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Research paper

Characterization of ternary solid dispersions of Itraconazole in polyethylene glycol 6000/polyvidone-vinylacetate 64 blends

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Abstract

The good compatibility between Itraconazole and polyvidone-vinylacetate 64 (PVPVA 64) was pointed out previously. However, the dissolution properties of these systems left room for improvement. Therefore polyethylene glycol 6000 (PEG 6000), known for its solubilizing and wetting properties, was added to the PVPVA 64 matrix. Physicochemical analysis showed that up to 10% of PEG 6000 could be mixed with PVPVA 64. Addition of 10%, 20% or 40% of Itraconazole rendered amorphous solid dispersions consisting of a ternary mixed phase and a PVPVA 64 rich amorphous phase. If the PEG 6000 fraction was elevated up to 25% of the carrier, the PEG 6000 crystallinity degree was around 73 ± 0.6%. Up to 20% of Itraconazole could be molecularly dispersed in the 25/75 w/w polymer blend. An Itraconazole melting peak could be detected for the sample containing 40% of drug. Dissolution experiments showed that no benefit was obtained by adding PEG 6000 to the PVPVA 64 matrix for samples containing up to 20% of Itraconazole. The dissolution of the ternary dispersions with 40% of Itraconazole on the other hand showed improvement compared to binary Itraconazole/PVPVA 64 dispersions.

Keywords: Ternary solid dispersion; MDSC; Powder X-ray diffraction; Dissolution; GC–MS; Itraconazole; PEG 6000; PVPVA 64

1. Introduction

Since many new compounds have problematic oral bioavailability due to low solubility, much research is focused on improving dissolution and solubility properties. A strategy with renewed interest is the formulation of solid dispersions [1]. The term solid dispersion was defined by Chiou and Riegelman as 'a dispersion of one or more active ingredients in an inert carrier or matrix', prepared by the melting, solvent, or melting solvent method [2]. If formulated as a solid dispersion the dissolution rate and the solubility of the active compound are often significantly increased. Contributing factors are particle size reduction, improved wetting and an enhancement of the solubility of the active compound in the solution that is formed as the carrier dissolves. Also, the carrier can have an influence on the crystallization kinetics in the supersaturated solution that is formed during the process of dissolution [3]. If the active compound is molecularly dispersed in the carrier, the term solid solution can be used. Since in this case the crystal lattice of the drug serves no longer as an obstacle, the dissolution becomes carrier controlled [4].

All the above-listed factors depend largely on the properties of the carrier. However, the amount of carriers that can be used for these purposes is still rather limited. There-

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fore, it is interesting to take a look at polymer blends that are made up of polymers with different characteristics. The properties of the carrier can thus be tailored to the needs of the system, e.g., stabilization of a solid solution or improvement of the dissolution rate.

The starting point of this study were the results that were obtained earlier by our research group. Six et al. attempted to improve the characteristics of Itraconazole/Eudragit E100 solid dispersions by blending Eudragit E100 with PVPVA 64 [5]. The model compound in this study, the weak base Itraconazole, suffers from extremely low solubility e.g., 1 ng/ml at a neutral pH and 4 μg/ml at pH 1 [6]. The reference point for the ternary systems were binary solid dispersions made up of Itraconazole and PVPVA 64. Interestingly, Itraconazole and PVPVA 64 were miscible in all ratios and the glass transitions of the binary dispersions corresponded to the values obtained with the Gordon–Taylor equation, indicating volume additivity and absence of strong heteromolecular forces [5,7]. On the other hand, the dissolution of these systems was rather slow and left room for improvement. Therefore, the present study aimed to further improve dissolution characteristics of Itraconazole/PVPVA 64 solid dispersions by adding polyethylene glycol 6000, known for its good solubilizing and wetting properties [8–10].

2. Materials and methods

2.1. Materials

Crystalline Itraconazole (purity more than 99%, melting temperature = 166.8 °C) was kindly donated by Janssen Pharmaceutica (Beerse; Belgium). Polyvidone-vinylacetate 64 (PVPVA 64) was obtained from BASF (Ludwigshafen, Germany) and polyethylene glycol 6000 (PEG 6000) was obtained from Acros Organics (Geel, Belgium).

2.2. Methods

2.2.1. Spray drying

Blends of PEG 6000 and PVPVA 64, binary dispersions of Itraconazole and PVPVA 64 and ternary dispersions made up of Itraconazole, PEG 6000 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_2Cl_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 in a vacuum oven at 40 °C for one week prior to analysis and further stored in a desiccator over P_2O_5 at 25 °C [10].

2.2.2. Physicochemical characterization

2.2.2.1. 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 3.9A (TA Instruments, Leatherhead, UK). Dry nitrogen (5.5) at a 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 that of the reference pan were taken into account for the calculation of the heat flow, the sample mass varing 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 room temperature to 180 °C. In order to detect the glass transition of PEG 6000 the sample was equilibrated at 80 °C and kept isothermal for 5 min. Subsequently the sample was cooled and equilibrated at −90 °C for 5 min and heated to 80 °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 PEG 6000 and Itraconazole was obtained from their respective recrystallization and melting enthalpies using the following formula:

$$\text{Crystallinity } (\%) = \frac{\Delta Hf_{\text{inblend}}}{(\Delta Hf \times w\%)} \times 100 \quad (1)$$

with $\Delta Hf_{\text{inblend}}$ being the enthalpy of fusion of Itraconazole or PEG 6000 in the blend and ΔHf being the enthalpy of pure spray dried PEG (199.9 J/g) or pure Itraconazole

Table 1
Compositions of the spray dried powders

Blends	
1.	10/90 PEG 6000/PVPVA 64
2.	25/75 PEG 6000/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 PEG 6000/PVPVA 64
2.	20% Itraconazole in 10/90 PEG 6000/PVPVA 64
3.	40% Itraconazole in 10/90 PEG 6000/PVPVA 64
4.	10% Itraconazole in 25/75 PEG 6000/PVPVA 64
5.	20% Itraconazole in 25/75 PEG 6000/PVPVA 64
6.	40% Itraconazole in 25/75 PEG 6000/PVPVA 64

(84.0 J/g). If present, 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.

2.2.2.2. 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 program (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 version March/2005 [10,12].

2.2.2.3. Analysis of the 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 (all D7000; Merck, Darmstadt, Germany). 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 being 4.6 min [10].

2.2.2.4. 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, then heated at 39.9 °C/min to reach 180 °C and kept at this temperature 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 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 TURBOMASS software (Perkin-Elmer). SIM (single ion mode recording) was used on mass fragments 49 and 84 starting at 2 min and ending at 5 min after injection and the dichloromethane retention time was 2.98 min.

Table 2
Headspace parameters

Thermostating temperature	105 °C
Thermostating 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

2.2.3. 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 SR8 plus 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, 180 and 240 min. These samples were filtered with 0.45 μm Teflon filters (Macherey-Nagel, Düren, Germany). The first 2 mm was discarded. The remainder was diluted with methanol (1/10) to avoid precipitation and analyzed with HPLC, as described above [10].

3. Results and discussion

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 99.2 and 102.4% ±0.3 of the theoretical values.

3.2. Dissolution

Dissolution experiments were carried out after drying the freshly prepared samples for one week. The dissolution profiles of the ternary dispersions were compared to the results of the binary Itraconazole/PVPVA 64 dispersions. Compared to the dissolution of the extruded Itraconazole/PVPVA 64 dispersions obtained by Six et al., the dissolution of the spray dried dispersions was considerably higher, ca. 60% after 4 h instead of ca. 40% [5]. Since the mixing behavior is the same for both the extruded and the spray dried binary Itraconazole/PVPVA 64 systems,

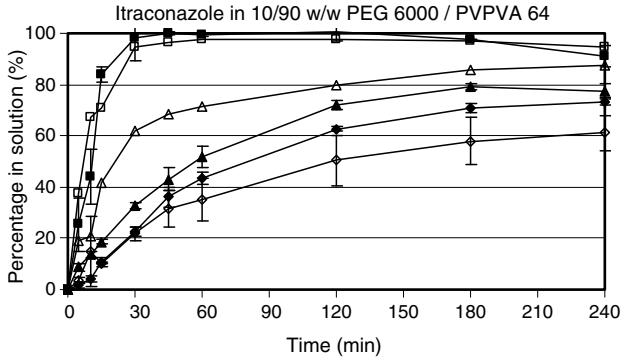

Fig. 1. Dissolution profiles solid dispersions of 10% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64 (■), 20% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64 (▲), 40% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64 (♦), 10% Itraconazole in PVPVA 64 (□), 20% Itraconazole in PVPVA 64 (Δ), 40% Itraconazole in PVPVA 64 (◇) ($n = 3$, error bars indicate SD).

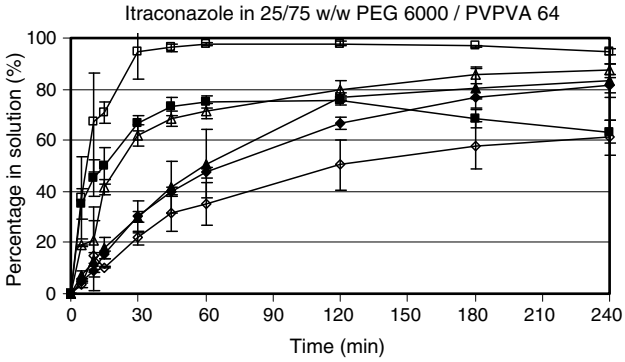

Fig. 2. Dissolution profiles of the solid dispersions of 10% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64 (■), 20% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64 (▲), 40% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64 (♦), 10% Itraconazole in PVPVA 64 (□), 20% Itraconazole in PVPVA 64 (Δ), 40% Itraconazole in PVPVA 64 (◇) ($n = 3$, error bars indicate SD).

this improvement must be due to the increased surface area of the smaller spray dried particles.

For both systems, the 10/90 series and the 25/75 w/w PEG 6000/PVPVA 64 series, similar results were obtained (Figs. 1 and 2). For the sample containing 10% of Itraconazole in 25/75 w/w PEG 6000/PVPVA 64 a poor result was obtained. For this sample the dissolution was only as high as for the binary dispersion with 20% of Itraconazole and after 2 h precipitation occurred. The sample with 10% Itraconazole in 10/90 PEG 6000/PVPVA 64 performed as good as the binary dispersion with a drug load of 10%. For both samples containing 20% of Itraconazole in either 25/75 or 10/90 w/w PEG 6000/PVPVA 64, there was no improvement of the ternary dispersion over the binary system. The ternary dispersions had a much slower dissolution and the difference after 4 h was still ca. 10%.

However, the samples containing 40% of Itraconazole both had an increased release compared to the binary reference dispersion. The increase was most pronounced for the sample with the 25/75 w/w PEG 6000/PVPVA 64 carrier for which a difference of 20% was observed after 4 h. For the other sample a difference of ca. 12% was observed after 4 h.

3.3. Physicochemical characterization

In order to explain the dissolution behavior of Itraconazole from the solid dispersions, the physical nature of the dispersions was investigated.

3.3.1. Characterization of the polymer blends

Co-spray drying of a mixture of 10% PEG 6000 to PVPVA 64 leads to formation of an amorphous powder with two glass transitions, one at 46.5 ± 0.9 °C and one at 97.5 ± 2.4 °C (Fig. 3). Considering the positions of the glass transitions of the reference materials, -51.4 ± 3.2 °C for PEG 6000 and 107.07 ± 0.16 °C for PVPVA 64, the lower glass transition is most likely a binary mixing glass transition and the higher glass transition is a PVPVA 64 rich amorphous phase. If the PEG 6000 concentration in the blend is raised to 25%, a separate crystalline PEG 6000 phase is formed. The crystallinity degree of PEG 6000, with reference to spray dried PEG 6000, was estimated at $73 \pm 0.6\%$ using the surface of the PEG melting peak. Interestingly, the melting temperature of PEG 6000 in these blends was 54.1 ± 2.4 °C, which is a decrease of approximately 4.8 °C compared to pure spray dried PEG 6000 which has a melting temperature of 58.9 ± 0.04 °C. This melting point depression is indicative of some degree of interaction between the polymers. X-ray diffractograms of the polymer blends confirmed the presence of a crystalline PEG 6000 phase in the 25/75 w/w blend since two diffraction peaks typical for polyethylene glycols were detected at ca. 19° and 23° 2θ (Fig. 4). From the estimation of the crystallinity degree it can be derived that approximately 27% of the dispersed PEG 6000 is still molecularly dispersed in the amorphous phases. Therefore it can be calculated that the ratio of the amorphously dispersed PEG 6000 to the PVPVA 64 fraction in the 25/75 w/w PEG

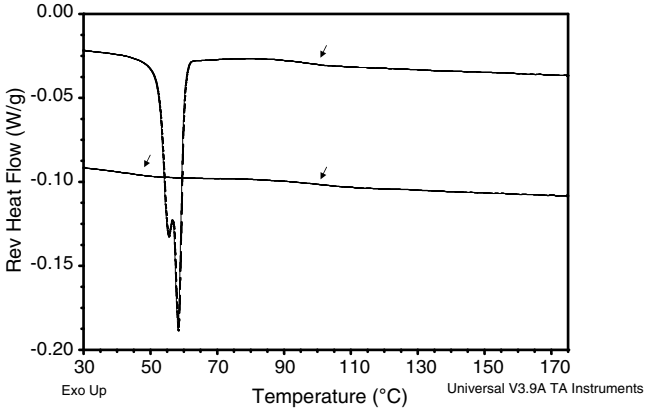

Fig. 3. Overlay of the reversing heat flow as a function of temperature of 25/75 and 10/90 w/w PEG 6000/PVPVA 64 polymer blends from top to bottom. Arrows indicate glass transitions, exotherms are up.

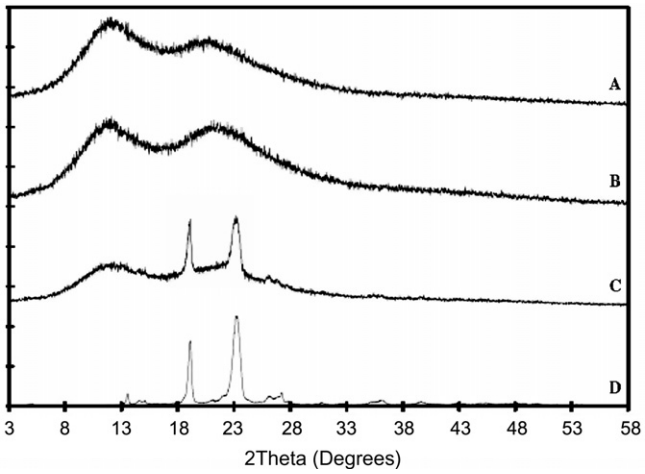

Fig. 4. Overlay of X-ray diffractograms with from top to bottom; (A) PVPVA 64, (B) 10/90 w/w PEG 6000/PVPVA 64, (C) 25/75 w/w PEG 6000/PVPVA 64 and (D) PEG 6000.

6000/PVPVA 64 sample is around 9%. The same calculation rendered a percentage of 11% for the 10/90 w/w PEG 6000/PVPVA 64 sample. Hence, the amount of amorphously dispersed PEG 6000 is quite constant for both samples and the miscibility limit is approximately 10%.

3.3.2. Characterization of the ternary solid dispersions

Ten, twenty or forty percent of Itraconazole was added to both polymer blends: the amorphous 10/90 w/w and the phase separated 25/75 w/w PEG 6000/PVPVA 64 blend. The solid dispersions with Itraconazole in 10/90 w/w PEG 6000/PVPVA 64 were completely amorphous, indicating that Itraconazole is not expelled from its protective PVPVA 64 matrix as described for similar systems with Itraconazole, Myrj and PVPVA by Wang et al. [7]. Fig. 5

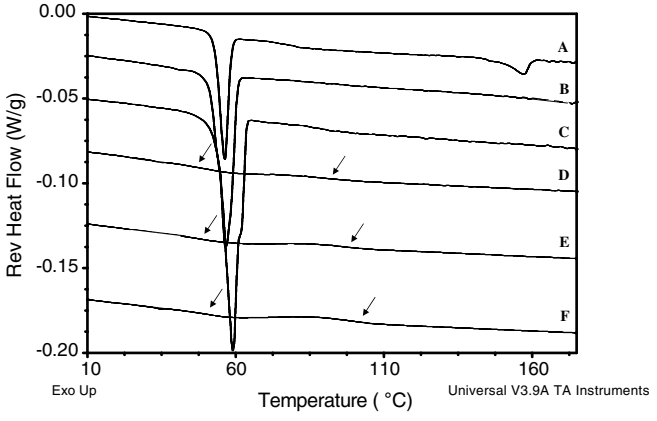

Fig. 5. Overlay of the reversing heat flow as a function of temperature of all ternary solid dispersions: (A) 40% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64, (B) 20% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64, (C) 10% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64, (D) 40% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64, (E) 20% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64, (F) 10% Itraconazole in 10/90 w/w PEG 6000/PVPVA, from top to bottom. Arrows indicate glass transitions, exotherms are up.

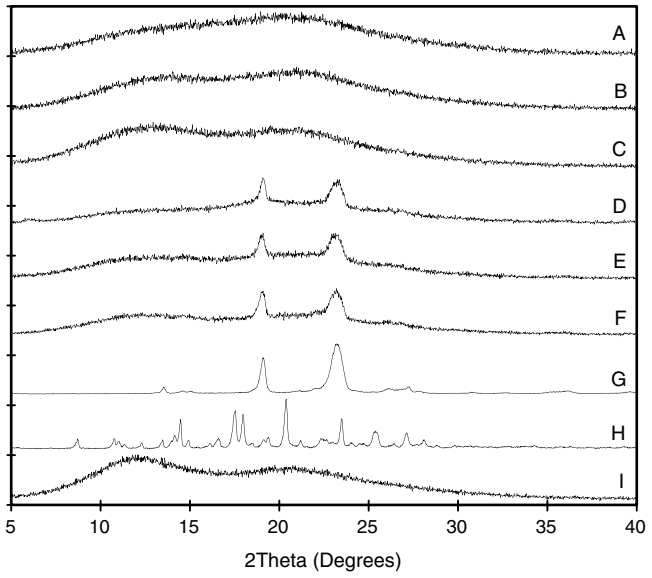

Fig. 6. X-ray diffractograms of the following samples from top to bottom: (A) 40% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64, (B) 20% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64, (C) 10% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64, (D) 40% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64, (E) 20% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64, (F) 10% Itraconazole in 25/75 w/w PEG 6000/PVPVA 64, (G) PEG 6000, (H) Itraconazole, (I) PVPVA 64.

depicts the reversing heat flow for all ternary dispersions, measured from room temperature to 180 °C. No melting peaks were observed for Itraconazole and PEG 6000 in the 10/90 series, hence both were molecularly dispersed. These findings were supported by the XRD diffraction data (Fig. 6). The reversing heat flow did show glass transitions. However, the position as well as the heat capacity change was highly variable. In general it can be stated that for all three compositions two glass transitions could be observed. The lowest glass transition was observed in the temperature region from 40 to 70 °C and the second glass transition was observed in the region from 90 to 100 °C. The second glass transition represents a more PVPVA 64 rich phase, the first glass transition possibly represents a ternary amorphous phase. The samples with 10, 20 and 40% of Itraconazole in 25/75 w/w PEG 6000/PVPVA 64 all contained a crystalline PEG 6000 phase. The average crystallinity degree of PEG 6000 after 1 and 6 weeks of drying is listed in Table 3 [11]. As indicated by the large standard deviations, these samples were also relatively heterogeneous and the crystallinity degree increased in time. The X-ray diffractograms clearly depict the typical PEG 6000 peaks (Fig. 6). In the samples with a drug load of 10% or 20%, all of the drug is molecularly dispersed. The sample with 40% of Itraconazole has a crystalline Itraconazole phase of approximately $13 \pm 3\%$. Hence, the samples become more and more unstable as the PEG 6000/PVPVA 64 miscibility limit is exceeded. Therefore it seems more advantageous to select compatible polymer blends. As for glass transitions this system only seemed to have a very slight heat capacity change between 80 and 90 °C,

Table 3
The average value and standard deviation ($n = 3$) of the heat of fusion of Itraconazole and PEG 6000 (J/g) after 1 week and 6 weeks of drying

Sample	Week 1	Week 6
Crystallinity of Itraconazole (%)		
10% Itra in 10/90 PEG/PVPVA	/	/
20% Itra in 10/90 PEG/PVPVA	/	/
40% Itra in 10/90 PEG/PVPVA	/	/
10% Itra in 25/75 PEG/PVPVA	/	/
20% Itra in 25/75 PEG/PVPVA	/	/
40% Itra in 25/75 PEG/PVPVA	13 ± 3	14 ± 1
Crystallinity of PEG 6000 (%)		
10% Itra in 10/90 PEG/PVPVA	/	/
20% Itra in 10/90 PEG/PVPVA	/	/
40% Itra in 10/90 PEG/PVPVA	/	/
10% Itra in 25/75 PEG/PVPVA	56 ± 2	68 ± 3
20% Itra in 25/75 PEG/PVPVA	52 ± 2	66 ± 2
40% Itra in 25/75 PEG/PVPVA	14 ± 16	76 ± 3

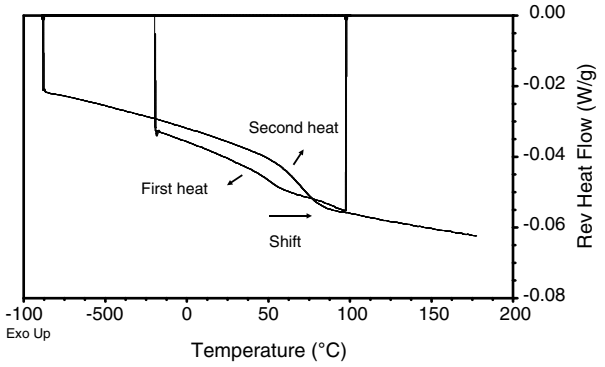

Fig. 7. Reversing heat flow as a function of temperature, the sample consisted of 40% Itraconazole in 10/90 w/w PEG 6000/PVPVA 64 and was first heated from −20 to 100 °C and kept at 100 °C for 10 min, consequently the sample was equilibrated at −90 °C and reheated to 180 °C. Arrows indicate glass transitions, exotherms are up.

hence a PVPVA 64 rich amorphous phase is present as well (Fig. 5).

Also, large endotherms were observed in the total heat flow signal. In order to identify these endotherms a heat–cool–heat sequence was applied in which the samples were heated from −20 to 100 °C and kept there for 10 min in order to remove potential residual solvents. Consequently they were measured again from −90 to 180 °C. In the second heating run the enthalpies of the endotherms were much smaller, but the peak maxima had shifted to the right (data not shown). Because of this temperature shift it seemed unlikely that the endotherms were representing evaporation of residual solvents. Therefore GC–MS analysis was performed in order to rule out the presence of large amounts of dichloromethane. The results of this analysis pointed out that all samples contained less than 1 ppm dichloromethane. Therefore it was concluded that the transitions were mainly due to enthalpy recovery endotherms associated with the glass transitions. The heat–cool–heat sequences of the amorphous samples from the 10/90 series were further investigated. Inspection of the reversing heat flow after applying the heat–cool–heat program pointed out that the glass transition had shifted to a higher temperature as well, which corresponds to the observations on the relaxation endotherms (Fig. 7). Also, no other glass or melt transitions could be observed in the second heat. Considering the fact that in most samples a slight glass transition could be observed in the temperature region near the PVPVA 64 glass transition, this shift is most possibly due to remixing of the ternary phase and the PVPVA 64 rich phase. However, removal of water during the drying step in the heat–cool–heat sequence could also have some influence on the position of the glass transition temperature.

In general the positions of the glass transition temperatures of the samples with Itraconazole in 10/90 w/w PEG 6000/PVPVA 64 blend did not vary significantly with the sample composition, as well in the first as in the second heating. Therefore, the Gordon–Taylor/Kelly–Bueche [13,14] equation in combination with the Simha–Boyer rule [15] was used to estimate the position of the glass transition temperature in case a compatible ternary amorphous phase would be formed. These equations have originally been derived for polymer blends but they have been proven to be applicable to small molecule/polymer systems as well.

$$T_{g_{mix}} = (w_1 T_{g_1} + K_1 w_2 T_{g_2} + K_2 w_3 T_{g_3})/(w_1 + K_1 w_2 + K_2 w_3) \quad (2)$$

Eq. (1) is the Gordon–Taylor equation in which w_1 and T_{g_1} are the weight fraction and the glass transition temperature (-51.4 ± 3.2 °C) of PEG 6000, respectively, w_2 and T_{g_2} are the weight fraction and the glass transition temperature (59.4 °C) of Itraconazole, respectively, w_3 and T_{g_3} are the weight fraction and the glass transition temperature (107.07 ± 0.16 °C) of PVPVA 64, respectively, K_1 and K_2 are constants that were calculated with the Simha–Boyer rule in which:

$$K \cong (\rho 1 T_{g_1})/(\rho 2 T_{g_2}) \quad (3)$$

$\rho 1$ and T_{g_2} are, respectively, the density and the glass transition temperature of the amorphous component with the lowest glass transition temperature, and $\rho 2$ and T_{g_2} are, respectively, the density and glass transition temperature of the amorphous component with the highest glass transition temperature. K_1 was calculated from the values for PEG 6000 and Itraconazole, K_2 was calculated from the values of Itraconazole and PVPVA 64. The densities were 1.085, 1.270 and 1.190 g/cm^3 for PEG 6000, Itraconazole and PVPVA 64, respectively [16,5]. The glass transition temperatures of the theoretical ternary amorphous phases are displayed in Table 4. They are indeed very close in temperature, which explains our experimental observations. Comparison of the glass transition temperatures in the second heating run in the heat–cool–heat sequence with the theoretical glass transition temperatures calculated with the Gordon–Taylor equation revealed that the experimental glass transition temperature is lower than the theoretical one. It was found that the amount of residual solvent is

Table 4
Comparison of the theoretical glass transitions calculated with the Gordon–Taylor equation and the experimental glass transitions measured in the second heating run during a heat–cool–heat temperature program

Sample	Experimental T_{g_1} (°C)	Gordon–Taylor T_{g_1} (°C)
10% Itra in 10/90	57.97 ± 0.02	87.46
20% Itra in 10/90	72.36 ± 1.95	86.99
40% Itra in 10/90	65.94 ± 0.35	82.02

The sample with 10% itraconazole in 10/90 w/w PEG 6000/PVPVA 64 displayed a melting endotherm of PEG 6000 and a glass transition of PVPVA 64 in the second heating run.

very low, hence the plasticizing influence of moisture on the glass transition temperature could largely be ruled out. Therefore the overall conclusion was that the experimental glass transition temperatures, after obtaining a single amorphous phase by applying a heat–cool–heat sequence, were located at a lower temperature due to loose heteromolecular interactions. These loose interactions in combination with the fact that the glass transition temperature of the ternary phase is quite low lead to high molecular mobility and render a less stable product.

Based on these observations it is difficult to generally state whether or not addition of PEG 6000 to the PVPVA 64 matrix is an improvement. In an attempt to link the dissolution results to the physicochemical properties of the samples it should be noted that the coexistence of several amorphous phases can lead to an unequal distribution of Itraconazole throughout the sample. Hence, the drug–carrier ratio can differ on a local scale. Therefore, the phase separation in the ternary dispersions might be an explanation for the weaker dissolution performance of some of these samples. A possible explanation for the better performance of the samples containing 40% of Itraconazole could be the fact that for this drug load the difference between the local drug/carrier ratios and the drug/carrier ratio of the binary sample was less pronounced. Therefore the positive effect of PEG was noticeable in these samples. In conclusion however, it is worth mentioning that fully amorphous ternary dispersions were obtained in the 10/90 w/w PEG 6000/PVPVA 64 series and that the dissolution of the samples with the highest drug load (40%) was slightly improved.

4. Conclusion

In this study an amorphous PEG 6000/PVPVA 64 10/90 w/w polymer blend was obtained. Addition of Itraconazole to 10/90 w/w PEG 6000/PVPVA 64 w/w led to the formation of amorphous solid solutions. Addition of Itraconazole to the phase separated 25/75 w/w PEG 6000/PVPVA 64 blend led to phase separation of PEG 6000 and of Itraconazole in case of a 40% drug load. For drug loads of 10% and 20%, the release of the ternary solid dispersions was lower than the release of the binary solid dispersions. For a drug load of 40% on the other hand, the dissolution of the ternary solid dispersion was improved compared to the binary solid dispersions. Therefore, the influence of PEG 6000 on the dissolution of Itraconazole from a PEG 6000/PVPVA 64 matrix is composition dependent.

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