is one of the limiting factors for its bioavalability. In some cases, high-dose therapy by the oral route then becomes necessary ,which could lead to adverse reactions such as gastro-intestinal disturbances and liver impairment [3, 4]. Futhermore the correct intake of doses is critical especially in veterinary medicine.

The improvement of water solubilty of ABZ by utilizing hydrophilic cyclodextrin appears to be one solution to these problems. Some authors carried out a complexation of ABZ with dimethyl-β-cyclodextrin [5]. In this study, we report the combination of ABZ and hydroxypropyl-β–cyclodextrin to achieve inclusion complexes which could be used in injectable formulations.

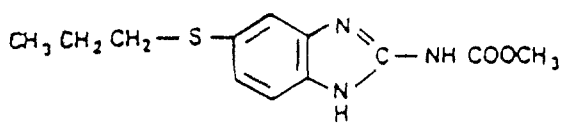

Fig. 1 Chemical structure of albendazole

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2. MATERIALS AND METHODS

2.1. Materials

Albendazole was supplied by Smith, Kline & French (France). 2-hydroxypropyl-β-cyclodextrin (BETA W 7 HP 0,9) was purchased from Wacker Chimie SA (Lyon, France). All other materials were of analytical grade.

2.2. Methods

2.2.1. Solubility studies and complex preparation

Solubilities of ABZ were determined by adding an excess amount of the drug (66 mg) to 25 ml of aqueous solutions containing increasing concentrations of HPβCD. Typically, seven samples of the following molar ratios ABZ/HPβCD were prepared: 1/2, 1/4, 1/6, 1/8 and 1/10. The suspensions formed were stirred at 37 °C for at least 6 days, after which equilibrium is reached. After cooling to 25 °C, the suspensions were filtered through a 0.45 μm membrane filter (Millipore HVLP). The supernatants were suitably diluted in water (HCl 0.1 M) and analyzed spectrophotometrically at 230 nm.

Preparation of the complex was carried out in the same way, with a molar ratio of 1/10 for ABZ and HPβCD respectively. 0.25 mmol of ABZ was suspended in 25 ml of aqueous solution containing 2.5 mmol of HPβCD. The suspension was also stirred for 6 days, but at a higher temperature (55 °C) than for the solubility studies. The supernatant obtained as described above was freeze-dried in order to give a solid state complex.

2.2.2. Characterization of the complex

The complex was studied by UV-spectrophotometry using a Varian UV-VIS spectrophotometer (Cary/1E). Circular dichroism spectra were observed using a Jobin Yvon Mark V spectrometer. An appropriate quantity of the solid inclusion compound of ABZ/HPβCD (6.55 mg ABZ per gramme of complex) was dissolved in distilled water to obtain a mother solution of 1.5 mg ABZ per ml. This solution was filtered through a 0.45 μm membrane filter and the filtrate was diluted 10 times with distilled water prior the UV and circular dichroism studies. An equivalent quantity of physical mixture ABZ/HPβCD was treated in the same way.

3. RESULTS AND DISCUSSION

3. 1. Solubility

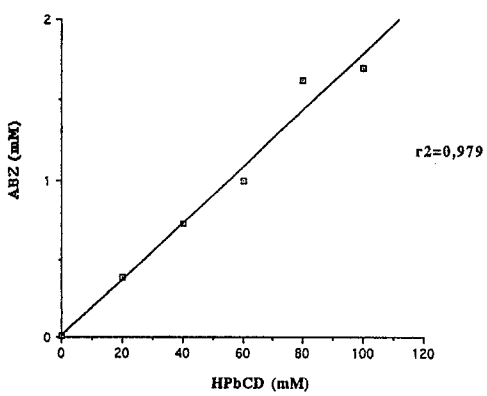

Fig. 2 The phase-solubility diagram of ABZ in aqueous HPβCD at 37 °C

The phase-solubility diagram of ABZ (Figure 2) appeared to be linear and could correpond to the type A, which mean a soluble inclusion is probably formed.

3.2. Characterization of ABZ/HPβCD complex

The interaction of ABZ with HPβCD in the liquid phase was first examined by UV-spectrophotometry. The spectra displayed in Figure 3 show a strong peak at about 220 nm and one very weak peak at 240 nm, which probably correspond to the absorbance of ABZ. The intensity of absorbance is higher for the inclusion compound than for the physical mixture, indicating a possible interaction between ABZ and HPβCD.

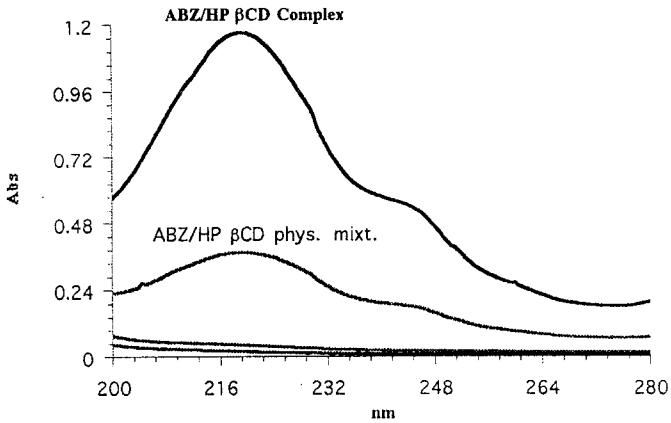

Fig. 3 UV-spectrum of ABZ/HPβCD complex and physical mixture

In the circular dichroism spectrum (Figure 4), a relatively strong broad negative peak is detected at about 220 nm. As in the UV spectum, the modification of dichroic spectrum is more important in the case of the complex.

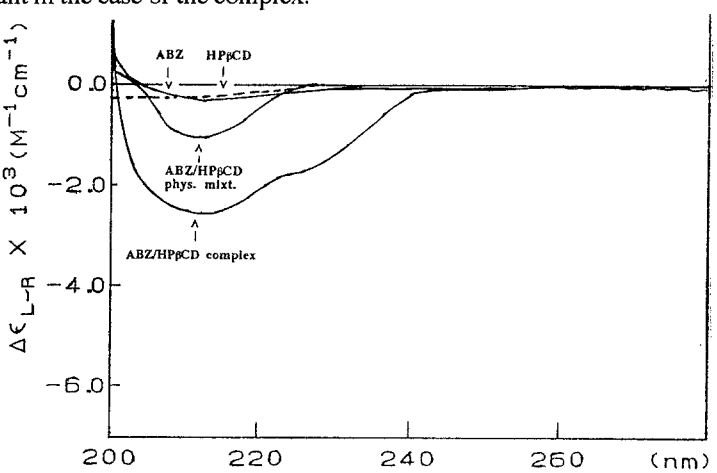

Fig. 4 Circular dichroism spectra of ABZ in the presence and absence of HPβCD

The increase in apparent solubility of ABZ, and the results of UV-spectrophotometry and circular dichroism obviously suggest the possible interaction of ABZ with the cavity of HPβCD.

The solubility study of ABZ from the solid complex (molar ratio of 1/10 ABZ/HPβCD) performed at 25 °C showed that 745 μg was rapidly dissolved in 1 ml of distilled water. Owing to the low water solubility of this drug, 0.2 μg/ml phosphate buffer, pH 7.4 [6], it could be assumed that the complex affords a significant solubility enhancement of ABZ, up to a 3500 times increase in solubility.

Recently, a pharmacokinetic study of albendazole was reported in swine following the oral administration of the drug suspended in water. One of their main conclusions was that albendazole displays very large differences on absorption, metabolism and elimination [7]. It seems obvious that the poor water solubility of the drug plays a role on the discrepancy observed. The combination of albendazole with hydrophilic cyclodextrins to give an aqueous solution of the drug could be beneficial for both oral and parenteral formulations.

CONCLUSION

The noticeable water solubility enhancement for albendazole could be obtained by its complexation with 2-HPβCD in the appropriate molar ratio 1/10. The good solubility of the complex makes possible the preparation of solutions for both oral and parenteral administration of the drug.

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