A Study Upon the Dissolution Properties of Bifonazole Through Complexation with Cyclodextrins

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Introduction: The aim of this study is to characterize the interaction in solution between the antimycotic bifonazole and two cyclodextrins: random methyl-beta-cyclodextrin and beta-cyclodextrin.
Material and method: The interaction in solution between bifonazole and random methyl-beta-cyclodextrin/beta-cyclodextrin was characterized using dissolution studies and phase solubility studies. The dissolution of bifonazole was characterized through the index of the rate of dissolution and the dissolution efficiency, and from the phase solubility study we calculated the apparent stability constant of the complex.
Results: The bifonazole – random methyl beta-cyclodextrin binary systems revealed better dissolution properties as compared to bifonazole alone, and to the bifonazole – beta-cyclodextrin binary systems. The phase solubility studies revealed the formation of soluble complexes in the cyclodextrin concentration range, and an apparent stability constant of 17956 M^{-1} for bifonazole – random methyl-beta-cyclodextrin complex, and of 873 M^{-1} for bifonazole – beta-cyclodextrin complex.
Discussions: The dissolution studies and the phase solubility studies demonstrated an improvement of the wettability of the particles of bifonazole, due to a better contact between bifonazole and cyclodextrin, and the formation of soluble complexes in the dissolution medium.
Conclusions: The complexation with cyclodextrins determined the increase in the dissolution properties of bifonazole. The best results were obtained with random methyl-beta-cyclodextrin, which demonstrates a better interaction within the components in the liquid medium and the better solubilization properties of this cyclodextrin.

Keywords: bifonazole, cyclodextrin, dissolution properties, phase solubility study

Introduction

Bifonazole (BIF) is an antimycotic imidazole derivative with a broad spectrum, used for the treatment of local fungal infections [1]. Bifonazole has a very low water solubility [2] which is a major drawback for its local bioavailability; the hydrophobic compounds have a weak penetration into hydrophilic human nail matrices and a low solubility into the aqueous phase of the dermatological formulations, considering that these formulations commonly consists of aqueous systems [3,4].

Cyclodextrins (CDs) have received increasing attention in pharmaceutical field because of their potential to change the physicochemical and biopharmaceutical properties of drugs by forming inclusion complexes. Cyclodextrins increase the water solubility, enhance the bioavailability and the topical availability of drugs by increasing their availability at the skin surface, improve stability and may reduce side effects [5,6,7,8, 9,10].

The interaction in solution between BIF and the CDs was characterized through the index of the rate of dissolution and through the dissolution efficiency [11] using the data obtained in our previous researches, regarding the dissolution of the physical mixture products (PM), kneaded products (KP) and spray-dried products (SD) in buffer solution (pH= 5.4) [12,13,14]. The binary systems were prepared in four molar ratios (drug: cyclodextrin) 2:1, 1:1, 1:2, 1:3 [12,13,14]. The phase solubility studies were done in order to determine the stability constant of BIF-CD complex, by Higuchi-Connors method [5].

Material and method

Bifonazole (1-[(R,S)-biphenyl-4-yl)phenylmethyl]-1-H-imidazole) was kindly provided by Gedeon Richter S.A. (Tîrgu Mureş, Romania). Random methyl-beta-cyclodextrin (RAMEB) (DS-12) and beta-cyclodextrin (β-CD) were purchased from Cyclolab R&D (Budapest, Hungary). Other chemical reagents were of analytical grade purity requested by the Romanian Pharmacopoeia 10th ed. and by the European Pharmacopoeia 7th ed.

Dissolution studies

Dissolution of the host molecule bifonazole, and of the binary systems with RAMEB and β-CD from the binary systems in buffer solution (pH = 5.4) was characterized through the index of the rate of dissolution (IRD), as the percent of drug dissolved after 10 min, and through the dissolution efficiency (DE) as index of the totality of the process, and it was calculated from the area under the dissolution curve at time t = 120 min, measured using the trapezoidal rule. DE was expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time t. We also calculated the relative increase of the concentration of the active substance from the binary systems, by dividing the concentration of the active substance

Table I. Values of the IRD and DE of the binary systems of BIF and RAMEB

	Binary system									
	PM 2:1	PM 1:1	PM 1:2	PM 1:3	KP 2:1	KP 1:1	KP 1:2	KP 1:3	SD 1:1	SD 1:2
IRD	93.64	114.13	96.90	92.86	125.55	144.44	136.79	103.25	138.34	139.70
DE	94.38	103.26	97.74	95.94	106.92	107.25	111.78	99.82	107.58	111.74

Table II. Values of the IRD and DE of the binary systems of BIF and β-CD

	Binary system							
	PM 2:1	PM 1:1	PM 1:2	PM 1:3	KP 2:1	KP 1:1	KP 1:2	KP 1:3
IRD	37.02	30.20	22.58	19.21	45.78	34.19	27.43	62.31
DE	71.66	68.55	65.18	72.87	77.35	70.58	71.74	85.81

from the binary system dissolved at time t = 5 min to the concentration of the uncomplexed bifonazole dissolved at time t = 5 min.

Phase solubility studies

An excess of BIF was added to the distilled water containing various concentration of RAMEB (10, 50, 100, 150, 200 mM) and of β-CD (2, 4, 6, 8, 10, 12, 14, 16 mM). The suspensions were shaken at room temperature (25°C) for 7 days. The concentration of dissolved drug was measured by UV spectrophotometry (λ_{max} = 256 nm; y = 0.0771x; R^2 = 0.9983), after filtration and proper dilution. This study was done in triplicate. The apparent stability constant of the complex, $K_{1:1}$, was calculated from the initial straight-line of the solubility diagram, according to the following equation:

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

where S_0 represents the intrinsic solubility of BIF in the absence of cyclodextrin, tgα is the slope pf the phase solubility line.

Results

Dissolution studies

We calculated for BIF an IRD of 56.5 and an DE of 74.6. In Table I are presented the IRD and DE values of the physical mixtures (PM), kneaded products (KP) and spray-dried (SD) binary systems of BIF–RAMEB and in Table II, the IRD and DE values for the binary systems of BIF with β-CD.

Table III. The parameters of the phase solubility studies

System	Medium	S_0 (× 10^{-3} M)	tg α	$K_{1:1}$ (M^{-1})	Type of the diagram
BIF + RAMEB	Buffer solution (pH = 5.4)	8.49	0.1324	17956	AP
BIF + β-CD	Distilled water	12.3	0.011	873	AL

An overall representation of the increasing of the concentration of BIF from the two type of binary systems in the dissolution medium in the first 5 min is represented in Fig. 1.

Phase solubility studies

The parameters of the phase solubility studies are presented in Table III.

Discussions

Dissolution studies

All the BIF–RAMEB binary systems studied, revealed superior values of the IRD and a DE, as compared to uncomplexed BIF. We obtained values over 100% for these parameters which may be correlated with the formation of a metastable solution in the first 10–15 min of the experiment. Regarding the complexation method, the kneaded method and the spray-dried products revealed superior dissolution properties as compared to the physical mixture products, which demonstrates an improvement of the humectability of the particles due to a better contact between bifonazole and the cyclodextrin and the formation of more soluble inclusion complexes in the dissolution medium. The spray-dried products did not offer better results as compared to the kneaded products, so the kneaded method is to be considered the most suitable

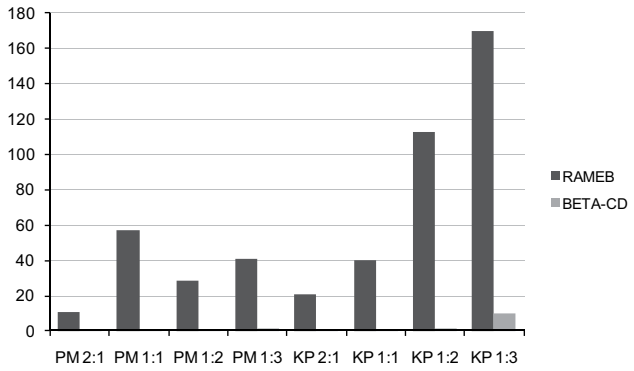

Fig. 1. The relative increase of the concentration of BIF from the binary systems at t = 5 min

method in obtaining inclusion complexes between BIF and RAMEB.

Regarding the BIF – β-CD binary systems, the PM did not revealed better dissolution properties as compared to BIF alone. The KP revealed superior values as compared to the PM, which underlines the importance of the preparation method in improving the dissolution properties of BIF.

The studies of Mura et al (1999) upon the influence of the preparation method on the dissolution properties of binary systems of econazole with β-CD and methyl-β-CD, characterized by the IRD and DE, also revealed less interaction between the imidazole derivative and β-CD and a much stronger interaction between the components, in the binary systems with methyl- β-CD.

Phase solubility studies

The solubility of BIF in the dissolution medium of pH = 5.4, increases with the increase of the concentration of RAMEB, with a positive deviation from linearity, giving an AP type of diagram. This type of isotherm is attributed to the formation of soluble complexes in the dissolution medium with an increase in the stoichiometry of the CD. The increase in the solubility of BIF at the end of the experiment was of 3158 fold.

The phase solubility study for BIF in aqueous solution with β-CD is characterized by a linear increase in BIF concentration as a function of β-CD concentration, showing an AL type diagram, attributable to formation of soluble inclusion complexes with a 1:1 stoichiometry. The solubility of BIF at the end of the experiment, increases 13 fold. Morin et al (1999) also reported, according to their phase solubility studies, the obtaining of an A type diagram and the formation of soluble complexes between BIF and β-CD in the same dissolution medium.

The solubility increase of BIF and the stability constant obtained with RAMEB were much greater than those obtained with β-CD, due to their different physicochemical properties.

Conclusions

The complexation with cyclodextrins determines the increase in the dissolution properties of BIF. The best results were obtained with RAMEB which demonstrates a better interaction within the components in the liquid medium and the better solubilization properties of this cyclodextrin.

The molar ratio influences the dissolution properties of BIF. For the binary systems with RAMEB, the best results were obtained for the 1:1 molar ratio. For the binary systems with β-CD, an increase in the molar ratio does not reveal better performances.

The preparation method of the inclusion complexes influences the dissolution properties of BIF.

The phase solubility isotherm of the BIF–RAMEB binary system and the value of the stability constant demonstrated the better capacity of interaction of RAMEB with BIF in solution, as compared to β-CD and they are attributed to the amorphous nature and higher hydrosolubility of RAMEB. The increase in the hydrosolubility of BIF in the presence of the two cyclodextrins is considered to be due to the formation of soluble complexes in the concentration range of the cyclodextrin.

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