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Influence of preparation method on itraconazole oral solutions using cyclodextrins as complexing agents

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In the literature, solubility values of itraconazole complexed with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) were found which were still much too low to obtain the target concentration of 1 g itraconazole/100 ml, the concentration of the marketed itraconazole formulation Sporanox® (Janssen Pharmaceutica). Therefore, we compared two preparation methods: the classical and the dissolving method to investigate if the method of preparation can have an influence on the solubility of itraconazole complexed with cyclodextrin (CD). With the classical method, the active compound and the CDs are jointly dissolved with a co-solvent, propylene glycol, in water. With the dissolving method, the active compound is first dissolved separately in a solvent in which it dissolves well, while the CDs are dissolved in water, before mixing. Three different CDs were used and compared for their complexing capacity with itraconazole. The complex formation of itraconazole with HP-β-CD, sulfobutylether-7-β-cyclodextrin (SBE-7-β-CD) and maltosyl-β-cyclodextrin (malt-β-CD) was investigated at pH 2, in the presence of 10% propylene glycol for an oral solution. These three CDs were chosen as they can also serve in formulations for parenteral use. The method of preparation had an important influence on the complex formation. With the dissolving method, a much higher solubility of itraconazole was obtained using the same CD concentration than with the classical method. Inclusion capacity obtained with the dissolving method was comparable for HP-β-CD and SBE-7-β-CD: 1 g itraconazole/100 ml of 25% HP-β-CD or of 30% SBE-7-β-CD. In 100 ml of 40% malt-β-CD only about 500 mg of itraconazole could be dissolved. With the classical method only around 160 mg itraconazole could be dissolved with 100 ml 40 % HP-β-CD or SBE-7-β-CD. Due to the fast preparation, once the CD amount is known by pretests, the dissolving method shows also an advantage for industrial production.

1. Introduction

Itraconazole is a triazole antifungal agent with a broad spectrum of activity (De Beule and Van Gestel 2001; MacCallum and Odds 2001; Willems et al. 2001). It is active against most human fungal pathogens, e.g. *Candida* sp., also due to the active metabolite hydroxy-itraconazole (De Beule and Van Gestel 2001). It is also the only currently available azole antifungal agent that is effective against *Aspergillus* sp. (Willems et al. 2001).

Itraconazole is practically insoluble in water (European Pharmacopoeia 2001): at physiological pH, less than 1 μg/ml can be dissolved and somewhat more in 0.1 N HCl (4 μg/ml) (Stevens 1999). These properties lead to a poor oral bioavailability with large individual variations (Van Peer et al. 1989). Itraconazole has good solublility in propylene glycol. The pK_a is 3.7 (DAB 1999). It is soluble in extremely acidic media (Hostetler et al. 1992). The absorption of itraconazole is dependent on gastric acidity. It was shown that the absorption is enhanced by drinking Cola, an acidic beverage with a pH of 2.5 (Jaruratanasirikul and Kleepkaew 1997). Furthermore, it was demonstrated that the bioavailability of itraconazole is increased when administered as an oral solution prepared with 2-hydroxypropyl-β-cyclodextrin HP-β-CD instead of using capsules or a suspension (Barone et al. 1998). An oral solution has been developed using HP-β-CD at a concentration of 40% and with 10% propylene glycol as co-solvent (Cedilla et al. 1998). The addition of propylene glycol in water made the inclusion strength of HP-β-CD weaker, because propylene glycol works as a competing agent (Miyake et al. 1999).

The commercial oral solution of 1 g itraconazole/100 ml HP-β-CD solution (Sporanox®, Janssen Pharmaceutica) demonstrates significantly greater bioavailability than preparations without cyclodextrins (CDs). CDs have been shown to improve solubility, stability and bioavailability of drugs by forming inclusion complexes (Loftsson and Brewster 1996; Rajewski and Stella 1996; Holvoet et al. 2005a, b). HP-β-CD is a well known CD derivative, also usable for parenteral administration (Irie and Uekama 1997; Strickley 2004). Other CD derivatives, such as (sulfobutylesther-β-cyclodextrin) (SBE-7-β-CD) (Strickley 2004; http://www.cydexinc.com 2006) and (maltosyl-β-cy-

clodextrin) (malt-β-CD) (Loftsson and Brewster 1997), which also are suitable for parenteral use, were compared in this study, as their combination with itraconazole was not yet described in the literature.
For patients seriously ill with fungal infections, oral antifungal medication should not be employed because of swallowing, obturation or vomiting problems. Optimal absorption of orally administered agents also may be prevented by achlorhydria and diarrhea (Zhou et al. 1998). In high-risk patients, requiring intensive care, oral administration of itraconazole is neither suitable (Vandewoude et al. 1997), requiring the availability of an intravenous formulation.
It was the purpose of this work to compare the inclusion capacity of HP-β-CD for itraconazole with that of two other CDs, useful for oral and parenteral solutions, i.e. malt-β-CD and SBE-7-β-CD, in order to find the minimum CD-concentration to dissolve 1% (m/v) itraconazole for an oral solution. Solubility studies were performed with the classical and the dissolving methods and the results compared.

2. Investigations, results and discussion

2.1. Analytical method

The analytical HPLC method was based on methods developed by Compas et al. (1996) and Jacobson et al. (1995). To avoid precipitation by dilution of the itraconazole-CD complex, which is necessary for analysis, a mixture of MeOH-HCl/DMF (95/5 (v : v)) was used prior to HPLC-analysis. The calibration line was linear in the region from 1 to 60 mg% (m/v) ($r = 0.9997$). The retention time of itraconazole standard was around 5 min.
The method is considered precise as the repeatability of the method was below 1.2%, while the injection repeatability of itraconazole and of itraconazole-CD samples was $\leq$0.7%. The method is accurate, as the selected itraconazole formulations (1 g itraconazole/100 ml 25% HP-β-CD or 1 g itraconazole/100 ml 30% SBE-7-β-CD, see further) were analysed and quantitative recovery of itraconazole was obtained (values between 98.3% and 100.3%).

2.2. Phase solubility techniques

Solubility values of around 160 mg itraconazole/100 ml in a 40% HP-β-CD are described by Miyaki et al. (1999) following the classical method described by Higuchi and Connors (1965). With this method the target concentration of 1 g/100 ml could not be achieved. Nevertheless, it must be possible to enhance the solubility of itraconazole using HP-β-CD, as in the marketed Sporanox® formulation 1 g itraconazole is dissolved in 100 ml of a 40% HP-β-CD solution. Therefore, we compared the solubility studies, performed with either the classical method or with the so-called dissolving method. Also, three cyclodextrins, all very soluble in water and suitable for oral and parenteral purposes, are compared. Then the best results could be starting points to an oral solution (or to a parenteral solution).
A pH of 2.0 was chosen for the oral preparation, as itraconazole is more soluble in acidic solutions (Miyake et al. 1999). The dissolution of itraconazole in an aqueous acidic CD medium is very slow. Therefore, 10% propylene glycol as co-solvent was added to shorten and to simplify the production process (Cedilla et al. 1998). Sorbitol was added as sweetener because of the acid taste due to the low pH, and of a bitter taste from itraconazole and possibly from the co-solvent (Cedilla et al. 1998).

2.2.1. Classical method

As there is a positive non-linear increase in solubility with increasing CD concentration, A_p diagrams (positive deviation from linearity), were obtained (Fig. 1) (Higuchi and Connors 1965). This indicates higher-order complexation: at higher CD concentrations more than one CD molecule is complexed with the guest (Brewster et al. 1989). This type of diagram was also described for itraconazole and HP-β-CD in acidic solutions in the work of Miyake et al. (1999) and Peeters et al. (2002), attributed to the formation of higher-order (1 : 2) complexes. Our results of itraconazole solubility increase with HP-β-CD are in accordance with those of Miyake et al. (1999), i.e. around 160 mg itraconazole could be dissolved in 100 ml of 40% HP-β-CD. From our results, we can conclude that the increase in solubility was slightly higher with HP-β-CD (163 mg itraconazole in 100 ml 39% HP-β-CD) than with SBE-7-β-CD (144 mg itraconazole in 100 ml 38% SBE-7-β-CD), but remains far from the target concentration of 1 g itraconazole/100 ml. Therefore, the classical solubility study was not performed with malt-β-CD.
It is well known that the use of co-solvents can influence complex formation with CDs (Szejtli 1988). Often, this influence is negative, due to competition of co-solvent and active compound for complex formation with CD. Also other authors mentioned the addition of alcohol (Pitha and Hoshino 1991) or propylene glycol (Miyake et al. 1999) to aqueous solutions reduces the degree of complexation, possibly by occupying the lipophilic CD cavity and thus, preventing the drug molecules from entering (Loftsson et al. 1993).
Because of a slow dissolution of itraconazole in an aqueous acidic CD medium without co-solvent and our similar results obtained for solubility curves of itraconazole at pH 2.0 with propylene glycol (see above), we decided not to perform the classical solubility method without propylene glycol. From the solubility studies of Miyake et al. (1999) and Peeters et al. (2002) it was deduced that approximately 400–500 mg itraconazole can be dissolved in 100 ml 40% HP-β-CD at pH 2.0 without additives. This is already a remarkable increase in solubility, but still only about half of the target concentration of 1 g itraconazole/100 ml can be reached.
With the classical method, it was impossible to reach our aim. Therefore, another preparation method, providing a

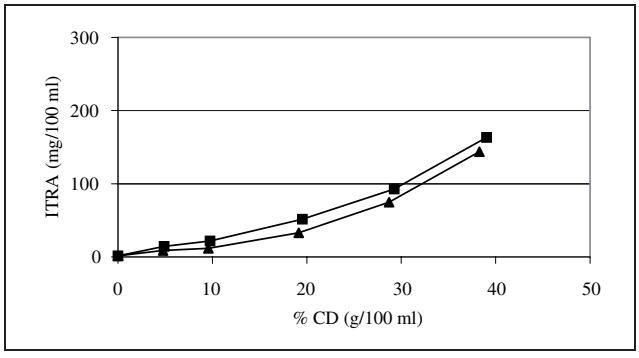

Fig. 1: Complexation of itraconazole (ITRA) (mg/100 ml) as a function of the CD concentration (g/100 ml) at 25 °C and pH 2.0, following the classical method
■ HP-β-CD, ▲ SBE-7-β-CD

better solubility enhancement, was looked for. Cedilla et al. (1998) described 1% (w/v) itraconazole-solutions with 40% HP-β-CD. Therefore, we also used the dissolving method for two other CD derivatives: malt-β-CD and SBE-7-β-CD, in order to find the minimum CD-concentration to dissolve 1% (m/v) itraconazole for an oral solution.

2.2.2. *Dissolving method*

Itraconazole, dissolved in propylene glycol in acid medium (pH 1) was mixed with given amounts of a concentrated CD-solution to obtain 1% (m/v) itraconazole and varying CD concentrations (see Experimental). For the oral solution, sorbitol was added as sweetener and the pH of the solutions was adjusted to pH 2.0. The seven solutions of each CD (HP-β-CD and malt-β-CD) were analysed for itraconazole content after dilution. At the lower CD-concentrations (<20% CD), an excess of itraconazole was present, which could not be complexed by CD and an immediate precipitation occurred. This precipitate was centrifuged after 1 day of shaking and the clear supernatant analysed. The results are shown in Fig. 2a. It is seen that 1% (w/v) itraconazole can be dissolved in solutions with at least 20% HP-β-CD. Nevertheless, precipitation occurred later in the samples with 20% HP-β-CD and increased with time. No precipitation was noted within 30 days in the solutions with at least 25% HP-β-CD. This was not the case for malt-β-CD: even in the solutions with more than 20% CD precipitation occurred after some days. In the solutions with lower CD concentrations, where immediate precipitation was observed, additional precipitation was seen the following days. The results in Fig. 2a are thus overestimated as in all samples with $\leq$20% HP-β-CD and in all samples with malt-β-CD, precipitation occurred later. A possible explanation is that when mixing itraconazole and CD solutions, the concentration of propylene glycol decreases to 10% and itraconazole precipitates at those conditions where the amount of CD is too low to keep it dissolved. The process takes time to occur, but was observed in all samples with malt-β-CD and those with $\leq$20% HP-β-CD.

Therefore, equilibrium conditions (the time after which the maximal amount of complex between itraconazole and CD is formed) were determined by analysing new samples during several days (dissolving method: 1 g itraconazole with 12.5% HP-β-CD, 2 series of 7 samples each (Table). Series 1 was stored without shaking, while series 2 was shaken continuously. The results of this experiment are summarised in the Table. Equilibrium was only reached after one week to 14 days depending whether shaking was applied or not. The phase solubility diagrams were again constructed for $\geq$20% CD, now with equilibrium values (shaking during 14 days), to ensure no precipitation will occur over time. The results are summarised in Fig. 2b. The phase solubility diagrams for $<$20% CD were not reconstructed, as precipitation occurred. From Fig. 2b, it can be noted that 1 g itraconazole can effectively be dissolved in 100 ml of a 25% HP-β-CD or of a 30% SBE-7-β-CD solution. With 40% malt-β-CD only 444 mg itraconazole can be dissolved per 100 ml formulation containing 40% of CD. A preparation based on malt-β-CD was therefore excluded from further evaluation. Fig. 3 compares the equilibrium versus non-equilibrium values of itraconazole with malt-β-CD, demonstrating that precipitation did not occur immediately.

Table: Concentration itraconazole retrieved (mg % m/v) in the supernatant of 12.5% HP-β-CD as a function of time, 1 g itraconazole was added

Day	Series 1 without shaking	Series 2 continuous shaking
1	239	204
2	191	142
6	181	128
10	157	127
14	126	126
15	125	126
30	126	127

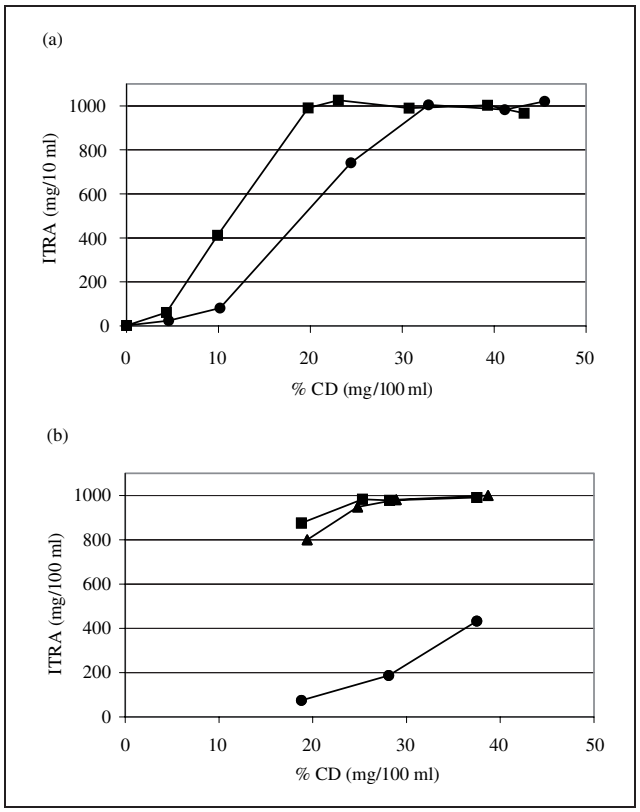

Fig. 2: Complexation of itraconazole (ITRA) (mg/100 ml) as a function of the CD concentration (g/100 ml) at 25 °C and pH 2.0, following the dissolving method (a) non equilibrium values, 1 day of shaking; (b): equilibrium values, 14 days of shaking
■ HP-β-CD, ▲ SBE-7-β-CD, ● malt-β-CD

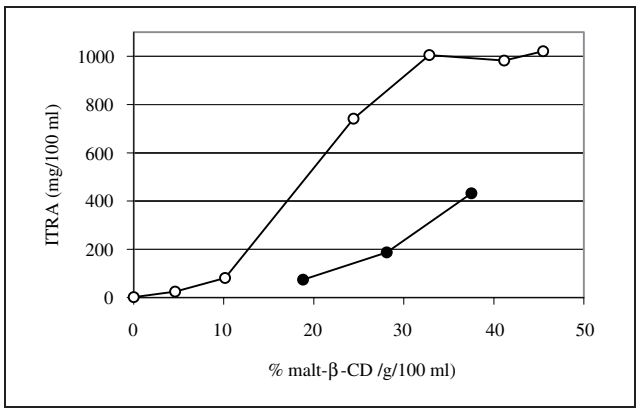

Fig. 3: Comparison of none equilibrium versus equilibrium values for the complexation of itraconazole (ITRA) (mg/100 ml) as a function of malt-β-CD concentration (g/100 ml) at 25 °C and pH 2.0, following the dissolving method
○ non equilibrium, ● equilibrium

Both HP-β-CD and SBE-7-β-CD (Fig. 2b) can serve for preparing an oral formulation with itraconazole. A preparation containing 1 g itraconazole in a 100 ml 25% HP-β-CD or 30% SBE-7-β-CD aqueous solution containing 10% propylene glycol and 19% sorbitol seemed possible at a pH 2.0. When the necessary amounts of CD to dissolve the required active compound are known by pretests, preparation needs only a few hours time. Further experiments have to reveal if the proposed amounts of CDs are sufficient to allow, for instance, temperature changes during processing and storage.

The sequence of dissolving seems to influence the complexation capacity. In the classical method the solution is from the start composed of CDs, itraconazole, water, propylene glycol and sorbitol. Propylene glycol competes immediately with the activum for complex formation with CD (see higher). In the dissolving method both the CDs and itraconazole were first dissolved separately in water and in propylene glycol at pH 2, respectively. Then the two solutions are mixed, and sorbitol is added afterwards. It is suggested that itraconazole is solvated by propylene glycol molecules, forming a more hydrophilic outer layer. When adding to the aqueous CD solution, for unknown reasons, itraconazole seems to better enter the CD cavity. Adding sorbitol afterwards also creates a situation that sorbitol is not competing with, for instance, CD for hydratation with water molecules. This factor also might influence complex formation in some way.

2.3. Evaluation of the oral formulations

The taste of the selected oral formulations is awfully bitter. Therefore, 10 flavours, butterscotch, caramel, cherry, lemon, mango, orange juice, orange peel tincture, raspberry, strawberry and vanilla, were added to the formulations in two concentrations (0.2 and 0.5%). All flavours were initially judged by three persons. Only the as best selected (caramel, cherry, orange juice, orange peel tincture and raspberry, all in concentrations of 0.5%) were further assessed. A panel of 20 test persons choose raspberry as the best flavour. Addition of sodium saccharin did not improve the taste.

2.4. Conclusion

At this moment, it is unknown whether the dissolving method will systematically allow dissolving more active ingredient than the classical method. This observation should be verified by more case studies before this method generally could be recommended to enhance inclusion capacity of cyclodextrins for oral use.

3. Experimental

3.1. Materials

3.1.1. Chemicals

Itraconazole (Mr 706.6) was provided by Precise Chemipharma PVT.LTD, (Mumbai, India). Hydroxypropyl-β-cyclodextrin (HP-β-CD, Mr 1380) was purchased from Roquette (Lestrem, France), sulfobutylether-β-cyclodextrin (SBE-β-CD, Mr = 2200) from CyDex (Overland Park, Kansas, USA) and maltosyl-β-cyclodextrin (malt-β-CD, Mr 1797) from Cyclodextrin Technology Development (High Springs, Florida, USA).

Acetic acid (glacial), HCl 37%, NaOH, *N*,*N*-dimethylformamide (DMF), methanol (MeOH) and oxalic acid were obtained from Merck (Darmstadt, Germany), acetonitrile for HPLC from BDH Laboratory supplies (Poole, England, U.K.), diethylamine (DEA) from UCB (Brussels, Belgium), sorbitol 70% and propylene glycol from α-Pharma (Zwevegem, Belgium) and dimethylsulfoxide (DMSO) from Federa (Brussels, Belgium). MilliQ (mQ) water was obtained in-house from a milli-Q water purification system (Millipore, Molsheim, France). Butterscotch, caramel, cherry, lemon, mango, orange juice, raspberry, strawberry and vanilla, all from Firmenich (Neuilly-sur-Seine, France), orange peel tincture and sodium saccharin from α-Pharma (Nazareth, Belgium), were used as flavours.

3.1.2. Apparatus

The itraconazole solutions were analysed, using an HPLC Lachrom apparatus (Merck-Hitachi, Tokyo, Japan), consisting of a Lachrom L-7100 pump, a variable wavelength UV detector (L-7420 UV-VIS), and a Lachrom D-7500 integrator. As stationary phase a monolithic C_{18}-column (Chromolith, RP-C_{18}, 100 × 4.6 mm, 5 μm) from Merck was applied.

The solids were weighed on a Sartorius basic analytical balance (Sartorius, Göttingen, Germany). The pH measurements were performed using a Radiometer Copenhagen PHM 26 pH meter (Copenhagen, Denmark) calibrated daily using pH 4.00, 7.00 and 10.00 standard buffers (Merck, Darmstadt, Germany). The pH of small volumes was measured by a WTW Multical pH meter (Metro Parkway, Florida).

3.2. Methods

3.2.1. High-performance liquid chromatography (HPLC)

The mobile phase was composed of acetonitrile/H_2O/DEA: 58/42/0.05 v/v/v) adjusted to pH 6 by adding glacial acetic acid. It was filtered through a 0.2 μm membrane filter (Schleicher & Schuell, Dassel, Germany) and degassed on a Bransonic 5210E-MT ultrason bath (Branson Ultrasone Cooperation, Connecticut, US). The detection wavelength was 258 nm. The injection volume was 20 μl and the flow rate 1.0 ml/min.

For the calibration line, first a stock solution of itraconazole was prepared by dissolving ca. 60 mg itraconazole (exactly weighed) in 5 ml of *N*,*N*-dimethylformamide and then adding MeOH-HCl/DMF 95/5 (v : v) (diluting solvent) up to 100.0 ml. The methanolic HCl (MeOH-HCl) solution was prepared by adding 830 mg HCl 37% to 100 ml methanol. From the stock solution 10 dilutions were prepared ranging from 1 to 50 mg% (m/v) itraconazole in the diluting solvent.

Precision. An itraconazole standard of 3 mg% was six times prepared and injected. The repeatability of injection was checked by six replicate injections of two itraconazole standard concentrations (3 and 10 mg%), of a 1.6 mg itraconazole/ml 39%HP-β-CD solution and of a 1.4 mg itraconazole/ ml 38% SBE-7-β-CD solution.

Accuracy. The selected itraconazole oral formulations, which consisted of 1 g itraconazole/100 ml 25% (w/v) HP-β-CD or 1 g itraconazole/100 ml 30% (w/v) SBE-7-β-CD), were prepared and injected 3 times after a 100 times dilution. The content was determined relative to the above calibration line.

3.3. Phase solubility techniques

3.1.1. Classical method

The classical method of Higuchi and Connors (1965) was followed. A solution of 10% propylene glycol and 19% sorbitol in water was prepared and adjusted to pH 2 by adding 1 N HCl. In this solution, stock solutions of 40% HP-β-CD or malt-β-CD were prepared, and diluted in screw capped vials in the range 0 to 40%. The moisture contents of the CDs were taken into account when drawing the phase solubility diagrams. An excess of itraconazole was then added to 10.0 ml and shaken (1 week) at room temperature (23 °C) up to equilibrium. The pH was measured daily and when necessary, pH-adjustment was performed by adding 0.1 N HCl. After 1 week of shaking, the suspensions were centrifuged (Certa centrifuge, International Equipment Company, Bedfordshire, England) at 5000 × g for 15 min. The supernatant was diluted 50 times with the diluting solvent. A flocky precipitation occurred due to sorbitol. Therefore, the samples were centrifuged (15 min, 5000 × g) a second time and the itraconazole concentration in the supernatant was determined with the HPLC procedure described above.

3.1.2. Dissolving method

Itraconazole (1 g) was dissolved in 10 ml propylene glycol at pH 1 (by adding 1 N HCl) by warming (warm water bath). Of each CD, 21 g was dissolved in 25 ml water. All mixtures were shaken until dissolution. The itraconazole and CD solutions were mixed in different ratios to obtain 1% itraconazole and several concentrations of CDs, ranging from 0 to 46%. Seven preparations were made containing 0, 4, 10, 21, 34, 42 and 46% of CD, respectively. The solutions were acidified to pH 2.0 (with 0.1N HCl) after adding sorbitol 70% until a final concentration of 19% was reached and brought nearly to volume with milliQ water. At low CD-concentrations, a fraction of the dissolved itraconazole precipitated. This fraction was centrifuged at 5000 × g for 15 min and, when necessary, filtered through a regenerated cellulose filter of Alltech (Lokeren, Belgium). The clear solutions were diluted with the diluting solvent till a concentration in the linear range of the calibration line and analysed by HPLC.

3.4. Preparation and evaluation of the oral formulations

The dissolving method was applied: 1 g of itraconazole was first dissolved in 10 ml propylene glycol at pH 1 by warming, and 25 g HP-β-CD or 30 g SBE-7-β-CD was dissolved in 50 ml water. Both solutions were mixed. Then 19 ml of sorbitol 70% and 0.5 g raspberry flavour are added and the solution nearly brought to volume with mQ water. This solution is acidified to pH 2.0 by adding (1 N or 0.1 N) HCl and the volume adjusted to 100.0 ml with water.

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