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ORIGINAL ARTICLE

Solubilization of itraconazole as a function of cyclodextrin structural space

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Abstract Cyclodextrins are functional pharmaceutical excipients, which can dynamically include poorly water-soluble drugs and drug candidates resulting in improved solubility, stability and oral bioavailability. A number of formulations containing ''natural'' and chemically modified cyclodextrins have reached the market and are enjoying widespread attention and use. One such example is itraconazole, a broad-spectrum antifungal agent which is available in an aqueous hydroxypropyl-β-cyclodextrin (HPβCD) vehicle for both oral and parenteral use (Sporanox Oral Solution and Sporanox Intravenous Injection®). While the interaction of itraconazole and HPβCD is well described, its ability to form complexes with other cyclodextrins is less understood. This creates an intriguing opportunity of screening the structural space of available cyclodextrin derivates by assessing their complexation with a single chemical probe, in this case itraconazole. To this end, a number of cyclodextrin derivatives were assess with regard to their ability to improve the water solubility of the test substrate. In some instances, more detail assessments including the effect of pH and the physical form of the drug probe were also completed. The various cyclodextrins solubilized itraconazole to varying extents (micrograms to milligrams) and by varying inclusion mechanisms and stoichiometries.

Keywords Cyclodextrin derivatives · Itraconazole · Solubilization · Crystalline · Amorphous · Supersaturation

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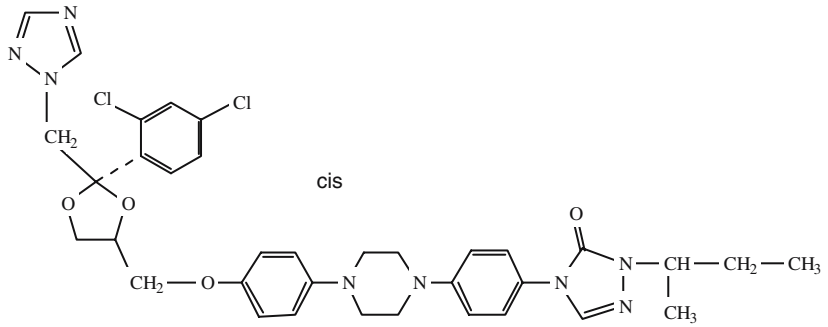
Introduction

Itraconazole (Sporanox®) is a useful broad-spectrum triazole antifungal agent which has gained widespread acceptance. Itraconazole is the first marketed orally bioavailable antifungal agent to be useful in both the treatment of *Candida* sp. and *Aspergillus* sp., the two most commonly occurring fungal pathogens [1, 2]. Physicochemically, itraconazole present significant challenges to the formulator. The compound can be characterized as a very poorly water-soluble, weak base with aqueous solubility estimated at approximately 1 ng/ml at neutral pH and ~6 μg/ml at pH 1. The pK_a was determined to be 4 with other relevant data including the melting point of approximately 169 C and a log P greater than 5. The calculated log P was 6.2 [3]. This information as well as permeability, fraction absorbed and oral bioavailability data confirmed that itraconazole can be classified as a type II compound (i.e., poorly soluble but GI permeable) based on the Biopharmaceutical Classification System (BCS) meaning that dissolution rate or solubility improvement will optimize the dosage form [3, 4].

Structure



Itraconazole

A number of formulation approaches have been assessed in order to improve the pharmaceutical performance of itraconazole including the use of nanosuspension, solid dispersions and solutions [3, 4]. The first formulation to have reached the market was based on solid solution technology in which the drug and hydroxypropylmethylcellulose in a solvent were sprayed on an inert sugar sphere in a closed Wurster process [5]. After drying and capsule filling of the beads, itraconazole is present in a molecularly dispersed solid solution, which dissolves to give a supersaturated solution of the drug in the stomach. The supersaturated solution is sufficiently stable to allow for significant absorption and bioavailability [3].

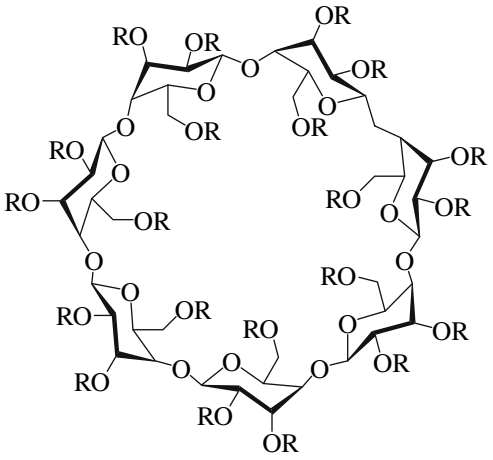
To improve the formulation especially for use in systemic fungal infections, two aqueous formulations for itraconazole (an oral solution and i.v. product) were developed through the use of cyclodextrin complexation with 2-hydroxypropyl-β-cyclodextrin (HPβCD) chosen as the functional excipient. The selected cyclodextrin, HPβCD, is a safe and well-tolerated material and effects drug solubilization through the formation of dynamic (non-covalent) complex formation [3].

Since the formulation development of HPβCD-based itraconazole formulation, a number of other chemically modified cyclodextrins have become available and one, sulfobutylether-β-cyclodextrin (SBEβCD) has reached the market. The purpose of the current work was to assess the interaction of a number of cyclodextrins and cyclodextrin derivatives with itraconazole with the aim of looking for an even better complexing agents as well as of screening cyclodextrin space as a function of itraconazole inclusion [6, 7].

Experimental section

Cyclodextrins were obtained from various vendors (including Chinoin, Amaizo, Medinpex, Cyclolab, Wacker and others) and characterized as appropriate for the materials. Abbreviation used include: α-, β- and γ-cyclodextrin (α-CD, β-CD and γ-CD), 2-hydroxypropyl-β-cyclodextrin (HPβCD), dimethyl-β-cyclodextrin, (DMβCD), randomly methylated-β-cyclodextrin (RAMβCD), ethylated β-cyclodextrin (EthylβCD), acetylated β-cyclodextrion (AcetylβCD), maltosyl-β-cyclodextrin (MaltosylβCD), hydroxypropyl-γ-cyclodextrin (HPγCD), carboxymethyl-β-cyclodextrin (CMβCD), 2-(carboxymethoxy)-propyl-β-cyclodextrin (CBMPβCD), sulfated β-cyclodextin (SulfatedβCD), sulfobutylether-β-cyclodextrin (SBEβCD), carboxymethyl-γ-cyclodextrin (CMγCD), acetylated hydroxypropyl-β-cyclodextrn (AcetylHPβCD), succinylated hydroxypropyl-β-cyclodetrin (SuccinylHPβCD), carboxymethylated hydroxypropyl-β-cyclodextrin (CMHPβCD), cyanoethyl-β-cyclodextrin (CNETβCD), carboxyethyl-β-cycldextrin (CBEβCD), aminopropyl-β-cyclodextrin (APβCD), sulfated hydroxyethyl-β-cyclodextrin (SulfateHEβCD), dimethylaminoethyl-β-cyclodextrin (DMAEβCD). The structures are summarized in Scheme 1. Crystalline and amorphous itraconazole was obtained from Janssen Pharmaceutica.

Complexes were prepared by first sonicating an excess of either crystalline or amorphous itraconazole in various concentrations of the desired cyclodextrin adjusted to an appropriate pH condition using HCl. After 10 min of sonication, the systems were equilibrated for 2 days at which time the pH was checked and adjusted as necessary. The samples were then agitated at appropriate temperatures with itraconazole concentrations measured a various time intervals. At a specified time point, a small volume of the supernatant was withdrawn and filtered through a 0.45 μ polyvinylidene difluoride membrane (Nihon Millipore). Samples were then diluted with 0.01 N HCl and analyzed by UV (at 254 nm) using a Hewlett Packard 8451B diode array spectrophotometer. In certain cases, the chemical stability of itraconazole was confirmed in the



Cyclodextrin	R = H or
β-Cyclodextrin	-H
2-Hydroxypropyl β-cyclodextrin	$-CH_2CHOHCH_3$
Sulfobutylether β-cyclodextrin sodium salt	$-(CH_2)_4SO_3^- Na^+$
Methylated β-cyclodextrin	$-CH_3$
Ethylated β-cyclodextrin	$-CH_2CH_3$
Acetylated β-cyclodextrin	$-COCH_3$
Carboxymethyl β-cyclodextrin	$-CH_2COOH$
2-Carboxymethoxypropyl β-cyclodextrin	$-(CH_2)_2(OCH_2COOH)CH_3$
Sulfated β-cyclodextrin	$-SO_3^- Na^+$
Acetylated Hydroxypropyl β-cyclodextrin	$-COCH_3$ and $-CH_2CHOHCH_3$
Succinylated Hydroxypropyl β-cyclodextrin	$-CO(CH_2)_2COOH$ and $-CH_2CHOHCH_3$
Carboxymethylated Hydroxypropyl β-cyclodextrin	$-CH_2COOH$ and $-CH_2CHOHCH_3$
Cyanoethyl β-cyclodextrin	$-CH_2CH_2CN$
Carboxyethyl β-cyclodextrin	$-CH_2CH_2COOH$
Aminopropyl β-cyclodextrin	$-CH_2CH_2CH_2NH_2$
Sulfated Hydroxyethyl β-cyclodextrin	$-SO3^- Na^+$ and $-CH_2CH_2OH$
Dimethylaminoethyl β-cyclodextrin	$-CH_2CH_2N(CH_3)_2$
Maltosyl β-cyclodextrin	Maltosyl group

Scheme 1

storage conditions by HPLC. The systems configuration included a Varian LC 9010 solvent pump, a Varian 9096 autosampler fitted with a 10 μl sample loop and a Varian 9065 Polychrom diode array detector (for itraconazole, λ = 268 nm) dedicated to a Compac Descpro PC. Samples were eluted on an RP 18 Hypersil ODS column (10 cm × 4.0 mm i.d., 3 μ particle size) using a flow rate of 1.6 ml/min and a mobile phase composition of ammonium acetate (0.5%): methanol: acetonitrile (35:14:51). Dibutyl phthalate served as the internal standard. Under these conditions, the retention time of itraconazole was 4 min and for the internal standard, 4.62 min. The relationship between solubilizer and drug solubilized was analyzed using the phase-solubility approach described by Higuchi and Connors [8]. Stability constants were calculated using the formalism of Higuchi and Kristiansen [9] as well as that of Peeters et al. [3].

Results and discussion

The solubilizing capacity of various cyclodextrins was assessed using either crystalline or amorphous itraconazole. In the first series of experiments, crystalline itraconazole was investigated. Two general screening approaches were used as indicated in Figs. 1 and 2. In Fig. 1, the solubility of itraconazole in a 10% w/v solution of the cyclodextrin derivative in 0.01 N HCl (pH 2.3) was measured while in Fig. 2, the solubilizing potential of the cyclodextrin in water was determined. Figure 1 suggests that the best solubilizer of those assessed was DMβCD with HPβCD being the second best material. MaltosylβCD and HPγCD were less useful. If water is used as the solvent, the alkylated cyclodextrins are efficient solubilizing excipients as was the acylated cyclodextrin, acetylβCD. Carboxylated, sulfated and sulfobutylated cycloextrins were poor solubilizers for itraconazole under these conditions. Phase-solubility analysis for these cyclodextrins and itraconazole are given in Figs. 3, 4 and 5.

The rate-limiting step in the generation of optimal itraconazole solutions in HPβCD from crystalline itraconazole was the phase-to-phase transition of the material as gauged by changes in concentration over time (Fig. 6). By contrast, use of amorphous itraconazole was associated with high initial concentration of the drug, which decreases over time suggesting the formation of an initially supersaturated system. As indicated in Fig. 6, even after one month, the cyclodextrin-based itraconazole solutions derived from the amorphous drug substance were more concentrated that those derived from crystalline itraconazole. These data also suggested to us an analysis of amorphous itraconazole in various cyclodextrins. To this end, a similar screening assessment was completed.

As illustrated in Fig. 7, amorphous itraconazole generates high initial concentrations in various cyclodextrin including alkylated β-cyclodextrins (methylated and ethylated) as well as aminopropylated, cyanoethylated and acetylated β-cyclodextrin derivatives. In many cases this high initial solubility decrease over time as was observed in the case of HPβCD such that day 30 values were only 11% of the original solubilization, 18% for CMHPβCD, 10% for CBETβCD and 29% for APβCD. On the other hand, a number of cyclodextrins were able to maintain the high initial solubility including the AcetylβCD (102%), the DMβCD (94%) and to a lesser extend the EthylβCD (65%) suggesting strong solubilization together with

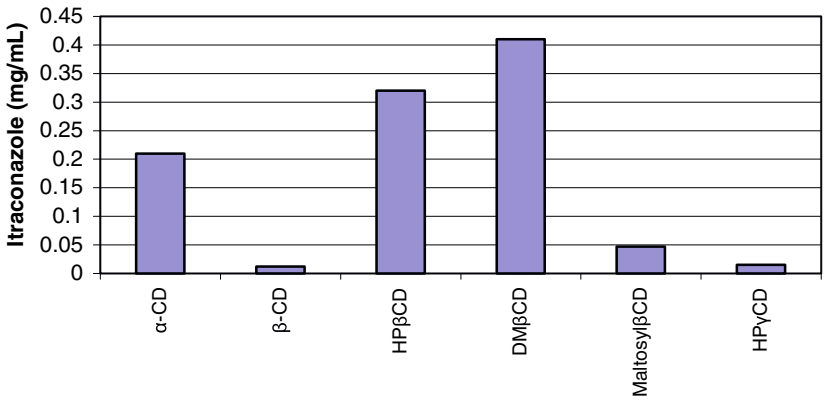


Fig. 1 Solubility of itraconacole in 0.01 N HCl in 10% w/v solutions of various cyclodextrin derivatives (Note due to solubility limitations, the β-CD sample was prepared at 1% w/v)

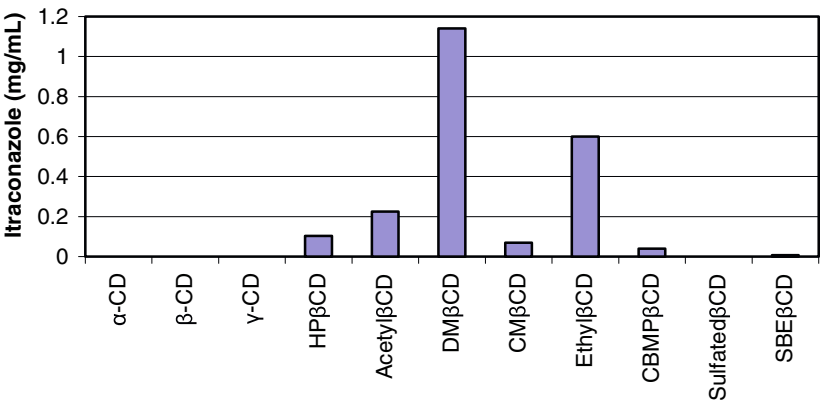


Fig. 2 Solubility of itraconazole in water in 10% w/v solutions of various cyclodextrin derivatives

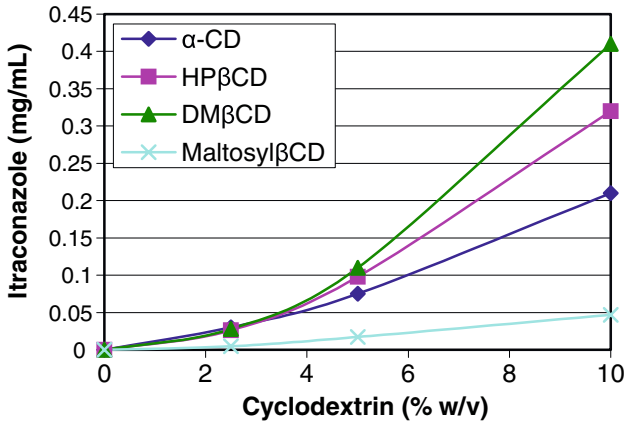


Fig. 3 Phase-Solubility analysis of itraconazole in various cyclodextrins at pH 2.3 (in 0.01 N HCl)

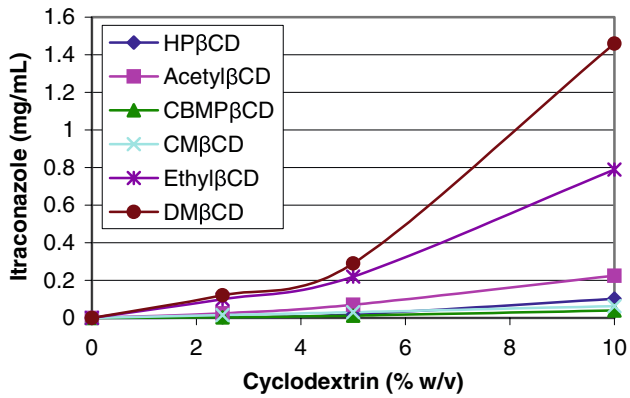


Fig. 4 Phase-Solubility analysis of itraconazole in various cyclodextrins in water

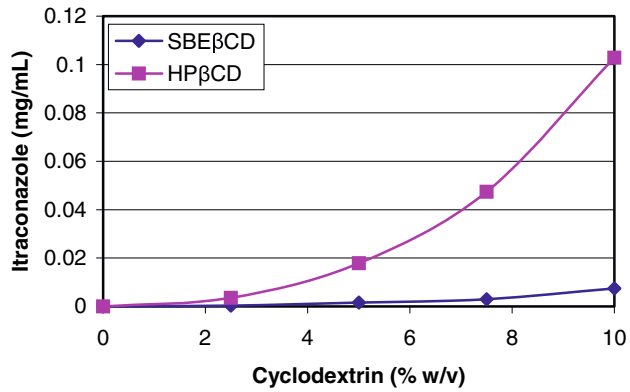


Fig. 5 Phase-Solubility analysis of itraconazole in HPβCD and SBEβCD

inhibition of nucleation and/or inhibition of crystal growth.

A second observation in assessing the solubilization of itraconazole using amorphous drug substance is a tendency for changes in the solubility isotherm over time. Figure 8 shows Day 1 and 30 data for two

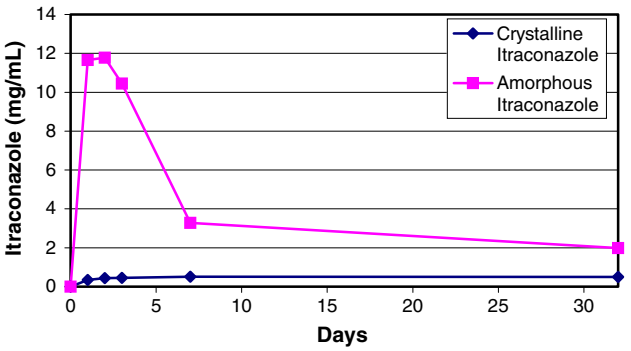


Fig. 6 Solubilization of either crystalline or amorphous itraconazole in 20% w/v HPβCD over time (0–32 days)

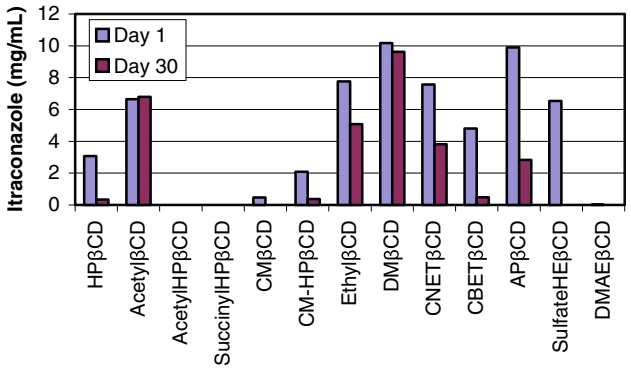


Fig. 7 Solubility of itraconazole after 1 or 30 days of equilibration following the addition of amorphous itraconazole in 10% w/v solution of various cyclodextrins in water

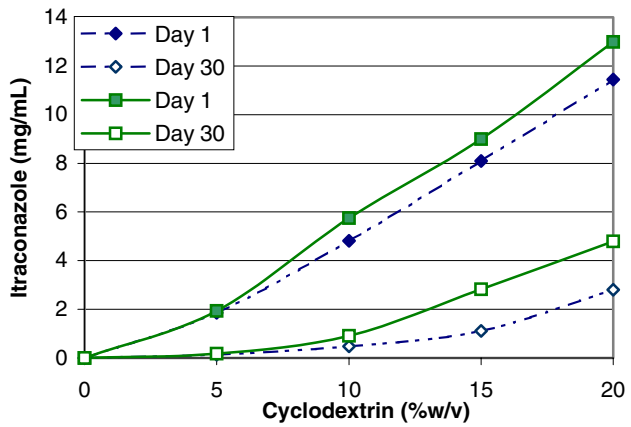


Fig. 8 Phase solubility analysis for carboxyethyl-β-CD (CBETβCD, dotted lines) and aminopropyl-β-CD (APβCD, solid lines) as measured 1 and 30 days after equilibration of amorphous itraconazle

examples (APβCD and CBETβCD). In both cases the curvature of the phase-solubility isotherm increases (as indicated by deviations from linearity) with equilibration time suggest a change in either complex stoichiometry or mechanism.

Conclusions

By investigation the interaction of itraconazole in its crystalline or amorphous state with various cyclodextrin families, knowledge on how this difficult-to-formulate material can be solubilized is increased. Alkylated cyclodextrins are the most useful for solubilizing crystalline itraconazole. Several days are required to reach maximum solubility. When amorphous itraconazole is used, supersaturation occurs and several days are needed for reaching stable solubility values. The combination of using amorphous itraconazole, a judiciously selected cyclodextrin and an optimal pH combine to generate useful dosage forms.

References

1. De Beule, K., Van Gestel, J.: Pharmacology of itraconazole. Drugs **61**(Suppl. 1), 27–33 (2001)
2. Jain, S., Sehgal, V.: Itraconazole: an effective oral antifungal for onychomychosis. Int. J. Dermatol. **40**, 1–5 (2001)
3. Peeters, J., Neeskens, P., Tollenaere, J.P., Van Remoortere, P., Brewster, M.E.: Characterization of the interaction of 2-hydroxypropyl-β-cyclodextrin with itraconazole at pH 2, 4 and 7. J. Pharm. Sci. **91**, 1414–1422 (2002)
4. Brewster, M.E., Verreck, G., Chun, I., Rosenblatt, J., Mensch, J., Van Dijck, A., Noppe, M., Arien, T., Bruining, M., Peeters, J.: The use of polymer-based electrospun nanofibers containing amorphous drug dispersions in the delivery of poorly water-soluble pharmaceuticals. Die Pharmazie **59**, 387–391 (2004)
5. Gilis, P.A., De Conde, V., Vandecruys, R.: Beads having a core coated with an antifungal and a polymer. Janssen Pharmaceutica US Patent 5633015 (1993)
6. Strickly, R.G.: Solubilizing excipients in oral and liquid formulations. Pharm. Res. **21**, 201–230 (2004)
7. Davis, M.E., Brewster, M.E.: Cyclodextrin-based pharmaceutics: Past, present, future. Nat Rev Drug Discov **3**, 1023–1035 (2004)
8. Higuchi, T., Connons R.A. In: Reilly, C.N. (ed.) Advances in Analytical Chemistry and Instrumentation, vol. 4, pp. 117–212 Wiley-Interscience, New York (1965)
9. Higuchi, T., Kristiansen, H.: Binding specificity between small organic solutes in aqueous solution: Classification of some solutes into two groups according to binding tendencies. J. Pharm. Sci. **59**, 1601–1608 (1970)