Effect of water-soluble polymers on the aqueous solutility and complexing abilities of bropirimine with dimethyl-β and hydroxypropyl-β-cyclodextrin

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1. Introduction

Bropirimine (2-amino-5-bromo-6-phenyl-4(3)-pyrimidinone, ABPP) is an orally active immunomodulator that increases endogenous alpha-interferon and other cytokines. Its low aqueous solubility determines a low oral bioavailability (1).

Cyclodextrins CD are water-soluble, hydrophobic torus-shaped cyclic oligosaccharides, that can accommodate in their cavities water-insoluble drugs to form water-soluble inclusion complexes. Because of these properties CD have been used to enhance drug solubility, stability and bioavailability (2-4). Hydroxypropyl β-cyclodextrin derivatives have been extensively used in pharmaceutical formulation owing to its high water solubility (>50 % w/v) and low toxicity (5-6). Besides, methylated β-cyclodextrins show an improvement on water solubility of the natural parent and the complexation capability improves significantly (7).

Polymers are know to interact with CDs and, it have been shown that at low concentrations, hydrophilic polymers, such as hydroxypropyl methylcellulose (HPMC), carboximethylcellulose sodium salt (CMC Na) or polyvinylpyrrolidone (PVP), increase the complexing abilities of CDs (8).

The purpose of this study was to investigate the effect of various water-soluble polymers on the cyclodextrin complexation of bropirimine. The efficiency of complexation was evaluated by determining the solubilizing effects of two cyclodextrin derivatives, dimethyl-β- and hydroxypropyl-β-cyclodextrin.

2. Material and methods

2.1 Materials

Bropirimine was a gift of Laboratorios Inibsa, S.A. (Spain). Dimethyl-β-cyclodextrin (DIMEβ) was purchased from Cyclolab (Hungary) and hydroxypropyl-β-cyclodextrin (average degree of substitution 2.7) (HPβCD) donated by Janssen Pharmaceutica N.V. (Belgium), hydroxypropyl methylcellulose E4M (HPMC) was purchased from The Dow Chem. Corp. (USA) and, carboximethyl cellulose sodium salt of medium viscosity (CMC Na) and plyvinylpyrrolidone of molecular weight 40.000 (PVP) from Sigma (Spain). All other chemicals were of analytical-reagent grade.

2.2 Quantitative determination

Quantitative determinations of the ABPP were performed on a reversed-phase HPLC consisted of an auto-injector Waters 600 Controlled (20 ml), a Waters 717 plus Autosampler and a Waters 996 Photodiode Array Detector, controlled by Waters Millennium PDA software. For the stationary phase, a reverse-phase column (Symmetry C-18, FX 5166, 150 x 3.9 mm) was used. The mobile phase was a mixture of methanol, water (acetic acid 0.2%) 48:52 v/v with a flow rate of 1 ml min^{-1} and, was deaerated on-line bubbling helium gas. Detection was performed at 233 nm.

2.3 Solubility studies

An excess amount of DIMEβ or HPβCD and/or the drug was added to water or aqueous polymer solution. The suspension formed was heated in an autoclave in sealed containers (120°C for 20 min). After equilibration at room temperature (20°C) for 3 days, the suspension was filtered through a 0.45 mm membrane filter (Millipore, USA), diluted with methanol-water solution if necessary and drug concentrations determined by HPLC. The apparent stability constants of the ABPP-CD (1:1) complexes were determined from the phase-solubility diagrams according to the method of Higuchi and Connors (9).

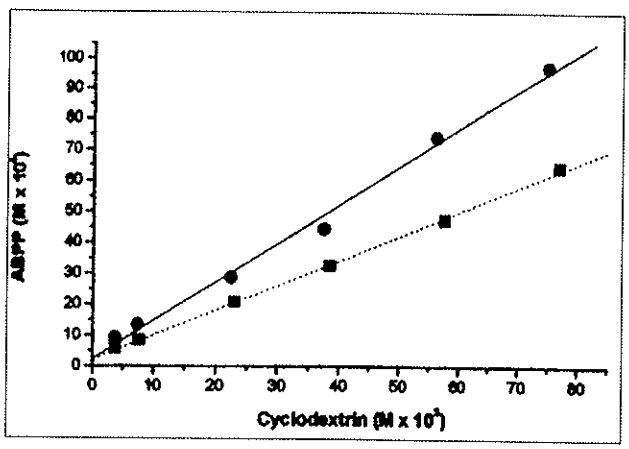

Figure 1. Phase solubility diagram of ABPP in aqueous HPβCD (■) and DIMEβ (●) solution

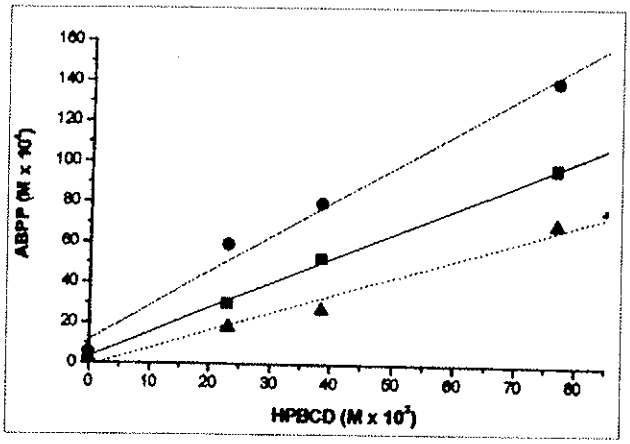

Figure 2.Effect of CMC Na, 0.25% (▲), HPMC, 0.1% (●) and PVP, 0.25% (■) on the complexation of ABPP into HPβCD.

3. Results and discussion

Figure 1 shows the phase solubility diagram of ABPP in aqueous solutions of the CD derivatives. The solubility diagrams were all of Higuchi's AL-type, i.e. linear increase was observed with unchanged stoichiometry.

The values of the stability constants for selected ABPP-CD complexes were 540.1 M^{-1} for ABPP-DIMEβ complex and 461.0 M^{-1} for the ABPP-HPβCD complex. This higher stability constant for the DIMEβ complex may reflect better spatial compatibility of the guest molecule, attributed to the flexible structure of the CD (10) and, the strength of the interaction by partial fit of the drug into the CD cavity (11).

The solubilizing effect of both cyclodextrins was modified when water-soluble polymers were present in the solution (Figure 2 and 3).

With HPβCD (Fig. 2), phase solubility diagram are, in all cases Higuchi's A_L-type. The increase of the solubility is notably larger when HPMC or PVP were present but not with CMC Na. The stability constant of the ABPP-HPβCD inclusion complex calculated were: 804.6 M-1 with 0.1% HPMC, 539.4 M^{-1} with 0.25% PVP and 375.3 M with 0.25% CMC Na in the solution. The increase obtained with HPMC and PVP represent a 74% and 17%, respectively, but CMC Na does not modify significantly the interaction of ABPP and the CD.

In the case of DIMEβ, phase solubility diagrams of ABPP in the presence of water-soluble polymer correspond with Higuchi's A_N type, compared to A_L type when no polymer is present. The origin of this diagram is not clear and it has been associated with an alteration in the effective nature of the solvent in the presence of large concentrations of host (9), and therefore, modify the interaction between the drug and the CD derivative.

On the other hand, the solubilizing effect was improved from 11 to 123% (S/So = 1.1-2.3) with HPβCD (10% w/v) but not with DIMEβ (10% w/v), when polymers are present (Table I).

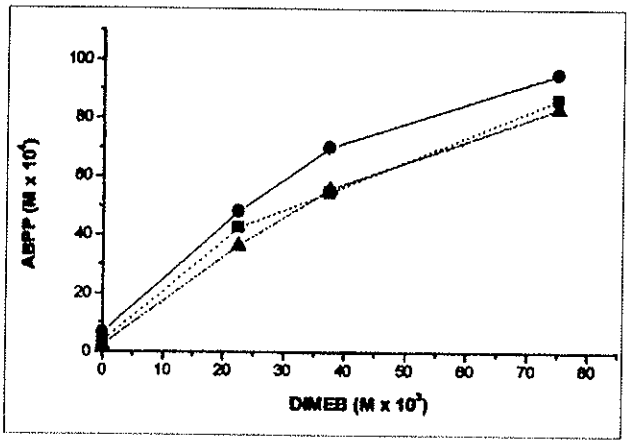

Figure 3. Effect of CMC Na, 0.25% (▲), HPMC, 0.1% (●) and PVP, 0.25% (■) on the complexation of ABPP into DIMEβ

Table I. *Effect of polymers on the solubilization of ABPP in aqueous cyclodextrin solutions.*

CD	Polymer	Solubility mg/ml	S/S0*
HPβCD (10% w/v)	-	1.7	-
	0.1%HPMC	3.8	2.2
	0.25% PVP	2.6	1.5
	0.25% CMC Na	1.9	1.1
DIMEβ (10% w/v)	-	2.6	-
	0.1%HPMC	2.5	0.9
	0.25% PV	2.3	0.9
	0.25% CMC Na	2.2	0.8

* S = Solubility in aqueous 10% (w/v)cyclodextrin solution.
S_p = Solubility in aqueous solution containing both 0.25% (w/v) PVP or CMC Na, or 0.1% (w/v) HPMC and 10% (w/v) CD.

In conclusion, both cyclodextrin derivatives can be used to increase the solubility of the drug. The effect increases when water-soluble polymers, especially HPMC, and HPβCD are present toghether in the solution. This could be useful in the development of a liquid oral formulation. Nevertheless, water-soluble polymer does not interact with DIMEβ and therefore, no effect on the solubility of ABPP was found.

Acknowledgments:

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