SOLUBILIZATION OF BIFONAZOLE IN THE PRESENCE OF CARBOXYMETHYLATED-β-CYCLODEXTRIN

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Recently, many technological methods of enhancing the solubility and dissolution characteristics of poorly water soluble drugs have been reported in the literature. Cyclodextrins are able to form water-soluble non-covalent inclusion complexes with many poorly soluble lipophilic drugs. The purpose of this study is to evaluate the possibility of interaction of the antifungal drug Bifonazole (BFZ) through complexation with carboxymethylated-β-cyclodextrin (KM-β-CD). Based on the data obtained, we can conclude that the presence of KM-β-CD improves solubilization of BFZ more than 50 times.

Keywords: cyclodextrins, solubility, poorly-water soluble drugs, bifonazole

Currently, many technological approaches of enhancing the solubility and dissolution characteristics of poorly water soluble drugs have been reviewed in the literature. However, conventional methods used to prepare these systems suffer from serious limitations on their applicability in the market, often involving physical instabilities of the solid dispersions on storage, problems of grinding or difficulties in removing the toxic organic solvent [1]. The therapeutic effectiveness of a drug depends on its bioavailability and ultimately on the solubility of the drug molecule. Usually, only solubilized molecules can be absorbed by the cellular membrane to reach the specific site of drug action. So, now much attention is paid to the ability of cyclodextrins (CD) to form inclusion complexes with various organic substrates. Cyclodextrins are able to form water-soluble non-covalent inclusion complexes with many poorly soluble lipophilic drugs of proper size and polarity, leading to changes in their physicochemical and biopharmaceutical properties, which enhance their solubility, dissolution rate, chemical stability and bioavailability and reduce their side effects and toxicity. Cyclodextrins are also able to form non-inclusion complexes, aggregates and micelle-like structures, which also effectively solubilize poorly-water soluble drugs [2, 3].

Bifonazole (BFZ) ((RS)-1-[phenyl(4-phenylphenyl)methyl]-1H-imidazole) (Fig. 1) is a substituted imidazole antifungal agent that is structurally related to other drugs from the azole group. It possesses a broad spectrum of activity in vitro against dermatophytes, molds, yeasts, dimorphic fungi, and some Gram-positive bacteria [4]. It has a double mechanism of action as it works by preventing the 14-α-demethylation of 24-methylene-dihydrolanosterol, consequently preventing the formation of the cellular membrane by inhibiting the production of ergosterol, and also causes direct damage to the membrane [5]. It also shows an anti-inflammatory effect on erythema caused by histamine [6, 7].

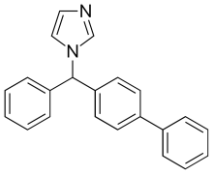

Fig. 1. Constitutional formula of BFZ

Due to the imidazole cycle, BFZ is a basic compound (pKa 9.30), and due to the presence of the aromatic rings it is a lipophilic substance (log P 4.77) which is almost insoluble in water. BFZ has a water solubility of 0.7 μg/ml at 25^{o}C [8].

The purpose of this study is to evaluate the possibility of interaction of the antifungal drug BFZ through complexation with carboxymethylated-β-cyclodextrin (KM-β-CD).

So, we investigated the solubilization process for slightly soluble BFZ in the presence of KM-β-CD in comparison with other derivatives of cyclodextrin, like (2-Hydroxypropyl)-β-cyclodextrin (HP-β-CD), Methyl-β-cyclodextrin (β-CD-Met) and derivative of starch - carboxymethylated-starch (KM-Str.) by using method of UV-spectroscopy. Application of β-CD's derivatives and KM-Str. leads to improved solubilization of BFZ (Fig. 2). Based on these data, we can conclude that involving of β-CD and starch derivatives improves solubilization of BFZ nearly in 6-12 times. The best dissolution of the drug can be seen, while using KM-β-CD, in this case the solubility of BFZ is increased more than 50 times.

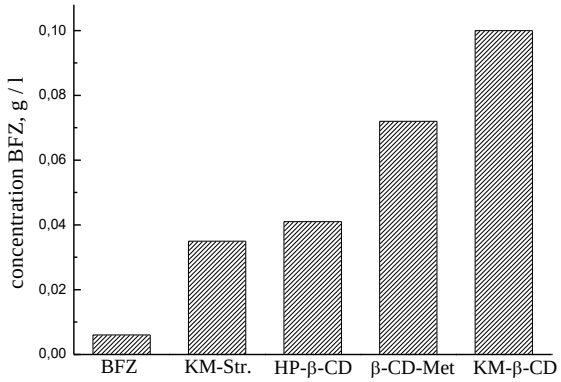

Fig. 2. Solubilization of BFZ

The obtained result can be explained by the double effect of the KM-β-CD: the presence of a hydrophobic cavity and active substitutes, which, apparently, participate in the protonation of the molecule BFZ. Thus, KM-β-CD significantly improves solubilization of BFZ, while the derivatives of β-CD and KM-Str. are less effective than KM-β-CD.

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