Research paper

Formulation and characterization of ternary solid dispersions made up of Itraconazole and two excipients, TPGS 1000 and PVPVA 64, that were selected based on a supersaturation screening study

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Abstract

Both D-α-tocopheryl polyethylene glycol 1000 (TPGS 1000) and polyvidone-vinylacetate 64 (PVPVA 64) provided an increase in the degree of supersaturation and stability of supersaturated Itraconazole solutions, compared to a blanc without excipient. Therefore, both components were combined as carrier in order to make ternary solid dispersions of Itraconazole by spray drying. This way, TPGS 1000 could be incorporated into a powder. Dissolution experiments on the ternary solid dispersions revealed that during the first hour the release was much higher than for the binary Itraconazole/PVPVA 64 solid dispersions. For some compositions a release of more than 80% was reached after 10 min. However, after the first hour the drug started to precipitate. The ternary solid dispersions were all XRD amorphous, but MDSC revealed the coexistence of multiple amorphous phases and a crystalline Itraconazole phase, depending on the composition. Therefore the burst effect during the first hour can be ascribed to an accelerated dissolution of the amorphous Itraconazole fraction in the presence of TPGS 1000. The precipitation after 1 h, however, is probably due to the combination of the surfactant properties of TPGS and the small crystalline Itraconazole fraction.
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1. Introduction

A large percentage of potential drug candidates suffer from low aqueous solubility and/or low dissolution rate. This results in low drug concentrations at the absorptive sites and hence low oral bioavailability [1]. Amidon et al. classified such drugs in the Biopharmaceutical Classification System as class II compounds [2]. The formulation of solid dispersions of BCS II compounds either by copre-cipitation of drug and carrier from a common solvent or by co-melting and quench cooling is a popular strategy to reduce the drug particle size and hence increase the dissolution rate [3]. If a drug is molecularly dispersed into its carrier the term solid solution can be used and the dissolution of the carrier becomes the rate limiting step [1,4]. Also, the solution that is generated in this way will have a drug concentration that is far beyond its thermodynamic solubility. Consequently, the excessive amount of drug will tend to precipitate until a saturated solution is formed [5,6]. Therefore, one of the rationales to select an excipient for the formulation of solid dispersions should be its influence on the stability of the supersaturated solution that is generated upon dissolution. On the other hand the properties of the solid are extremely important both in terms of dissolution

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as in terms of physical stability. In order to improve the dissolution and physical stability it is preferable to avoid the formation of crystalline drug clusters which can result from recrystallization of amorphous drug clusters. Therefore, the formulation of a solid solution in which the drug is stabilized by drug-carrier interactions and/or antiplasticizing effects of the carrier is desirable [7]. Since the number of carriers that provides both molecular dispersion and improved dissolution is rather limited, this study aims to develop carrier blends in order to meet these requirements.

In this paper, Itraconazole, a BCS II compound with an extremely low aqueous solubility of 4 μg per mL at pH 1, was used as a model compound to screen for excipients that improve the degree of supersaturation and/or improve the stability of the solution [8]. Based on this screening procedure TPGS 1000 and PVPVA 64 were selected to prepare ternary solid dispersions by spray drying. In these dispersions PVPVA 64 should provide molecular dispersion of Itraconazole and TPGS 1000 should provide an increased dissolution [9,10].

2. Materials and methods

2.1. Materials

Crystalline Itraconazole (purity more than 99%, melting temperature = 166.8 °C) was kindly donated by Johnson and Johnson Pharmaceutical Research and Development (Beerse, Belgium). The following polymers were used in the supersaturation screening: Polyvidone K-25 (PVP K-25) (BASF, Ludwigshafen, Germany), Polyvidone-vinylacetate 64 (PVPVA 64) (BASF, Ludwigshafen, Germany), Hydroxypropylmethylcellulose 2910 E5 (HPMC 2910 E5) (Johnson and Johnson Pharmaceutical Research and Development, Beerse, Belgium), Polyethylene glycol 6000 (PEG 6000) (Acros Organics, Geel, Belgium), Polyethylene glycol 100 000 (PEG 100 000) (Sigma–Aldrich, Steinheim, Switzerland), Polymethacrylate E 100 (Eudragit E 100) (Röhm, Darmstadt, Germany), Polyvinylalcohol polyethylene glycol copolymer IR (Kollicoat IR) (BASF, Ludwigshafen, Germany), Polyethylene–propylene glycol copolymer 188 (Poloxamer 188) (BASF, Ludwigshafen, Germany), Polyethylene–propylene glycol copolymer 407 (Poloxamer 407) (BASF, Ludwigshafen, Germany) and Polyacrylic acid (PAA) (BASF, Ludwigshafen, Germany). The following surfactants were used; Polyoxyethylene 20 sorbitan monolaurate (Tween 20) (Uniqema, Everberg, Belgium), Polyoxyethylene 20 sorbitan monooleate (Tween 80) (Federa, Brussels, Belgium), Glycerol polyethylene glycol oxystearate (Cremophor RH40) (BASF, Ludwigshafen, Germany), Glycerol polyethylene glycol ricinoleate (Cremophor EL) (BASF, Ludwigshafen, Germany), Polyoxyl 20 stearate (Myrj 49) (Uniqema, Everberg, Belgium), Polyoxyl 40 stearate (Myrj 52) (Uniqema, Everberg, Belgium), Polyoxyl 100 stearate (Myrj 59) (Uniqema, Everberg, Belgium), d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS 1000) (Eastman Chemical Company, Anglesey, UK), Poly-ethylene glycol 1500 glyceryl laurate (Gelucire 44/14) (Gattefossé, Saint-Priest, France), Polyethylene glycol 660 12-hydroxystearate (solutol HS 15) (BASF, Ludwigshafen, Germany), Sodium lauryl sulfate (Certa, Braine-l'Alleud, Belgium).

2.2. Methods

2.2.1. Supersaturation assay

In order to obtain supersaturated solutions the co-solvent method was used, i.e. 500 μL of a 3% Itraconazole in N,N-dimethylformamide (DMF, Acros Organics, Geel, Belgium) solution was added to 10 mL of simulated gastric fluid without pepsin (SGF$_{sp}$; USP 24) with or without (blanc) excipient, in 12 mL glass vial with stopper. The vials were mixed in a rotary mixer (Snijders Scientific, Tilburg, The Netherlands) and 500 μL samples were taken and filtered with a 0.45 μm Teflon filter (Macherey-Nagel, Düren, Germany) after 5, 30, 60 and 120 min. The first 300 μL was discarded and 100 μL of the remaining filtrate was diluted with 900 μL of 1:1 DMF:SGF and mixed with a vortex. Exactly 200 μL of this solution was filled into a UV transparent 96 flat bottom well plate (Greiner Bio-one, Frickenhausen, Germany) and the UV absorbance was measured with a microplate reader (Tecan Infinite M200, Salzburg, Austria). The Itraconazole content was determined using Beer's law with reference to a series of dilutions in the same solvent. Possible interference of the excipients was ruled out since analysis of the excipient solutions spiked with a fixed amount of Itraconazole rendered the added amount. For the above-listed polymers the following concentrations were used; 0.01; 0.05; 0.1; 1; 4 and 8%. For the surfactants the following range was used; 0.01; 0.05; 0.1; 1 and 2% (w/v).

2.2.2. Spray drying

Blends of TPGS 1000 and PVPVA 64, binary dispersions of Itraconazole and PVPVA 64 and ternary dispersions made up of Itraconazole, TPGS 1000 and PVPVA 64 were prepared in a Buchi mini spray dryer B191 (Buchi, Flawil, Switzerland), (Table 1). The powders were spray dried from a 5% solution of the powder blend in CH$_2$Cl$_2$, the inlet temperature was set at 80 °C and the outlet temperature varied from 50 to 35 °C. The aspirator was set at 100%, the pump at 45%, the air flow was 800 L/h. All spray dried powders were dried for one week prior to analysis and further stored in a dessicator over P$_2$O$_5$ at 25 °C.

2.2.3. Physicochemical characterization

2.2.3.1. Modulated temperature differential scanning calorimetry (MTDSC). All spray dried samples and starting materials were analyzed in triplicate. MTDSC measurements were carried out using a Q2000 Modulated DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. Data were analyzed mathematically using Thermal Analysis software version 3.9 A (TA Instruments, Leatherhead, UK). Dry nitrogen (5.5) at a

Table 1
Compositions of the spray dried powders

Blends
1.	10/90 TPGS 1000/PVPVA 64
2.	25/75 TPGS 1000/PVPVA 64
3.	40/60 TPGS 1000/PVPVA 64

Binary solid dispersions
1.	10/90 Itraconazole/PVPVA 64
2.	20/80 Itraconazole/PVPVA 64
3.	40/60 Itraconazole/PVPVA 64

Ternary solid dispersions
1.	10% Itraconazole in 10/90 TPGS 1000/PVPVA 64
2.	20% Itraconazole in 10/90 TPGS 1000/PVPVA 64
3.	40% Itraconazole in 10/90 TPGS 1000/PVPVA 64
4.	10% Itraconazole in 25/75 TPGS 1000/PVPVA 64
5.	20% Itraconazole in 25/75 TPGS 1000/PVPVA 64
6.	40% Itraconazole in 25/75 TPGS 1000/PVPVA 64

flow rate of 50 mL/min was used to purge the DSC cell. TA Instruments (Leatherhead, UK) open aluminum pans were used for all measurements. The mass of the empty sample pan and the reference pan was taken into account for the calculation of the heat flow, the sample mass varied from 1 to 6 mg. The enthalpic response was calibrated with an Indium standard and the temperature scale was calibrated with Octadecane, Indium and Tin. The heat capacity signal was calibrated by comparing the response of a sapphire disk with the equivalent literature value at 80 °C. Validation of temperature, enthalpy and heat capacity measurements using the same standard materials showed that the deviation of the experimental from the reference value was <0.5 °C for the temperature, <1% for the enthalpy and <1% for the heat capacity at 80 °C.

The amplitude used was 0.212 °C, the period was 40 s, and the underlying heating rate was 2 °C/min. The samples were heated from −90 to 180 °C. In order to detect the glass transition of TPGS 1000 the sample was heated to 60 °C and kept isothermal for 10 min. Consequently the sample was equilibrated at −80 °C for 10 min and heated to 60 °C. Glass transitions were analyzed in the reversing heat flow, recrystallization peaks were analyzed in the non-reversing heat flow and melting peaks were analyzed in the total heat flow signal. An estimation of the crystallinity degree of TPGS 1000 and Itraconazole was obtained from their respective recrystallization and melting enthalpies using the following equation (Eq. (1)):

$$\text{crystallinity } (\%) = \frac{\Delta H f_{\text{inblend}}}{(\Delta H f \times w\%)} \times 100 \qquad (1)$$

with $\Delta H f_{\text{TPGS}} = 108.6$ J/g and $\Delta H f_{\text{Itraconazole}} = 84.0$ J/g. The enthalpy of cold crystallization of Itraconazole was subtracted from its melting enthalpy in order to obtain an estimation of the initial crystallinity [11]. Each measurement was done in triplicate.

2.2.3.2. X-ray powder diffraction. X-ray powder diffraction was performed at room temperature with an automated

Philips PW 1710/80 diffractometer (Philips, The Netherlands) in Bragg-Brentano geometry. X-menu diffractometer control (Philips, The Netherlands) was used for data collection. Cu Kα-radiation ($\lambda = 1.54184$ Å) was obtained with a Ni-filter and a system of diverging, receiving and scattering slides of 1/4°, 0.2 mm and 1/4°, respectively, was used. The data were collected in step scan mode in the region of $2° \leqslant 2\theta \leqslant 60°$ with a step size of 0.02° and a counting time of 2 s. Instrument power used: a voltage of 40 kV and a current of 32 mA. The powders were side-loaded in a sample holder. The diffractograms were analyzed using WinPLOTR program, version March/2005 [12].

2.2.3.3. Analysis of Itraconazole content. The solid dispersions were dissolved in dimethylsulfoxide (DMSO) and the Itraconazole content was determined with HPLC using a series of dilutions of Itraconazole in DMSO. Experiments were done in triplicate. HPLC analysis was performed with a Merck Hitachi pump L7100, an ultraviolet (UV) detector (L7400), an autosampler (L7200), and an interface (D7000, all Merck, Darmstadt). A LiChrospher 100 RP-18 (5 μm, 12.5 × 4) (Merck, Darmstadt, Germany) column was used. Acetonitrile/tetrabutyl ammonium hydrogen sulfate 0.01 N (55:45; v/v) was used as mobile phase at a flow rate of 1.0 mL/min, all solvents used were of HPLC grade. The injection volume was 20 μL, and UV detection was used at a wavelength of 260 nm, the retention time for Itraconazole was 4.6 min [13].

2.2.3.4. Residual solvent determination by headspace gas chromatography/mass spectrometry (GC-MS). A quadrupole MS (mass spectrometer) coupled to HS-GC (headspace–gas chromatography) was used to identify and quantify residual dichloromethane. The GC instrument used was an Autosystem XL capillary gas chromatograph (Perkin-Elmer, Foster city, CA, USA) coupled to a Turbomass mass spectrometer (Perkin-Elmer). The headspace used was a Turbomatrix HS40XL (Perkin-Elmer) and the headspace parameters are listed in Table 2. The GC was equipped with a bonded polyethylene glycol (0.5 μm film thickness) coated capillary column (AT-Aquawax, 30 m × 0.53 mm i.d.). The oven temperature was programmed at 50 °C for 10 min, 39.9 °C/min to reach 180 °C and maintaining for 15 min. The injection port temperature was maintained at 140 °C. The carrier gas flow rate through the column was 4 mL/min. The MS ion source temperature

Table 2
Headspace parameters

Thermostatting temperature	105 °C
Thermostatting time	30 min
Needle temperature	115 °C
Transferline temperature	125 °C
Pressurization time	0.5 min
Injection time	0.04 min
Carrier gas pressure	180 kPa

was maintained at 200 °C. The ion energy used was −70 eV. The mass range investigated was 16–350 u. The data from the MS were collected and integrated by TUR-BOMASS software (Perkin Elmer). The data were acquired in SIM mode (single ion mode recording) on mass fragments 49 and 84 starting at 2 min and ending at 5 min after injection. The dichloromethane retention time was 2.98 min.

2.2.4. Dissolution testing

Dissolution experiments were performed in triplicate on the binary and ternary dispersions. The tests were performed according to the USP 24 method 2 (paddle method) in a Hanson SR8plus dissolution apparatus (Chatsworth, CA, US). To simulate the dissolution of a weak basic compound in the stomach, 500 mL of simulated gastric fluid without pepsin (SGF$_{sp}$; USP 24) was used as dissolution medium at a temperature of 37 °C and a paddle speed of 100 rpm. An amount of the spray dried powders, corresponding to an Itraconazole dose of 100 mg, was added to the dissolution medium. Five-milliliter samples were taken and immediately replaced with fresh dissolution medium at 5, 10, 15, 30, 45, 60, 120 min. These samples were filtered with 0.45 μm Teflon filters (Macherey-Nagel, Düren, Germany). The first two milliliter was discarded. The remainder was diluted with methanol (1/10) to avoid precipitation, and analyzed with HPLC, as described above [13].

3. Results and discussion

3.1. Supersaturation screening

In the blank experiment the supersaturation degree and stability was determined for a supersaturated Itraconazole solution without any excipient. The supersaturation degree, expressed as the amount of Itraconazole in solution after 5 min with reference to the amount added, was $44 \pm 1\%$. After 2 h there was $28 \pm 12\%$ of Itraconazole in solution with reference to the amount added. These data suggest that even without addition of an excipient a significant degree of supersaturation compared to the thermodynamic solubility can be obtained. For most of the polymers the stability of the supersaturated solution was superior compared to the blanc. However, in general the degree of supersaturation did not increase much. With PVPVA 64 however, a concentration dependent increase in the supersaturation degree as well as an improved stability was obtained [14] (Fig. 1).

Nearly all screened surfactants provided a large increase in the supersaturation degree after 5 min but did not prevent Itraconazole from precipitating. In fact, the degree of precipitation increased with the concentration and was far more pronounced than for the blanc. The explanation for these observations lies in the fact that surfactants increase the solubility and hence promote intermolecular collisions and the formation of nuclei [5,6]. One exception,
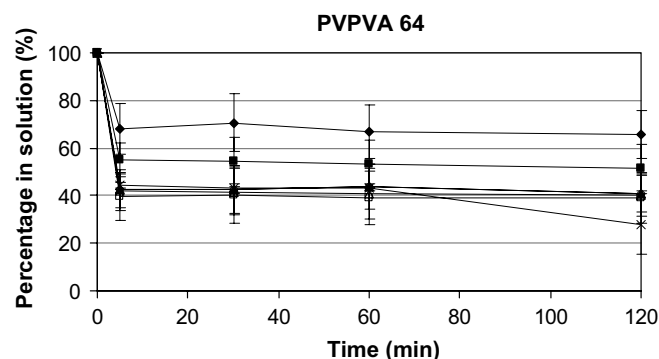

Fig. 1. Supersaturation assay with PVPVA 64; The percentage of Itraconazole (Y-axis) with reference to the amount added as a function of time (X-axis); 8% PVPVA 64 (◆), 4% PVPVA 64 (■), 1% PVPVA 64 (▲), 0.1% PVPVA 64 (◆), 0.05% PVPVA 64 (□), 0.01% PVPVA 64 (△), blanc (X), error bars represent the standard deviation ($n = 3$).

however, is TPGS 1000 for which at high concentrations (2 and 1%) an increase of ca. 50% compared to the blank was obtained. Unlike the other surfactants, this increase could also be maintained for a period of 2 h (Fig. 2). Based on the outcome of these experiments PVPVA 64 and TPGS 1000 were selected to formulate a ternary solid dispersion of Itraconazole. Previous investigations showed that up to 80% of Itraconazole can be molecularly dispersed in PVPVA 64, which is an additional benefit [9,10]. The solid state properties of TPGS 1000 are less beneficial with respect to powder properties, because of its low melting point (32.60 °C ± 0.01 °C). Therefore, TPGS 1000/PVPVA 64 blends were prepared and their miscibility limit was determined.

3.2. Characterization of TPGS 1000/PVPVA 64 blends

In order to obtain a compatible blend and a flowing powder the miscibility of PVPVA 64 and TPGS 1000 was investigated. The composition with 10/90 w/w TPGS 1000/PVPVA 64 rendered an amorphous product with a
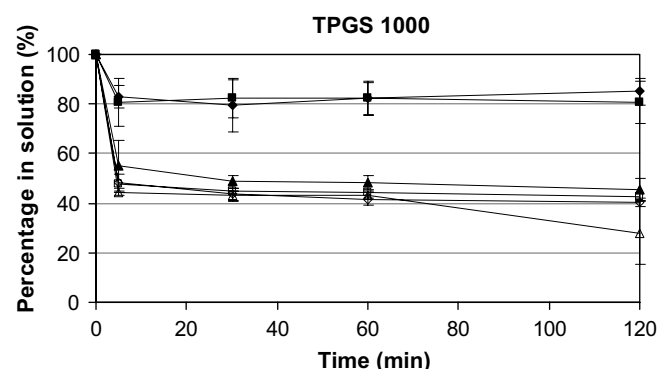

Fig. 2. Supersaturation assay with TPGS 1000; The percentage of Itraconazole (Y-axis) with reference to the amount added as a function of time (X-axis); 2% TPGS 1000 (◆), 1% TPGS 1000 (■), 0.1% TPGS 1000 (▲), 0.05% TPGS 1000 (◆), 0.01% TPGS 1000 (△), blanc (□), error bars represent the standard deviation ($n = 3$).

single mixing glass transition at $85.0 \pm 0.5\,°C$. Increasing the amount of TPGS to 25% resulted in a phase separated system with a small crystalline TPGS 1000 phase. A small melting peak was visible in the MDSC signal at $32.6 \pm 0.2\,°C$. In the reversing heat flow two mixing glass transitions were detected, one at $51.4 \pm 0.2\,°C$ and one at $76.4 \pm 1.7\,°C$. Blends with higher amounts of TPGS 1000 (40/60 and 50/50) resulted in a sticky material and a liquid, respectively. The X-ray diffractogram of the phase separated 40/60 w/w TPGS 1000/PVPVA 64 composition clearly depicts two diffraction peaks at 19 and $23°\ 2\theta$ corresponding to the semicrystalline polyethylene glycol chains of TPGS 1000 (Figs. 3 and 4).

Based on the outcome of these experiments two blends, one below and one right above the miscibility limit, 10/90 and 25/75 w/w, respectively, were selected for the formulation of ternary dispersions with 10, 20 or 40% Itraconazole.

3.3. Characterization of the solid dispersions

3.3.1. Itraconazole content of the solid dispersions

HPLC analysis was used to determine the exact content of Itraconazole in the binary and ternary dispersions. The obtained values were between 100.1 and $103.5\% \pm 0.1$ of the theoretical values.

3.3.2. Dissolution testing of solid dispersions

Comparison of the binary Itraconazole/PVPVA 64 solid dispersions with the ternary solid dispersions showed that addition of TPGS to the carrier matrix leads to a vast improvement of the dissolution characteristics, especially during the first hour (Figs. 5 and 6). Within the series with 25/75 w/w TPGS 1000/PVPVA 64, the sample with 10%

Itraconazole reached a dissolution of more than 90% after 10 min and after 2 h still more than 90% of the dose was in solution. After 1 h however, the binary dispersion with 10% Itraconazole in PVPVA 64 intersects the dissolution profile of the ternary dispersion. The release profiles of the samples with 20 and 40% of Itraconazole in 25/75 w/w TPGS 1000/PVPVA 64 were not significantly different (the error bars are overlapping). For both dispersions more than 80% of the dose was in solution after 5 min, a maximal release of $\pm 90\%$ was reached after 15 min and Itraconazole started to precipitate after 45 min. The intersection between the ternary and the binary dispersion occurs at 60 min for the samples containing 20% of Itraconazole and at 120 min for the samples with 40% Itraconazole (Fig. 5). Within the series with 10/90 w/w TPGS 1000/PVPVA 64 similar results were found for the sample containing 10 and 20% of Itraconazole. However, due to the lower concentration of TPGS the release for the sample with 20% Itraconazole is less high, ca. 80%. Also the precipitation after 2 h is more pronounced for these samples. The sample with 40% Itraconazole in 10/90 TPGS 1000/PVPVA 64 on the other hand shows a release profile that is similar to that of 40% Itraconazole in PVPVA 64. In this case, no precipitation was observed and the advantage over the binary dispersion is maintained during the whole sampling period. After 120 min a release of more than 80% is obtained for the ternary dispersion where-else the release is less than 70% for the binary dispersion (Fig. 6).

In general TPGS 1000 seems to have a double effect on the dissolution. At first the solubility of Itraconazole is enhanced, leading to superior dissolution. After 1 h however, the supersaturation can no longer be maintained even though this was not the case for the preliminary supersat-
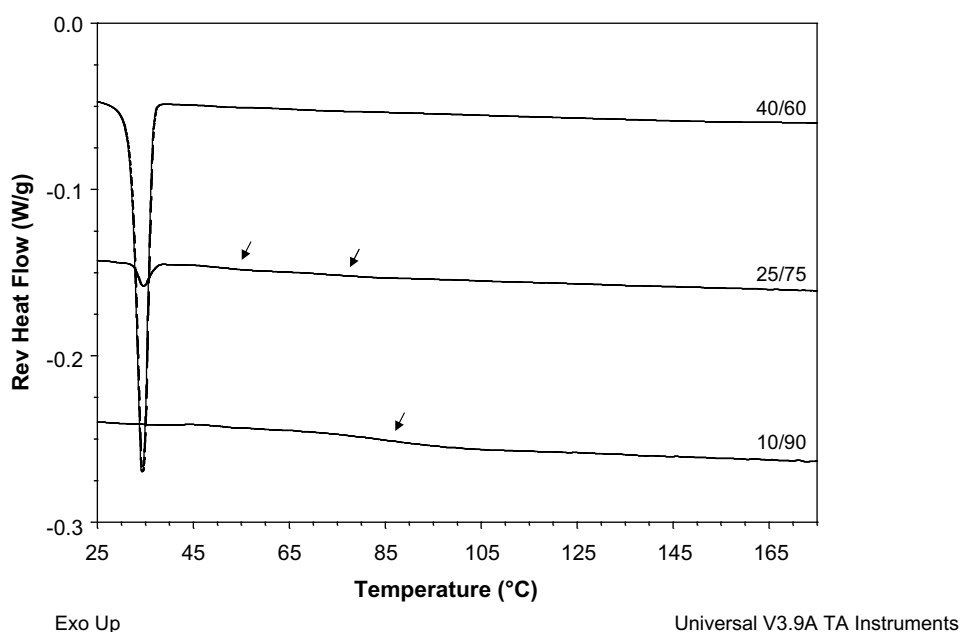

Fig. 3. Overlay of the reversing heat flow as a function of temperature of 40/60, 25/75 and 10/90 w/w TPGS 1000/PVPVA 64 from top to bottom. Arrows indicate glass transitions, exotherms are up.
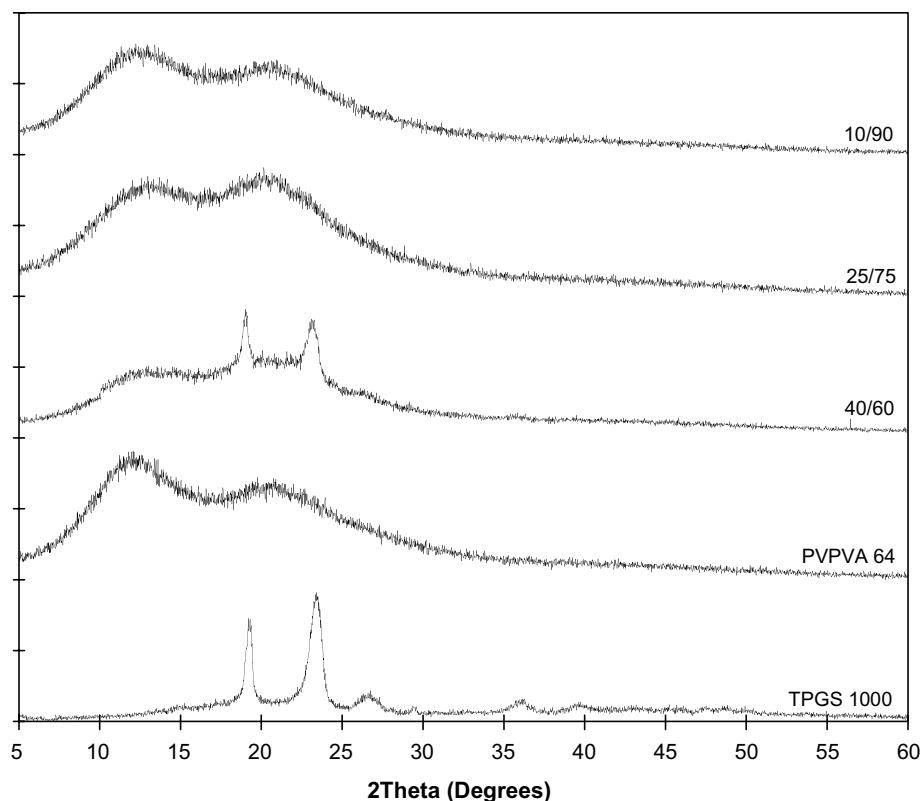
Fig. 4. Overlay of X-ray diffractograms with from top to bottom; 10/90, 25/75 and 40/60 w/w TPGS 1000/PVPVA 64, PVPVA 64 and TPGS 1000.
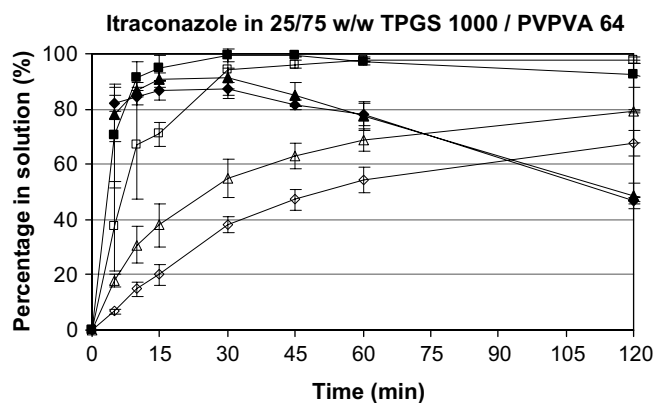

Fig. 5. Dissolution profiles solid dispersions of 10% Itraconazole in 25/75 w/w TPGS 1000/PVPVA 64 (■), 20% Itraconazole in 25/75 w/w TPGS 1000/PVPVA 64 (▲), 40% Itraconazole in 25/75 w/w TPGS 1000/PVPVA 64 (◆), 10% Itraconazole in PVPVA 64 (□), 20% Itraconazole in PVPVA 64 (△), 40% Itraconazole in PVPVA 64 (◆) (n = 3, error bars indicate SD).
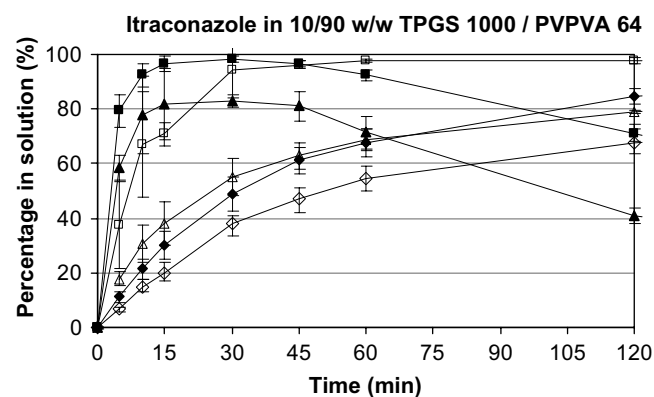

Fig. 6. Dissolution profiles solid dispersions of 10% Itraconazole in 10/90 w/w TPGS 1000/PVPVA 64 (■), 20% Itraconazole in 10/90 w/w TPGS 1000/PVPVA 64 (▲), 40% Itraconazole in 10/90 w/w TPGS 1000/PVPVA 64 (◆), 10% Itraconazole in PVPVA 64 (□), 20% Itraconazole in PVPVA 64 (△), 40% Itraconazole in PVPVA 64 (◆) (n = 3, error bars indicate SD).

uration screening results. It should be considered though, that the starting situation is different in both cases. In the supersaturation screening a solution was added to the dissolution medium where-else a powder was added to the dissolution vessels. The powder particles could contain some Itraconazole crystals or function as heterogeneous nuclei. Hence, crystal growth can start immediately where-else in the supersaturation experiment the nucleation process has to take place prior to crystal growth [5,6]. In

order to understand the differences between the dissolution characteristics of the binary and ternary dispersions a closer look should be taken at the physicochemical properties.

3.3.3. Physicochemical characterization

X-ray diffraction analysis showed that all solid dispersions, including the binary Itraconazole/PVPVA 64 and the ternary Itraconazole in 10/90 or 25/75 w/w TPGS

1000/PVPVA 64 dispersions, were X-ray amorphous after one week of drying. Since the detection limit of crystallinity degree for this method is in general 1–5% on the whole sample weight, and since the fraction of amorphous PVPVA 64 was relatively high in all samples, the sensitivity of X-ray diffraction might not be high enough to detect low percentages of crystalline drug.

MDSC analysis revealed that the single mixing glass transitions of the spray dried Itraconazole/PVPVA 64 samples were in agreement with the Gordon-Taylor equation, indicating perfect blend compatibility [9].

The thermograms of the ternary dispersions however revealed the presence of Itraconazole melting peaks that were sometimes preceded by cold crystallization exotherms. In order to get an estimation of the initial crystallinity of the sample, the heat of crystallization should be subtracted from the heat of fusion [11]. Still, the analysis of the initial crystallinity was quite arbitrary since several thermal events were taking place in the cold crystallization temperature region. Overlapping events such as broad glass transitions and endotherms made it difficult to locate the baseline. Therefore, the temperature region above the melting endotherm of Itraconazole was taken as a reference point to draw a baseline. All of these reasons explain the large standard deviations on the average heat of fusion in Table 3. Nevertheless, it can be concluded from the data obtained after one week and two weeks of drying, that crystalline drug clusters are present and that the crystallinity degree of Itraconazole increases with time. The crystallinity degree of Itraconazole is higher in the systems with 25/75 w/w TPGS 1000/PVPVA 64 than in the systems with 10/90 w/w TPGS 1000/PVPVA 64. Hence addition of TPGS 1000 to the protective PVPVA 64 matrix leads to phase separation and recrystallization of Itraconazole. The crystallinity of TPGS 1000 is <1% in the sample with 10% Itraconazole in 10/90 w/w TPGS 1000/PVPVA 64 and zero in the samples with 20 and 40% of Itraconazole in w/w 10/90 TPGS 1000/PVPVA 64. In the series with 25/75 w/w TPGS 1000/PVPVA 64, TPGS 1000 is partially crystalline

and the crystallinity increases as a function of time (Table 3). Hence, the miscibility limit of the excipients is not influenced significantly by the presence of Itraconazole.

In order to interpret the glass transitions in the reversing heat flow it had to be clarified whether the endotherms in the region from 40 to 100 °C were evaporation endotherms or relaxation endotherms. After two weeks of drying the size of the endotherms was still the same, therefore the samples were submitted to a heat–cool–heat temperature program. The samples were heated from room temperature to 100 °C and kept isothermal for 10 min. Consequently they were cooled to −90 °C and reheated to 180 °C. In the second heating run the endotherms had disappeared. GC–MS on the other hand pointed out that the residual dichloromethane on the samples was below 1 ppm. Therefore these results suggested that the samples had been dried well and the endotherms were largely due to relaxation enthalpy of the amorphous phases in the samples.

Indeed, three major glass transition areas were present in the samples. One below zero ranging from −50 to −10 °C, referring to a TPGS 1000 rich amorphous phase, one ternary mixing glass transition ranging from 30 to 60 °C, and one glass transition due to a PVPVA 64 rich phase, ranging from 70 to 100 °C (Fig. 7) The heat–cool–heat temperature program on the other hand induced further mixing of the amorphous phases leaving only one amorphous phase. Therefore, it can be assumed that the middle glass transition is indeed a ternary phase.

Since the position of the ternary mixing glass transition did not vary much with the sample composition, the theoretical ternary mixing glass transition was estimated with the Gordon–Taylor/Kelly–Bueche equation (Eq. (2)) [15,16]. The Gordon–Taylor equation has been derived for compatible polymers but can be applied to small molecules and polymers as well. It renders a theoretical mixing glass transition, assuming volume additivity.

$$Tg_{mix} = (w_1Tg_1 + K_1w_2Tg_2 + K_2w_3Tg_3)/(w_1 + K_1w_2 + K_2w_3) \qquad (2)$$

where Tg_1, Tg_2 and Tg_3 are the glass transition temperatures of TPGS 1000, Itraconazole and PVPVA 64, respectively, w_1, w_2 and w_3 are the weight fractions of TPGS 1000, Itraconazole and PVPVA 64, respectively, and K_1 and K_2 are constants calculated from the glass transitions and densities with the Simha–Boyer rule (Eq. (3)) [17],

$$K \cong (\rho_1Tg_1)/(\rho2Tg2) \qquad (3)$$

in which ρ_1 and ρ_2 are the densities of the amorphous component with the lowest and the highest glass transition, respectively. It was assumed that the density of amorphous TPGS 1000 was equal to the density of liquid TPGS 1000 at 50 °C, 1.055 g/cm³ [18], and the densities for glassy Itraconazole and PVPVA 64 were 1.27 and 1.19 g/cm³,

Table 3
The average value and standard deviation ($n = 3$) of the heat of fusion of Itraconazole and TPGS 1000 (J/g) after one week and two weeks of drying

| Sample	Week 1	Week 2
Crystallinity of Itraconazole (%)		
10% Itra in 10/90 TPGS/PVPVA	–	13 ± 6
20% Itra in 10/90 TPGS/PVPVA	16 ± 3	16 ± 4
40% Itra in 10/90 TPGS/PVPVA	7 ± 5	6 ± 1
10% Itra in 25/75 TPGS/PVPVA	4 ± 4	16 ± 5
20% Itra in 25/75 TPGS/PVPVA	28 ± 4	58 ± 5
40% Itra in 25/75 TPGS/PVPVA	25 ± 11	50 ± 7
Crystallinity of TPGS 1000 (%)		
10% Itra in 10/90 TPGS/PVPVA	0.9 ± 0.5	0.4 ± 0.1
20% Itra in 10/90 TPGS/PVPVA	–	–
40% Itra in 10/90 TPGS/PVPVA	–	–
10% Itra in 25/75 TPGS/PVPVA	14 ± 0.9	18 ± 0.3
20% Itra in 25/75 TPGS/PVPVA	7 ± 0.3	19 ± 3
40% Itra in 25/75 TPGS/PVPVA	7 ± 5	14 ± 2
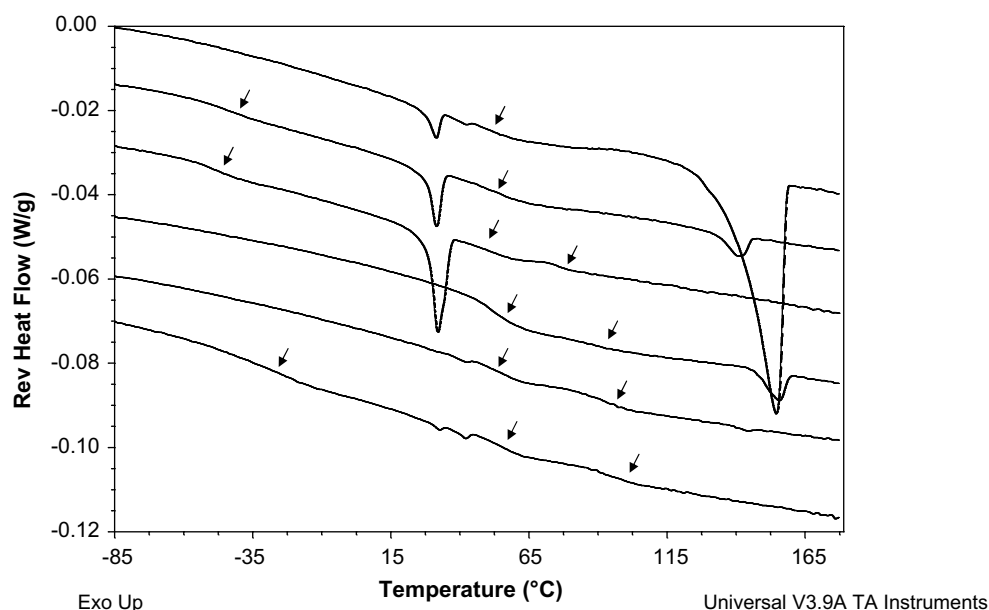
Fig. 7. Overlay of the reversing heat flow as a function of temperature of 40, 20 and 10% Itraconazole in 25/75 w/w TPGS 1000/PVPVA 64 and 40, 20 and 10% Itraconazole in 10/90 w/w TPGS 1000/PVPVA 64 from top to bottom. Arrows indicate glass transitions, exotherms are up.

respectively [9]. The values obtained for K_1 and K_2 were 0.66 and 0.93, respectively.

The glass transition temperature of Itraconazole is 59.4 °C [19] and the glass transition temperature of PVPVA 64 after spray drying was measured at 107.0 ± 0.2 °C. The glass transition temperature for TPGS 1000 was measured by equilibrating at -90 °C and heating up until 60 °C and was -7.5 ± 0.1 °C. However, a different temperature program including quench cooling from above the melting temperature rendered a glass transition temperature of -19.0 ± 0.1 °C. Interestingly, glass transitions of up to -50 °C could be detected in some of the ternary solid dispersions. Since in this case the plasticizing effect of residual solvents on the glass transition could largely be ruled out, the only explanation for this observation is that the glass transition temperature of TPGS depends very much on its thermal history. In order to estimate the theoretical glass transitions of the ternary amorphous phases it was assumed that the glass transition of TPGS 1000 was equal to -7.5 ± 0.1 °C. Either way Table 4 shows that the values that were obtained for the theoretical mixing glass transitions are indeed relatively close to each other in tempera-

ture. This explains the low variation of the experimental glass transition temperature of the ternary phases as a function of composition. Indeed, both Itraconazole and TPGS lower the glass transition temperature of PVPVA 64. Deviations of the experimental glass transitions towards the theoretical glass transitions are due to the fact that all samples consist of multiple phases, leading to incorrect weight fractions. Another factor could be a different magnitude for the heterogeneous interactions compared to the homogeneous interactions. Anyhow, since in none of the samples a single amorphous phase was obtained, even not after applying the heat–cool–heat temperature program, the magnitude of heterogeneous interactions in the samples cannot be derived from these measurements.

4. Conclusion

The physicochemical investigation pointed out that addition of as little as 10% of TPGS 1000 to the PVPVA 64 carrier matrix leads to destabilization of the molecular dispersion of Itraconazole, leading to the formation of crystalline Itraconazole clusters. Also, Itraconazole is partially embedded in metastable amorphous phases with a lower glass transition temperature and hence a higher molecular mobility than the binary Itraconazole/PVPVA 64 blends. One would expect that this phase separation, and in particular the formation of crystalline Itraconazole clusters, should give rise to a decrease in the dissolution rate compared to the molecular dispersions of Itraconazole in PVPVA 64. Nevertheless, addition of TPGS 1000 provided a large improvement in terms of dissolution. The instantaneous release in the first hour was possibly due to dissolution of the molecularly dispersed fraction of Itraco-

Table 4
Theoretical mix glass transition temperatures for all compositions based on the Gordon–Taylor equation and the Simha–Boyer rule

Sample composition	Theoretical mix glass transition (°C)
10% Itraconazole in 10/90 TPGS/PVPVA	92.3
20% Itraconazole in 10/90 TPGS/PVPVA	89.6
40% Itraconazole in 10/90 TPGS/PVPVA	83.5
10% Itraconazole in 25/75 TPGS/PVPVA	75.6
20% Itraconazole in 25/75 TPGS/PVPVA	74.3
40% Itraconazole in 25/75 TPGS/PVPVA	71.3

nazole enhanced by the solubilizing properties of TPGS 1000. In a second phase, the presence of crystalline Itraconazole clusters in combination with the presence of TPGS 1000 induces precipitation. As described above, the presence of surfactants enhances precipitation from supersaturated solutions by increasing the solubility and reducing the surface tension at the growing crystal [5]. Because of the good compatibility and the stabilizing effect of PVPVA 64 on Itraconazole, precipitation was not observed for the binary dispersions. Considering these data, the formulation of these compounds in such a way that a stable but closely mixed system is obtained is a challenge to be met.

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