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International Journal of Pharmaceutics 355 (2008) 100–107
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Physical stability of ternary solid dispersions of itraconazole in polyethyleneglycol 6000/hydroxypropylmethylcellulose 2910 E5 blends

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Received 21 June 2007; received in revised form 23 November 2007; accepted 29 November 2007
Available online 4 December 2007

Abstract

In order to understand the influence of temperature and moisture, polymer blends of polyethyleneglycol 6000 (PEG 6000) and hydroxypropylmethylcellulose 2910 E5 (HPMC 2910 E5) and solid dispersions of itraconazole in these polymer blends were spray dried, further dried for 2 weeks and stored at three different conditions: 25 °C, 0% relative humidity (RH); 25 °C, 52% RH; 60 °C, 0% RH. MTDSC analysis of the polymer blends revealed that at 25 °C, 52% RH, PEG 6000 recrystallized to a high extent. At 60 °C, 0% RH the two polymers were miscible, probably due to the removal of bound water. In the ternary dispersions the polymers behaved similarly. The crystallinity degree of itraconazole in samples stored at 25 °C, 52% RH and at 60 °C, 0% RH was increased compared to the samples stored at 25 °C, 0% RH, probably due to the plasticizing effect of moisture at 25 °C, 52% RH and to an increased mobility at 60 °C, 0% RH. XPS analysis revealed a redistribution of itraconazole at the surface as itraconazole recrystallized from the blend. Dissolution tests revealed that a decrease in the itraconazole release was directly related to its crystallinity degree, no correlation was found with the crystallinity degree of PEG 6000.

Keywords: Solid dispersion; Spray drying; MTDSC; Dissolution; Stability; XPS

1. Introduction

More and more new drug candidates have a very low aqueous solubility and hence a problematic oral bioavailability. Several strategies have been developed to overcome this problem such as complexation, solubilization, and the formulation of solid dispersions. Chiou and Riegelman (1971) defined solid dispersions as a dispersion of one or more active ingredients in an inert carrier or matrix, prepared by the melting, solvent, or melting solvent method. The increase in dissolution rate and solubility provided by solid dispersions can be explained by the mechanisms described by the Noyes–Whitney equation (Noyes and Whitney, 1897):

$$\frac{dM}{dt} = \frac{AD(C_s - C_t)}{h}$$

where dM/dt is the dissolution rate, A is the specific surface area of the drug particle, D is the diffusion coefficient, h is the diffusion layer thickness, C_s is the saturation solubility, and C_t is the drug concentration at time t. A significant particle size reduction can be obtained by manufacturing solid dispersions and in many cases the drug is molecularly dispersed in the carrier. Conversion of the physicochemical state of the drug, e.g. from crystalline to amorphous, as well as solubilization and supersaturation by the carrier, can cause an increase in the kinetic solubility and the dissolution rate (Leuner and Dressman, 2000). To obtain the ultimate in particle size reduction and an optimal contact between the dispersed drug and the carrier, the drug should be molecularly dispersed. In order to impede recrystallization of

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doi:10.1016/j.ijpharm.2007.11.054

the dispersed drug, polymeric carriers are often used because of their antiplasticizing effect (Matsumoto and Zografi, 1999). However, the number of polymeric carriers that is available today is rather limited. Therefore polymer blends with dispersing as well as solubilising or supersaturating properties are currently being explored. In a previous paper the use of a polyethyleneglycol 6000 (PEG 6000)/hydroxypropylmethylcellulose 2910 E5 (HPMC 2910 E5) blend as a carrier for itraconazole, a basic BCS II compound with an extremely low aqueous solubility of 4 μg/ml at pH 1, was compared to the use of the single polymers (Peeters et al., 2002; Amidon et al., 1995). The combination of the polymers led to an improvement of the dissolution compared to the single polymers. The miscibility of the two polymers and the drug however, was found to be less good than for itraconazole and HPMC 2910 E5 alone. Itraconazole and/or PEG 6000 appeared as separate crystalline phases, except for one composition with 20% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5, in which the relative amount of both itraconazole and PEG 6000 was the lowest (Janssens et al., in press).

Therefore a stability study was carried out in order to address the following questions: 'What is the influence of heat and moisture on the miscibility of the polymers and the drug?' What is the influence of recrystallization of itraconazole and/or PEG 6000 on the surface distribution of itraconazole? and 'What is the influence of changing physicochemical properties on the pharmaceutical performance?'

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). Polyethyleneglycol 6000 (PEG 6000) was obtained from Acros Organics (Geel; Belgium) and hydroxypropylmethylcellulose 2910 E5 (HPMC 2910 E5) was obtained from Dow (USA).

2.2. Sample preparation

Polymer blends (PEG 6000/HPMC 2910 E5) and ternary dispersions (itraconazole/PEG 6000/HPMC 2910 E5) were prepared in a Büchi mini spray dryer B191 (Table 1). The powders were spray dried from a 5% solution of MeOH/CH_2Cl_2 50/50 (v/v), the inlet temperature was set at 80 °C and the outlet temperature varied from 50 °C 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 further dried for 2 weeks in a vacuum oven at 40 °C (Janssens et al., in press). After drying the powders were split over three dessicators with different storage conditions: (i) 25 °C, 0% relative humidity (RH), (ii) 25 °C, 52% RH and (iii) 60 °C, 0% RH. Phosphorus-pentoxide was placed at the bottom of the desiccators to obtain a relative humidity of approximately 0% and a saturated solution of magnesium nitrate hexahydrate was used to obtain a relative humidity of approximately 52%.

Table 1
Compositions of the polymer blends and the ternary solid dispersions

Polymer blends
15/85 (w/w) PEG 6000/HPMC 2910 E5
20/80 (w/w) PEG 6000/HPMC 2910 E5
25/75 (w/w) PEG 6000/HPMC 2910 E5
Ternary solid dispersions
20% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5
20% itraconazole in 20/80 (w/w) PEG 6000/HPMC 2910 E5
20% itraconazole in 25/75 (w/w) PEG 6000/HPMC 2910 E5
40% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5
40% itraconazole in 20/80 (w/w) PEG 6000/HPMC 2910 E5
40% itraconazole in 25/75 (w/w) PEG 6000/HPMC 2910 E5

2.3. Characterization

2.3.1. Modulated temperature differential scanning calorimetry (MTDSC)

All ternary dispersions and polymer blends were analyzed in duplicate after drying and after 1–4 months, and 6 months. MTDSC measurements were carried out using a Q1000 Modulated DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. Data were analyzed mathematically using Thermal Solutions software (TA Instruments, Leatherhead, UK). Dry nitrogen (5.5) at a flow rate of 50 ml/min was used as the purge gas through the DSC cell. TA Instruments (Leatherhead, UK) aluminum open pans were used for all calorimetric studies. The mass of the empty sample pan was matched with the mass of the empty reference pan within ±0.1 mg, the sample mass varied from 1 mg to 5 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 measurement 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 analyzed in the range from 25 °C to 200 °C. Glass transitions were analyzed in the reversing heat flow and melting and recrystallization peaks were analyzed in the total heat flow. The non-reversing heat flow signal was used to determine the position of the limits of the recrystallization and the melting peak 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:

$$\text{crystallinity}\,(\%) = \frac{\Delta H_{\text{f, blend}}}{\Delta H_{\text{f}}\,\text{w}\%} \times 100$$

with $\Delta Hf_{PEG} = 180$ J/g and $\Delta H\text{fitra}_{\text{conazole}} = 80.3$ 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 (Six et al., 2002).

2.3.2. X-ray photoelectron spectroscopy (XPS)

After drying and after 2 and 6 months of storage, the ternary solid dispersions were analyzed with XPS. The Kratos AXIS ULTRA instrument with an Al Kα X-ray source (1486.6 eV) was operated at 15 mA emission current and 10 kV anode potential. Powders were glued on the sample bar by spraying them on double sided tape. Wide scans were run for 5–10 min at three different positions on the powder surface and each analysis area was 0.3 mm × 0.7 mm. The instrument was run using the CASAXPS software and the atomic percentage of N was calculated from the Kratos relative sensitivity factor library. The average nitrogen content over the three positions was used to estimate the percentage of itraconazole at the surface of the solid dispersions with reference to the average nitrogen value for pure itraconazole. Other sources of nitrogen could be excluded since none of the polymers, nor the tape, contained nitrogen. The itraconazole percentages that were found at the surface were plotted against the itraconazole weight percentages obtained by HPLC in order to get information about the distribution of the drug between the surface and the centre of the particle.

2.3.3. Determination of itraconazole content in the solid dispersions

The solid dispersions were dissolved in dimethylsulfoxide and the itraconazole content was determined using HPLC (Six et al., 2004), experiments were done in triplicate.

2.3.4. Dissolution testing of solid dispersions

Dissolution experiments were performed in triplicate on the ternary dispersions immediately after drying and after 2 and 6 months of storage. The tests were performed using the USP 24 method 2 (paddle method) in a Hanson SR8plus dissolution apparatus (Chatsworth, CA). 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. The spray dried powders (always containing 100 mg of itraconazole) were added to the dissolution medium. Five-milliliter samples were taken and immediately replaced with fresh dissolution medium at 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, and 120 min. These samples were filtered with 0.45 μm Teflon filters (Macherey–Nagel, Düren, Germany). The first 2 ml was discarded and the remainder was diluted with methanol (1/10) to avoid precipitation of the drug. The samples were analyzed with HPLC (Six et al., 2004).

2.3.5. HPLC analysis

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, Germany). A LiChrospher 100 RP-18 (5 μm, 12.5 × 4) (Merck, Darmstadt, Germany) column was used. Acetonitrile/tetrabutyl ammonium hydrogen sulfate 0.01N (55:45, v/v) was used as mobile phase at a flow rate of 1.0 ml/min, 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 (Six et al., 2004).

3. Results and discussion

3.1. Physicochemical stability

3.1.1. Modulated temperature differential scanning calorimetry

In order to understand the mixing behaviour of PEG 6000 and HPMC 2910 E5 the crystallinity degree of PEG 6000 in the polymer blends was followed as a function of time for all three storage conditions (Fig. 1a–c). The first time point is the crystallinity degree immediately after drying, before storage at various conditions of temperature and relative humidity. The results obtained at 25 °C and 0% RH show that the 15/85 (w/w) PEG 6000/HPMC 2910 E5 blend remained amorphous and for 20/80 (w/w) and 25/75 (w/w) PEG 6000/HPMC 2910 E5 the degree of crystallinity increased with the amount of PEG 6000 (Fig. 1a). At 25 °C and 52% RH the same trend was observed, only the degree of crystallinity was significantly higher than at 0% RH, indicating that moisture impedes mixing of PEG 6000 and HPMC 2910 E5, most likely by occupying sites for hydrogen bonds (Fig. 1b). Right after drying the 20/80 (w/w) and 25/75 (w/w) PEG 6000/HPMC 2910 E5 blends were partially crystalline (Fig. 1c). After storage at 60 °C and 0% RH however, all blends were amorphous at each time point (Fig. 1c), indicating that the polymers remixed upon storage at high temperature. Closer investigation of the reversing heat flow revealed the presence of a single broad glass transition for each blend in the region of 80–90 °C where-else the amorphous 15/85 (w/w) PEG 6000/HPMC 2910 E5 blend kept at 25 °C and 0% or 52% RH showed two glass transitions, one around 80–90 °C, due to a mixed PEG 6000/HPMC 2910 E5 phase, and one around 145 °C, due to an HPMC 2910 E5 rich phase (Fig. 2). This heat induced mixing can be ascribed to the high mobility around the melting temperature of PEG 6000. On the other hand Fuller et al. (2001) suggested that bound water hinders the formation of hydrogen bonds between the hydroxyl groups of HPMC and the ether oxygens of PEO. Hence, the thorough removal of water at 60 °C and 0% RH could facilitate H-bridging.

The addition of itraconazole, either 20% or 40%, has a complex influence on the interaction between PEG 6000 and HPMC 2910 E5. For the crystallinity of PEG 6000 in the ternary solid dispersions the same influence of the storage condition can be observed as for the polymer blends. The samples stored at 25 °C and 52% RH have a significantly higher degree of crystallinity than the samples stored at 25 °C, 0% RH and when stored at 60 °C and 0% RH, the crystallinity decreases over time (Fig. 3a–c). Interestingly there is a distinct influence of the sample composition. Crystallinity is especially high in the following three compositions: 20% itraconazole in 20/80 (w/w) PEG 6000/HPMC 2910 E5, 20% itraconazole in 25/75 (w/w) PEG 6000/HPMC 2910 E5 and 40% itraconazole in 25/75 (w/w) PEG 6000/HPMC 2910 E5. This indicates that apart from the percentage of PEG 6000 in the PEG 6000/HPMC 2910 E5 blend

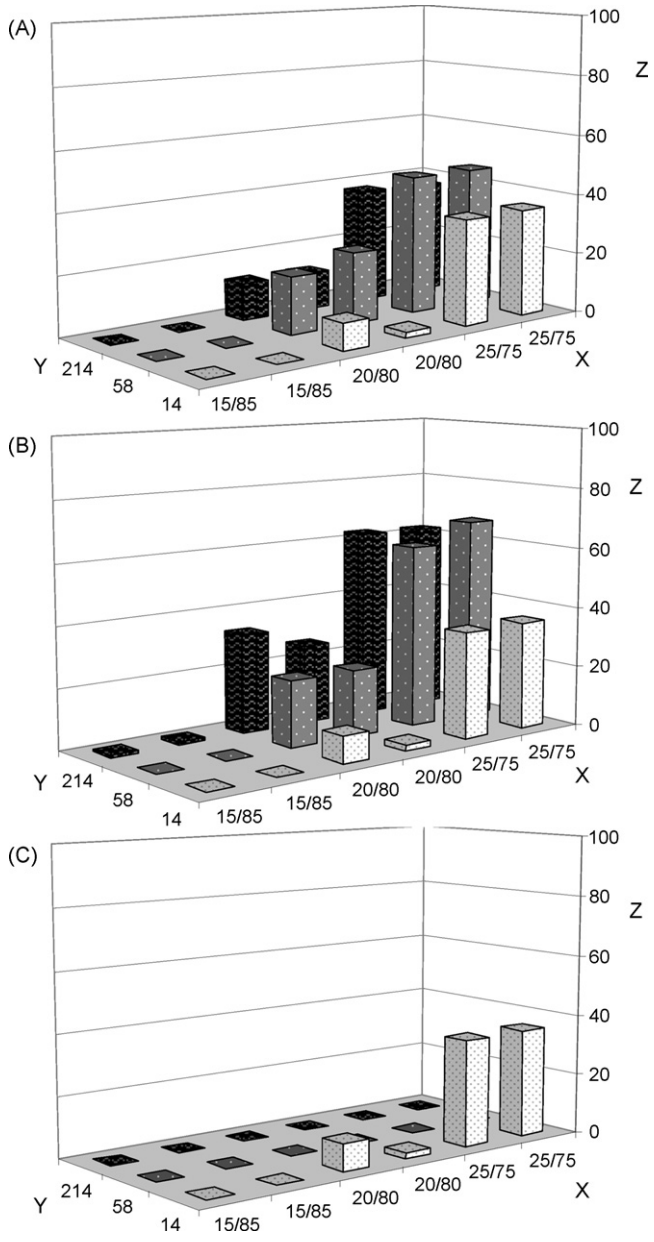

Fig. 1. Crystallinity degree (%, *Z*-axis) of PEG 6000 in 15/85 (w/w), 20/80 (w/w) and 25/75 (w/w) PEG 6000/HPMC 2910 E5 polymer blends (composition, *Y*-axis) as a function of time (days, *X*-axis), stored at: (A) 25 °C, 0% RH; (B) 25 °C, 52% RH; (C) 60 °C, 0% RH.

also the amount of itraconazole plays an important role in the recrystallization of PEG 6000, since the crystallinity of PEG 6000 is not significantly increased in the composition with 40% itraconazole in 20/80 (w/w) PEG 6000/HPMC 2910 E5. Apparently the formation of an itraconazole/PEG 6000/HPMC 2910 E5 mixed phase requires a certain composition (Janssens et al., in press).

The crystallinity of itraconazole is clearly dependent on the composition. In samples with a drug load of 40%, the degree of crystallinity is significantly higher than for the samples that contain 20% of itraconazole (Fig. 4a–c). Apparently a sufficient amount of carrier is required to impede recrystallization and keep the drug molecularly dispersed. Comparison of the results of

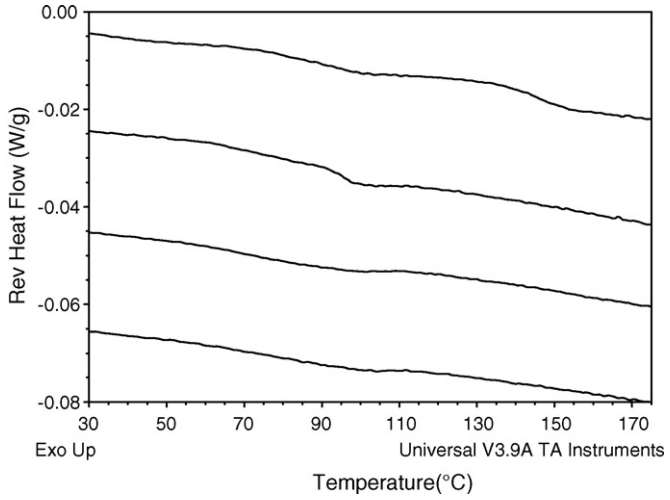

Fig. 2. Reversing heat flow vs. temperature for PEG 6000/HPMC 2910 E5 polymer blends with from top to bottom; 15/85 (w/w) PEG 6000/HPMC 2910 E5 stored at 25 °C, 0% RH; 15/85 (w/w) PEG 6000/HPMC 2910 E5 stored at 60 °C, 0% RH; 20/80 (w/w) PEG 6000/HPMC 2910 E5 stored at 60 °C, 0% RH and 25/75 (w/w) PEG 6000/HPMC 2910 E5 stored at 60 °C, 0% RH.

the three storage conditions reveals that moisture as well as heat have a deteriorating influence on the physicochemical stability of itraconazole. The degree of crystallinity increased the most when stored at 60 °C and 0% RH, but when stored at 25 °C and 52% RH the crystallinity degree was also increased compared to the storage condition at 25 °C and 0% RH. At 25 °C, 52% RH the absorbed water can act as a plasticizer and hence increase the mobility in the solid dispersion (Weuts et al., 2005). The high temperature at 60 °C, 0% RH increases the mobility of the system and allows the supersaturated molecular dispersion to demix. Interestingly the opposite was found for the polymer blends, suggesting that PEG 6000 and HPMC 2910 E5 are truly miscible (Fuller et al., 2001).

3.1.2. X-ray photoelectron spectroscopy

The itraconazole content at the top 10 nm of the powder surface was determined with XPS at three different spots of 0.3 mm × 0.7 mm and plotted against the total itraconazole weight percentage obtained by HPLC analysis. Since both polymers consist of carbon and oxygen in very similar ratios, it was not possible to distinguish them at the surface. Therefore, it was necessary to characterize the binary dispersions of itraconazole and PEG 6000 and/or HPMC 2910 E5, in order to get more information about the distribution of itraconazole and the polymers. From the XPS versus HPLC plot of the binary solid dispersions it can be concluded that in PEG 6000 solid dispersions more itraconazole is present at the surface than in the bulk (Fig. 5). This can be explained by the fact that itraconazole resides predominantly in the amorphous part of PEG 6000 (Schachter et al., 2004), which is more present at the surface because of its lower surface energy compared to the crystalline moiety (Lei et al., 2003). For the itraconazole/HPMC 2910 E5 blends the XPS results show that for a drug load of 20%, more itraconazole is present at the surface than in the centre and for a drug load of 40%, less drug is present at the surface than in the centre

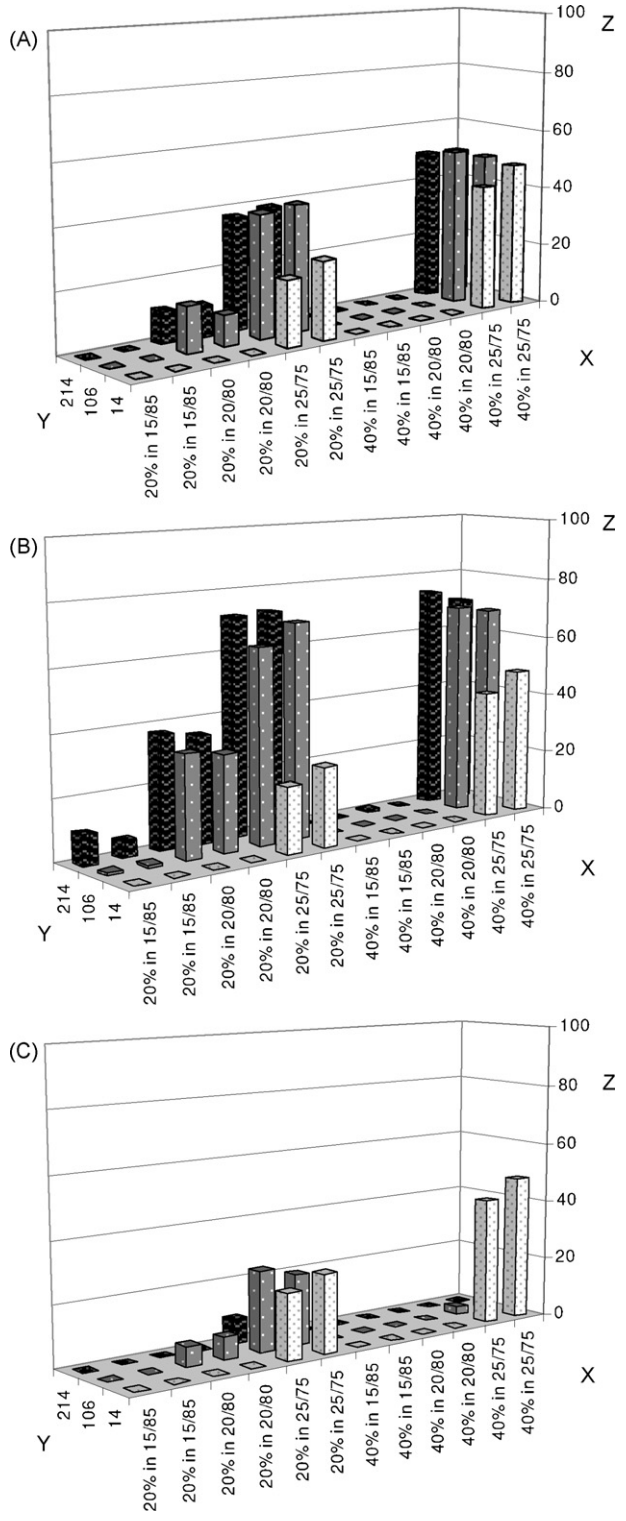

Fig. 3. Crystallinity degree (%, *Z*-axis) of PEG 6000 in ternary solid dispersions (composition, *X*-axis) as a function of time (days, *Y*-axis), stored at: (A) 25 °C, 0% RH; (B) 25 °C, 52% RH; (C) 60 °C, 0% RH.

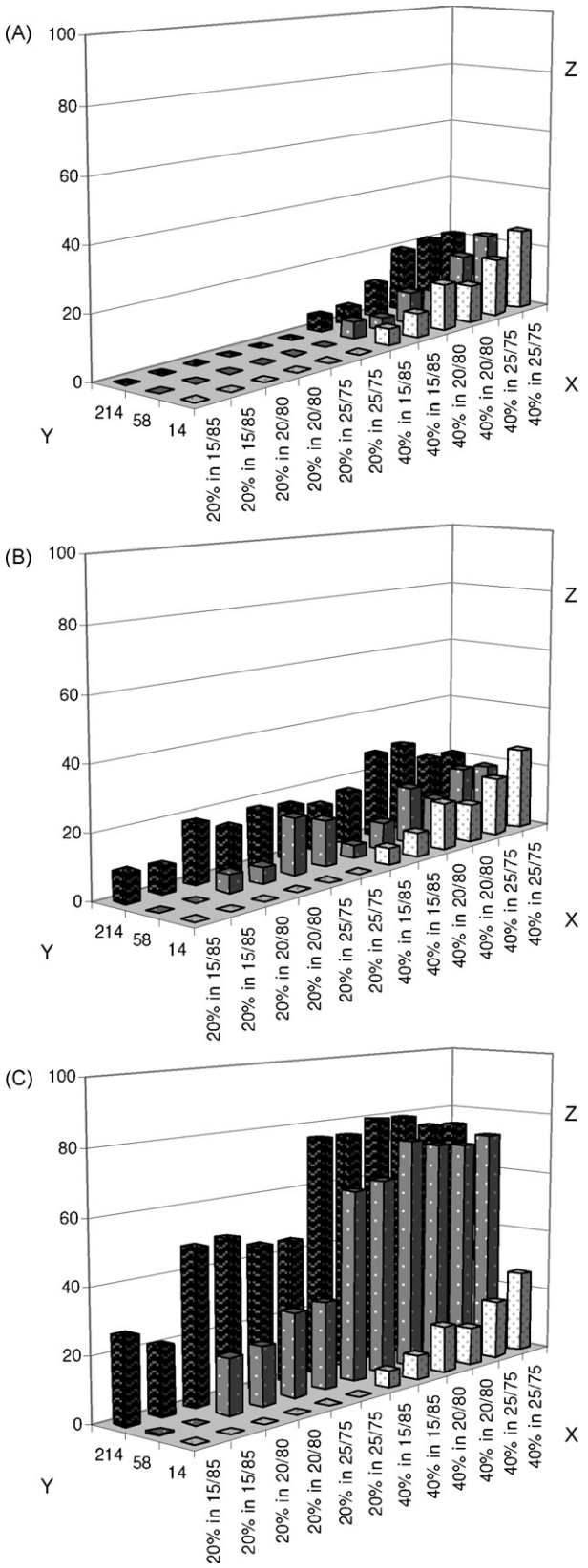

Fig. 4. Crystallinity degree (%, *Z*-axis) of itraconazole in ternary solid dispersions (composition, *X*-axis) as a function of time (days, *Y*-axis) stored at: (A) 25 °C, 0% RH; (B) 25 °C, 52% RH; (C) 60 °C, 0% RH.

(Fig. 5). This indicates that the binary itraconazole/HPMC 2910 E5 blends consist of more than one phase, even though a single glass transition is observed (Janssens et al., in press; Six et al., 2003).

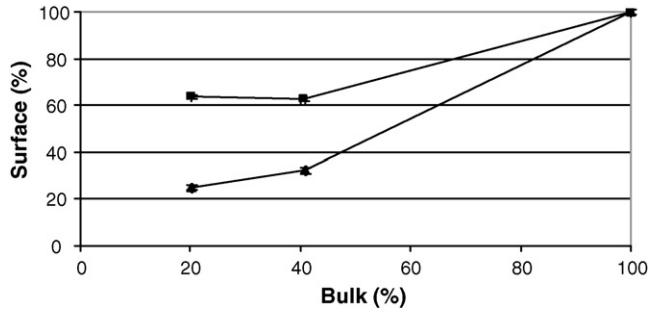

Fig. 5. The percentage of itraconazole at the surface, determined with XPS, vs. the total weight percentage of itraconazole, determined with HPLC, for binary solid dispersions of itraconazole in PEG 6000 (■) and itraconazole in HPMC (▲ ($n = 3$, X and Y error bars indicate S.D.).

The ternary solid dispersions were analyzed right after drying, after 2 months and after 6 months. The MDSC analyses showed that over a period of 6 months the sample with 20% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5 blend kept at 25 °C and 0% RH remained amorphous. In the sample with 40% of itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5 blend kept at 25 °C and 0% RH, PEG 6000 remained amorphous and the crystallinity degree of itraconazole was only ca. 5% after 6 months. These results correlate well with the surface distribution of itraconazole as a function of time, since for 20% and 40% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5 kept at 25 °C and 0% RH, the surface distribution remained more or less the same throughout the whole period of investigation. Interestingly, the surface distribution of itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5 was similar to the surface distribution of itraconazole in HPMC 2910 E5. In the samples with 20% or 40% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5 that were kept at 60 °C and 0% RH or 25 °C and 52% RH there was a redistribution of itraconazole at the surface (Figs. 6 and 7a). For both itraconazole in 20/80 (w/w) PEG 6000/HPMC 2910 E5 and itraconazole in 25/75 (w/w) PEG 6000/HPMC 2910 E5 there was a slight decrease of itraconazole at the surface over time for each storage condition (Figs. 6 and 7b and c). Since for these samples the redistribution of itraconazole at the surface did not vary significantly with the storage conditions it can be concluded that the surface distribution was governed by recrystallization of itraconazole rather than PEG

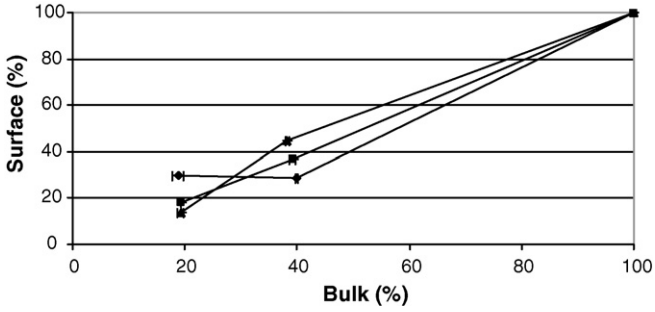

Fig. 6. The percentage of itraconazole at the surface, determined with XPS, vs. the total weight percentage of itraconazole, determined with HPLC, after drying for itraconazole in 15/85 (w/w) (♦), 20/80 (w/w) (■), and 25/75 (w/w) and (▲) PEG 6000/HPMC 2910 ($n = 3$, X and Y error bars indicate S.D.).

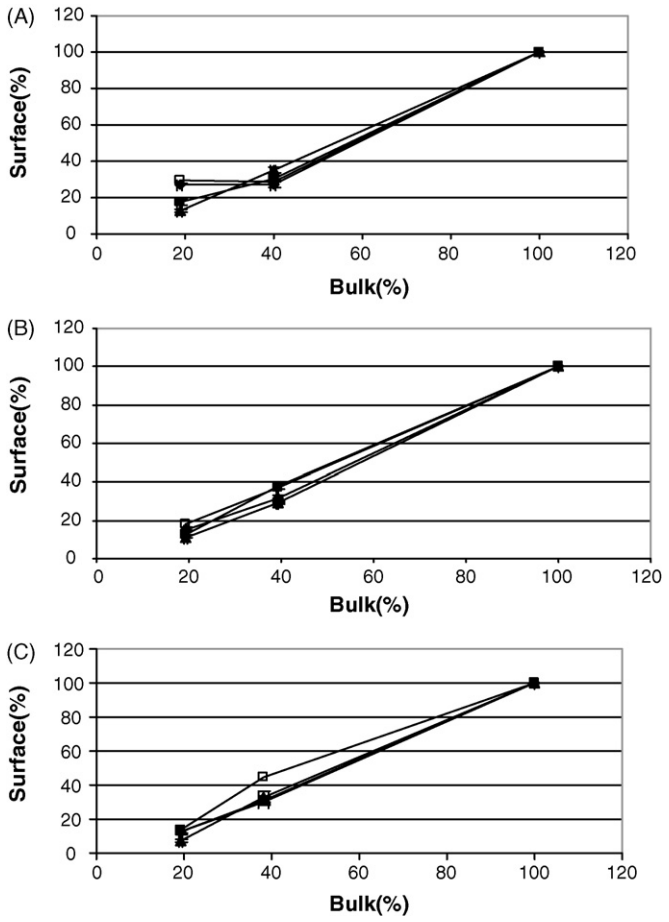

Fig. 7. The percentage of itraconazole at the surface, determined with XPS, vs. the total weight percentage of itraconazole, determined with HPLC, after 6 months of storage at 25 °C, 0% RH (♦), 25 °C, 52% RH (■), and at 60 °C, 0% RH (▲), and after drying (□) for itraconazole in 15/85 (w/w) (A), 20/80 (w/w) (B) and 25/75 (w/w) (C) PEG 6000/HPMC 2910 E5 ($n = 3$, X and Y error bars indicate S.D.).

6000. In general the XPS data show that for the ternary dispersions the distribution of itraconazole between the surface and the centre is more equal than for the binary solid dispersions. Several processes could be responsible for these observations, such as segregation of amorphous components to the surface or simple diffusion. The driving force for surface segregation of amorphous compounds with low surface energy is recrystallization at the surface, which leads to a higher surface energy (Lei et al., 2003). In this case, the recrystallization of itraconazole might have been the main driving force for amorphous fractions such as HPMC to segregate at the surface.

3.2. Chemical stability

The chromatograms of samples obtained by dissolution experiments were compared with a chromatogram of a blanc and peaks other than the solvent peak and the main itraconazole peak at 4.6 min were considered as degradation products. No degradation was found for all samples stored at 25 °C and 0% or 52% RH but for the samples stored at 60 °C and 0% RH small peaks due to degradation were observed already after 2 months

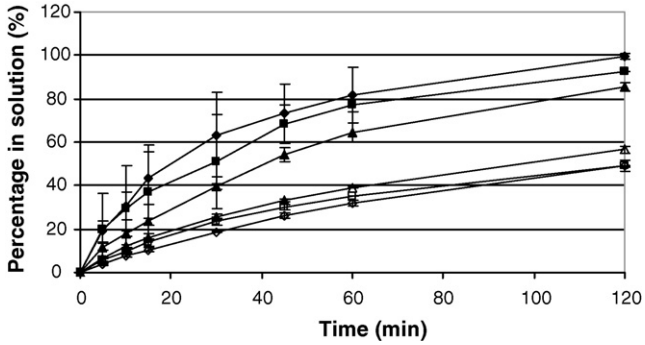

Fig. 8. Dissolution profiles of solid dispersions right after drying; (▲) 20% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5; (♦) 20% itraconazole in 20/80 (w/w) PEG 6000/HPMC 2910 E5; (■) 20% itraconazole in 25/75 (w/w) PEG 6000/HPMC 2910 E5; (△) 40% itraconazole in 15/85 (w/w) PEG 6000/HPMC 2910 E5; (◊) 40% itraconazole in 20/80 (w/w) PEG 6000/HPMC 2910 E5; (□) 40% itraconazole in 25/75 (w/w) PEG 6000/HPMC 2910 E5 ($n = 3$, error bars indicate S.D.).

of storage. It was also noticed that these samples were slightly yellow. In order to determine whether these decomposition products were originating from the polymers or from itraconazole, the polymer blends that were kept at 60 °C and 0% RH were analyzed in the same way. However, apart from the solvent peak no other peaks were observed, indicating that the observed peaks must be due to decomposition of itraconazole. Since one of these additional peaks overlapped with the main itraconazole peak, a quantitative determination of the itraconazole content in these samples was not possible.

3.3. Dissolution testing

Immediately after 2 weeks of drying, before storage at various conditions, dissolution experiments were carried out on the solid dispersions. The results were separated into two clusters, one with 20% of itraconazole and one with 40% of itraconazole. In the compositions with 20% of itraconazole the drug was completely amorphous, leading to a dissolution ranging from 85% to 100%. The compositions with 40% of itraconazole had dissolution of 50–60%, likely due to the fact that itraconazole is partially crystalline in these blends (Janssens et al., in press) (Fig. 8).

The dissolution profiles of the samples containing 20% and 40% of itraconazole in 15/85 (w/w), 20/80 (w/w) and 25/75 (w/w) PEG 6000/HPMC 2910 E5 blends after 6 months of storage are shown in Fig. 9a–c, respectively. For all samples with 20% of itraconazole that were stored at 25 °C, 0% RH, the initial dissolution profile was maintained, which agrees with the fact that in all of these samples itraconazole was completely amorphous. The samples containing 20% of itraconazole that were stored at 25 °C, 52% RH and at 60 °C, 0% RH showed a decrease in their dissolution corresponding to their increased degree of crystallinity. In the series of samples containing 40% of itraconazole, especially the samples stored at 60 °C and 0% RH had a very low release (between 10% and 20%) due to the high crystallinity degree of itraconazole. The difference between the two other conditions was less clear. Apparently there was no

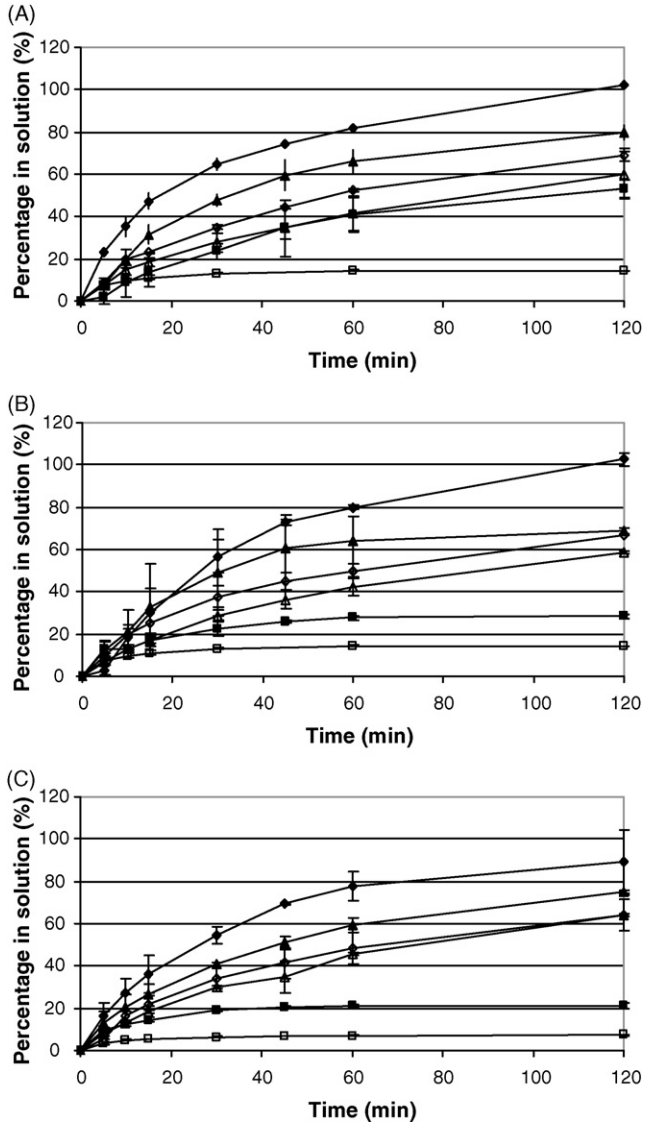

Fig. 9. Dissolution profiles of ternary dispersions after 6 months of storage. 20% of itraconazole stored at 25 °C, 0% RH (♦), 40% of itraconazole stored at 25 °C, 0% RH (◊), 20% of itraconazole stored at 25 °C, 52% RH (▲), 40% of itraconazole stored at 25 °C, 52% RH (△), 20% of itraconazole at 60 °C, 0% RH (■) and 40% of itraconazole at 60 °C, 0% RH (□), for itraconazole in 15/85 (w/w) (A), 20/80 (w/w) (B) and 25/75 (w/w) (C) PEG 6000/HPMC 2910 E5 ($n = 3$, error bars indicate S.D.)

influence of the crystallinity degree of PEG 6000 on the dissolution, since for all samples containing 20% of itraconazole that were stored at 25 °C, 0% RH the same release was found after 6 months, even though the various PEG 6000 fractions had different degrees of crystallinity.

4. Conclusion

This stability study revealed that removal of bound water leads to further mixing of PEG 6000 and HPMC 2910 E5. However, increased recrystallization of itraconazole at storage conditions where the mobility is increased either by temperature or by the presence of water, pointed out that the amorphous

compositions obtained after spray drying were supersaturated solid solutions.

The XPS data suggest that redistribution of itraconazole at the surface is governed by recrystallization of itraconazole rather than PEG 6000.

The dissolution data showed that an increase in the crystallinity of itraconazole was directly related to a decrease in the extent of dissolution. However, no correlation was found with the crystallinity degree of PEG 6000. These data suggest that in order to have a beneficial effect of PEG 6000 upon dissolution, miscibility between PEG 6000 and HPMC 2910 E5 is not required.

Acknowledgement

The onderzoeksraad K.U.Leuven (OT/03/60) is acknowledged for financial support.

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