PTR-114

The Use of Cyclodextrins in Preparing an Oral Liquid Dosage Form of Itraconazole

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Introduction

The preparation of oral liquid dosage form [OLDF] solutions is a challenge, taking into account that the formulation should mask any bad taste of the drug or other ingredients, to be also palatable and that the excipients used should be safe and able to increase the solubility of poorly soluble drugs. The aim of this work was to investigate the use of cyclodextrins [CDs] as excipients for OLDF. Cyclodextrins are known for their ability to increase the solubility of drugs by formation of both inclusion and non-inclusion complexes[1], as well as for their taste-masking properties[2]. Itraconazole was chosen as a model drug, known for its high LogP, poor solubility in water and bitter taste. An oral liquid of the drug containing 2-hydroxypropyl-β-cyclodextrin already exists on the market (Sporanox Oral Solution by Janssen Pharmaceuticals). However, that formulation also contains co-solvents, for instance propylene glycol, which could occasionally induce some undesirable intestinal effects and also has a bitter taste. Shehatta et al.[3] conducted a study on ITR using different CDs (α, β, γCD and 2-hydroxypropyl-β-cyclodextrin) to evaluate their efficiency for increasing the solubility of ITR. HPBCD was found to be most effective for this purpose. Taupitz et al.[4] conducted a study on enhancing solubilization by forming ternary systems with polymers in a dry complex. Furthermore, Holvoet et al.[5] studied the impact of changing the preparation method of the oral solution.

In this study we wanted to investigate the impact of γ-cyclodextrin (GCD), 2-hydroxypropyl-γ-cyclodextrin (HPGCD) and 2-hydroxypropyl-β-cyclodextrin (HPBCD) as highly water-soluble cyclodextrins suitable for use in liquids to enhance the solubility of ITR. HPGCD had not been studied with this API and it seemed to be a good candidate due to its high solubility and large cavity size. Furthermore, we studied the impact of the use of α-hydroxylic acids such as tartaric acid[6] and citric acid as well the amino acid L-arginine[7] in further enhancing the solubility through ternary systems with ITR and HPBCD. The target of this study was to improve the solubility to achieve a concentration of dissolved ITR of 10 mg/ml (1% formulation) without reverting to use of co-solvents or aggressive acids like hydrochloric acid used in the marketed product Sporanox.

Experimental Methods

Materials

Itraconazole (ITR) was obtained from RIA International LLC (East Hanover, NJ, USA). CAVAMAX™ W8 γ-cyclodextrin, CAVASOL* W7 2-hydroxypropyl-β-cyclodextrin and CAVASOL* W8 2-hydroxypropyl-γ cyclodextrin were produced by Wacker Chemie (Burghausen, Germany); L-tartaric acid (TAR) by Bernd Kraft (Duisburg, Germany); L-arginine ([ARG) and citric acid (CIT) by Applichem Panreac (Darmstadt, Germany); hydrochloric acid (HCl) by VWR Chemical (Radnor, USA); Plasdone™ S-630 copovidone (PVP/VA), Plasdone™ K-17 povidone (PVP) and Benecel™ E6 hypromellose (HPMC) by Ashland Inc. (Wilmington, DE, USA) and sucralose by Niutang Chemicals (Jiangsu, China).

Phase-Solubility Experiments (Binary systems)
Excess amounts of ITR (100 mg or 0.142 mmol), were added to 15 ml of unbuffered aqueous solutions of cyclodextrins: GCD 0–150 mmol/L, HPBCD 0–300 mmol/L and HPGCD 0–250 mmol/L. Solutions were stirred for 48 hours.

Solubility of Ternary Systems
Ternary systems were prepared and evaluated in the same manner as that used in the phase solubility study, only with HPBCD (1-300 mmol/L, 0-423 mg/mL) and with a drug addition of only 133 mg (= 0.18 mmol) to reflect a normal dosing of ITR. Acids were added to the mixture to achieve a pH value of around 3 (0.07 mmol TAR, 0.08 mmol CIT, 0.04 mmol HCl), while ARG was added in equimolar mass. The solutions were stirred for 24 h on a magnetic stirrer. pH values of solutions were measured using a FiveEasy FE20/LE409 pH meter (Mettler Toledo, Greifensee, Switzerland).

UV-Spectrophotometry
Aliquots were taken from the solutions and filtered with 0.22 µm filters. Filtered solutions were diluted with methanol:HCl 10:1 and analyzed using UV-spectrophotometry (Specord 200 Plus, Analytik Jena, Jena, Germany) at a wavelength of 258 nm.

Polymers as precipitation inhibitors
1 g ITR was dissolved in 10 ml ethanol with an addition of 1 ml concentrated HCl. 4.17 g of HPBCD was added to 9 ml of demineralized water together with either PVP/VA, PVP or HPMC. Both solutions were combined and stirred while heating for 2 hours to evaporate the ethanol. Afterward, demineralized water was added to achieve the final mass for a 1% ITR formulation.

Sporanox originator formulation
The originator formulation for the marketed product Sporanox, according to their filed patent[8], was used as a reference formulation.

Component	Quantity g/100 ml
Itraconazole	1
hydroxypropyl-Beta-cyclodextrin	40
propylene glycol	10
Sorbitol 70%	19
Acid or base to adjust pH to 2	q.s.
Sodium saccharin	0.06
Flavours	Up to 1
Caramel sweetener	0.02
Water	Qs 100mL

Table 1: Formulation according to patent WO9508993A1[8] by Janssen Pharmaceutica.

ITR and HCl are added to the propylene glycol and stirred to full dissolution. A 100% HPBCD in water solution is prepared and combined with the ITR solution. Afterward, sorbitol and sucralose (replacing the saccharin) are added and the solution is diluted to 100 ml. pH was adjusted to 2 with HCl. The procedure mentioned by Holvoet et al.[5] was used in our preparation of the final formula.

Results

Binary Systems
The results for the binary systems can be seen in Figure 1.

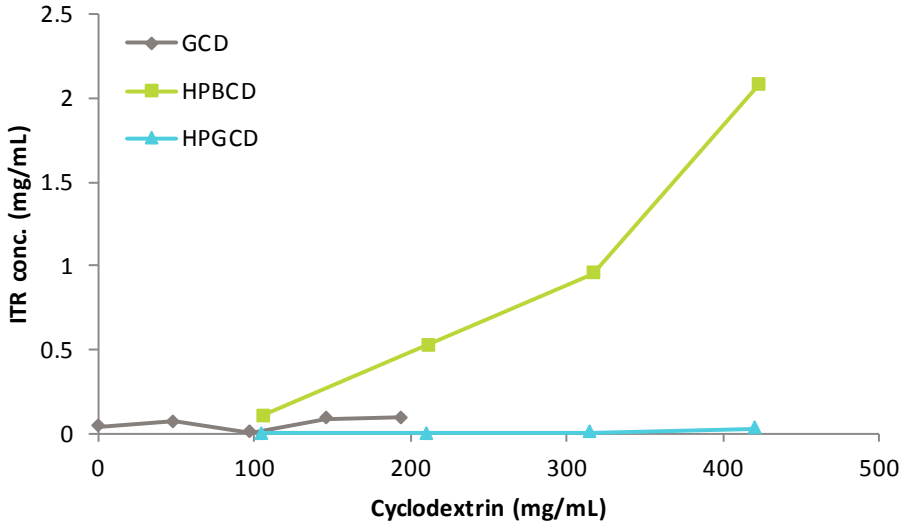

Figure 1: Phase solubility of Itraconazole in CD solutions

None of the investigated cyclodextrins achieved the target solubility of 10 mg/ml. The results show by far the largest increase in solubility for HPBCD with a solubility of ITR of 2.08 mg/ml (= 2.95 mmol/l). Results are in accordance with those of a study conducted by Peeters et al.[9] at pH=7. The isotherm of the complex with HPBCD shows an A_p (non-linear with positive deviation) curve type, indicating that possibly more than one cyclodextrin molecule is contributing to the formation of the complex.
Both GCD and HPGCD only marginally improved the solubility of ITR.

Preliminary taste results (n=1, by author) showed an improvement in taste with less bitterness of the solution and an increase in the sweetness. HPBCD was used for all further experiments for its superior solubilization of ITR.

Ternary Systems
Results of the ternary systems with HPBCD can be seen in Figure 2. All increased the solubility of ITR further compared with their binary counterparts, especially TAR, followed by ARG and HCl. However, still none of the investigated systems achieved the desired concentration of 10 mg/ml of ITR.

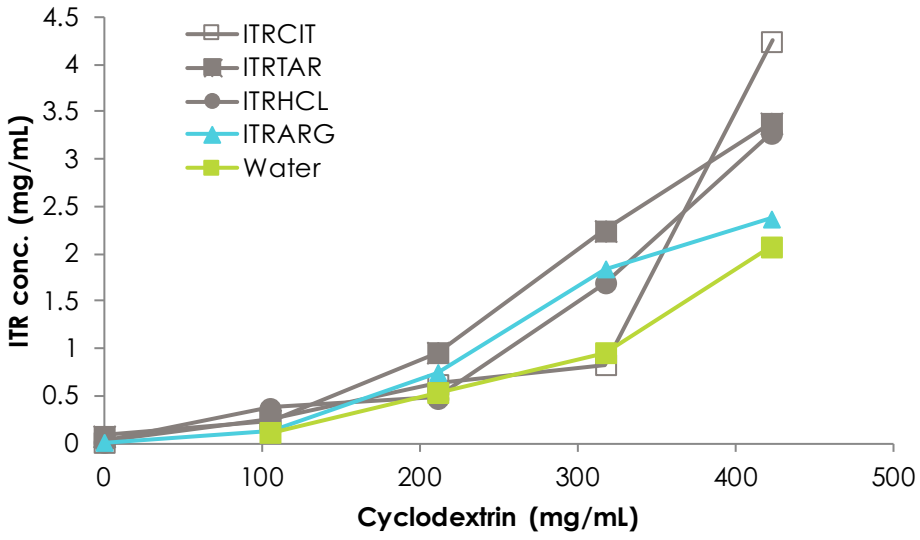

Figure 2: Ternary systems with HPBCD

Systems containing HCl, CIT and TAR were set at a pH value of approximately 2, and those containing ARG had a pH value in the range of 7.9 to 9.6.

Polymers as precipitation inhibitors in comparison with Sporanox formulation

Several polymers were tested using the procedure for "preparation of the binary and ternary inclusion complexes" described by Taupitz et al.[4], however, in an OLDF instead of in a spray-dried complex. All formulations, including one without polymer addition, initially showed no precipitation at all with slightly varying yellow coloring, possibly due to the polymers that were used to create the formulations. The measured initial pH values ranged from 0.5 to 0.55, values that are not suitable for administration in any route.

To create a formulation with a more suitable pH value, the same formulations were manufactured with only 0.12 ml of a 1 molar HCl solution to achieve a final pH value of 2. In this case, however, most of the ITR did not dissolve in the ethanol/HCl mixtures prior to addition to the HPBCD solution (see methods). The desired concentration of 10 mg/ml of ITR was not achieved. The pH of this formulation was gradually lowered using a 1 molar HCl solution while stirring, until all of the precipitate was dissolved. At this point the pH was measured again showing a pH of 0.83, which is still not suitable for oral administration.

None of the investigated formulations and methods were able to achieve results as good as those of the originator formulation. We were successfully able to reproduce the formulation mentioned in the patent and elaborated by Holvoet et al[5].

Discussion and Conclusion

HPBCD proved to be the most effective solubilizer of the investigated cyclodextrins and was used for all further investigations after the survey of binary systems. All of the investigated ingredients for ternary systems increased the solubility of ITR to some degree. However, none of the ternary systems improved solubility of ITR to achieve the target dose of 10 mg/ml. Unlike the case with loratadine pediatric oral liquid (PTR-113) the nature of the acid in the ternary systems did not have a remarkable impact on solubility enhancement, leading to the conclusion that indeed the pH value and thus the degree of ionization of the drug was the most dominant factor.

As an attempt to further increase the solubility, several Ashland polymers were investigated for their ability to prevent precipitation of already dissolved ITR in complexes with HPBCD in water/ethanol mixtures. None of the investigated formulations showed results applicable for oral medication as the drug was only soluble at very low pH-values. Itraconazole needed a combination of complexation with HPBCD, ionization at pH value of 2 and the use of propylene glycol, a potent co-solvent, to achieve solubility for the target dose.

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