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Research paper

Evaluation of the formulation of solid dispersions by co-spray drying itraconazole with Inutec SP1, a polymeric surfactant, in combination with PVPVA 64

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ABSTRACT

In order to improve the in vitro performance and stability of co-spray-dried itraconazole/Inutec SP1 systems, the influence of adding PVPVA 64, a polymer that is compatible with itraconazole, was evaluated. Dissolution tests were carried out on several itraconazole/PVPVA 64/Inutec SP1 compositions and spray-dried itraconazole/PVPVA 64 powders were used as references. The physicochemical properties of the samples were assessed with modulated temperature differential scanning calorimetry (MDSC), X-ray powder diffraction (XRD) and environmental scanning electron microscopy (ESEM). Physicochemical analysis revealed that there is no interaction between itraconazole and Inutec SP1 and that sufficient amount of PVPVA 64 is required to keep the drug molecularly dispersed. The improvement of the ternary solid dispersions over the binary solid dispersions was composition dependent. On one hand the increased drug/PVPVA 64 ratio in the ternary systems slowed dissolution down, on the other hand this was compensated by the solubilizing power of Inutec SP1.

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1. Introduction

Inutec SP1 is a poorly water soluble (<1%) polymeric surfactant derived from Inulin by grafting alkyl groups on primary or secondary hydroxyl groups of the polyfructose backbone via alkylisocyanates. A potent polymeric surfactant is thus obtained in which the alkyl groups tend to adsorb onto hydrophobic surfaces, leaving the polyfructose loops dangling out into the aqueous solution, providing steric stabilization (Fig. 1). Because of its excellent surfactant properties, low toxicity and biodegradability, Inutec SP1 has found its way to the food and cosmetics industry [1,2]. A recent publication of Van den Mooter et al. introduces this interesting polymer as a suitable carrier for the formulation of solid dispersions of poorly soluble drugs [3]. The formulation of solid dispersions either by coprecipitation 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 its dissolution rate [4]. 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 [5]. Moreover, the carrier often has a stabilizing effect on the obtained drug solution [6]. The study of Van den Mooter et al. revealed that with a 20/80 w/w itraconazole/Inutec SP1 extrudate a dissolution of 100% could be obtained after 30 min. The same composition prepared by spray drying; however, gave rise to a dissolution of only 50%. Based on DSC and XRD results it could be concluded that the crystallinity degree of itraconazole in the extrudates was around 12.8%, where-else it was only 2% for the spray-dried solid dispersions. These findings are in contrast with the observation that the degree of dissolution of the extruded dispersions was much higher. Therefore the authors concluded that due to high shear forces, itraconazole was much more intensely mixed with Inutec SP1 during the extrusion process than after spray drying [3]. Therefore, the aim of this study is to improve the characteristics of spray-dried itraconazole/Inutec SP1 solid dispersions by adding a polymer that can molecularly disperse high levels of itraconazole, polyvidone-vinylacetate 64 (PVPVA 64) [7]. Hence, the degree of dispersion of itraconazole would increase and this would reflect in an increase of the dissolution. Furthermore, a molecular dispersion of itraconazole would also improve the stability of the product. Additionally, this paper aims to contribute to the exploration of new, combined carriers for the

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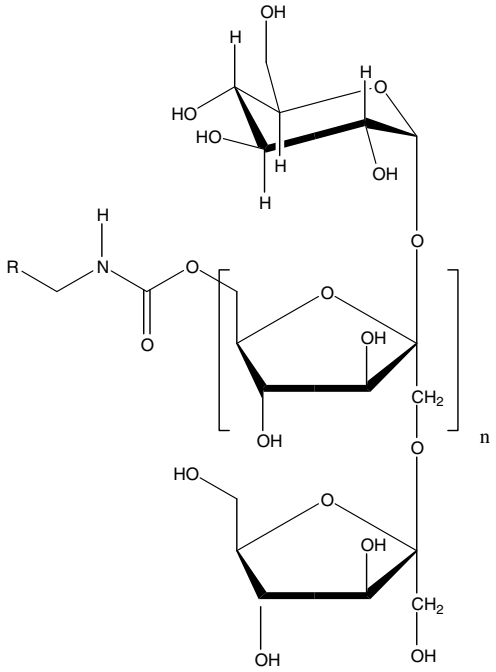

Fig. 1. Chemical structure of Inutec SP1.

formulation of poorly soluble compounds via solid dispersions. Indeed, the literature describes the formulation of solid dispersions in carrier blends, based on the rational of tailoring the properties of the carrier to the needs of the drug [7–12].

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 Inutec SP1 was generously provided by Orafti Non-Food (Tienen, Belgium).

2.2. Methods

2.2.1. Spray drying

Binary itraconazole/PVPVA 64 dispersions and ternary dispersions made up of itraconazole, PVPVA 64 and Inutec SP1 were prepared in a Buchi mini spray dryer B191 (Buchi, Flawil, Switzerland), (Table 1). Powder blends were added to CH_2Cl_2 and stirred with a magnetic stirrer in order to dissolve itraconazole and PVPVA 64 and to keep the CH_2Cl_2 insoluble Inutec SP1 homogenously suspended. The total amount of powder was 5 g per 100 mL. 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. The solutions with suspended Inutec SP1 were further stirred during spray drying. All spray-dried powders were dried for one week in a vacuum oven at 40 °C prior to analysis and further stored in a desiccator over P_2O_5 at 25 °C [13].

2.2.2. Physicochemical characterization

2.2.2.1. Modulated temperature differential scanning calorimetry (MDSC). All spray-dried samples and starting materials were analyzed in triplicate. MDSC measurements were carried out using a Q2000 Modulated DSC (TA Instruments, Leatherhead, UK)

Table 1
Composition of spray-dried solid dispersions

Binary solid dispersions	
2.	20/80 Itraconazole/PVPVA 64
3.	40/60 Itraconazole/PVPVA 64
Ternary solid dispersions	
1.	20% Itraconazole in 2/1 PVPVA 64/Inutec SP1
2.	30% Itraconazole in 2/1 PVPVA 64/Inutec SP1
3.	40% Itraconazole in 2/1 PVPVA 64/Inutec SP1
4.	40% Itraconazole in 3/1 PVPVA 64/Inutec SP1
5.	40% Itraconazole in 4/1 PVPVA 64/Inutec SP1
6.	40% Itraconazole in 1/2 PVPVA 64/Inutec SP1

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 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 of the temperature was 0.212 °C, the period was 40 s, and the underlying heating rate was 2 °C/min [14]. The samples were heated from −90 to 180 °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 itraconazole was obtained from the 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 in the blend and ΔHf being the enthalpy of pure itraconazole (80.3 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 [14]. 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 X'Pert PRO diffractometer (PANalytical, The Netherlands) in Bragg-Brentano geometry with a flat sample stage spinning with a rotation time of 4 s. X'Pert Data Collector version 2.2 c (PANalytical, The Netherlands) was used for data collection. In the incident beam path a 0.04 rad soller slit, a 10 mm mask and a programmable divergence slit were installed. In the diffracted beam path a programmable anti scatter slit and a 0.04 rad soller slit were installed. Cu $K\alpha_1$-radiation (λ = 1.540598 Å) was obtained with a 0.02 mm Ni-filter. The irradiated and observed area was 100 mm^2. The irradiated and the observed length was 10 mm. The diffracted beams were detected with an X'celerator RTMS detector with an active length of 2.122°. The data were collected in continuos mode in the region of $4° \leqslant 2\theta \leqslant 40°$ with a step size of 0.0021° 2θ and a counting time of 19.7 s. The X-ray tube was set up at a voltage of 45 kV and a current of 40 mA. The diffractograms were analyzed using X'pert Data Viewer version 1.2a.

2.2.2.3. Environmental scanning electron microscopy. The morphology of the spray-dried ternary solid dispersions and Inutec SP1 was characterized with a Philips XL30 ESEM FEG environmental scanning electron microscope (FEI, The Netherlands) operating at 25 kV accelerating voltage and a vacuum of 1.9 Torr. The samples were sprayed on double-sided carbon tape that was mounted on conventional SEM stubs. Samples were imaged with a GSED (gaseous secondary electron detector).

2.2.2.4. 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 sulphate 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 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 [14].

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 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, and 120 min. These samples were filtered with 0.45 μm Teflon filters (Macherey-Nagel, Düren, Germany). The first 2 ml were discarded. The remainder was diluted with methanol (1/2) to avoid precipitation, and analyzed with HPLC, as described above [14].

3. Results and discussion

3.1. Itraconazole content of the solid dispersions

Due to the fact that Inutec SP1 was suspended and stirred during the spray drying process, the variation on the itraconazole content (89–106.8% ± 1.8) is much larger for the ternary solid dispersions than for the binary itraconazole/PVPVA64 solid dispersions that were sprayed from a plain solution (101–102% ± 0.1). The actual itraconazole content was taken into account for the expression of the percentage drug dissolved in the dissolution experiments.

3.2. Dissolution

Dissolution experiments were carried out on fresh samples after one week of drying. In Fig. 2 the results of samples containing 20% and 40% of itraconazole in pure PVPVA 64 are compared to the results obtained with 20% and 40% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1. Compared to the results of the spray-dried 20/80 w/w itraconazole/Inutec SP1 solid dispersion reported by Van den Mooter et al. [3], the addition PVPVA 64 to the formulation led to a vast improvement of the degree of dissolution: after 1 h approximately 90% is dissolved. With respect to the dissolution of 20% itraconazole in PVPVA 64, the dissolution rate and the degree of dissolution are higher in the first two hours. The ternary solid dispersion containing 40% of itraconazole had a slightly higher dissolution than the binary dispersion of 40% itraconazole in PVPVA 64 for each time point.

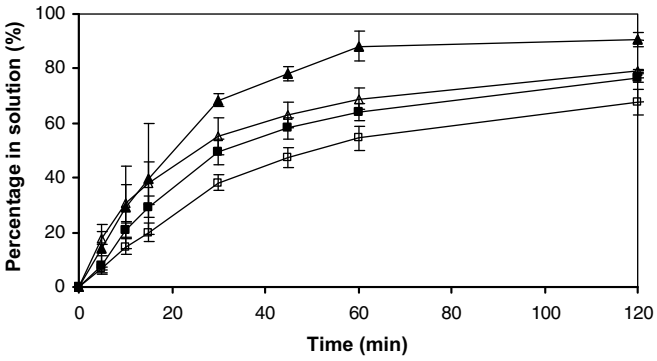

Fig. 2. Dissolution profiles of solid dispersions of 20% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (▲), 20% itraconazole in PVPVA 64 (□), 40% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (■), 40% itraconazole in PVPVA 64 (□), (n = 3, error bars indicate SD).

Fig. 3 depicts the dissolution profiles of ternary solid dispersions containing 40% of itraconazole in several ratios of PVPVA 64/Inutec SP1 compared to the binary dispersion of 40% itraconazole in PVPVA 64. The following two ratios, 2/1 and 1/2 w/w PVPVA 64/Inutec SP1, give rise to, respectively, the highest and the lowest dissolution. 40% itraconazole in 3/1 and 4/1 w/w PVPVA 64/Inutec SP1 give rise to very similar dissolutions profiles that are slightly higher or lower than the binary dispersion of 40% itraconazole in PVPVA, depending on the time point.

In order to understand the influence of the composition on the dissolution profiles, a closer look should be taken at the solid state properties of the solid dispersions.

3.3. Physicochemical characterization

3.3.1. X-ray diffraction

Fig. 4 shows the diffractograms of the ternary solid dispersions and crystalline itraconazole. All ternary dispersions are completely XRD amorphous except for 40% itraconazole in 1/2 w/w PVPVA 64/Inutec SP1, where very slight reflections are present at 2θ values consistent with the crystalline itraconazole diffraction peaks. The detection limit for crystalline itraconazole was determined to be ca. 5% (data not shown).

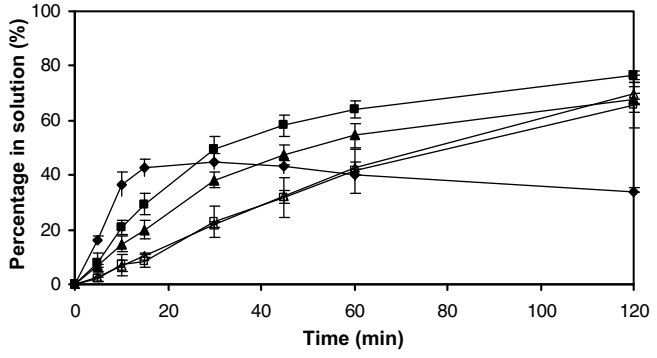

Fig. 3. Dissolution profiles of solid dispersions of 40% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (■), 40% itraconazole in 3/1 w/w PVPVA 64/Inutec SP1 (□), 40% itraconazole in 4/1 w/w PVPVA 64/Inutec SP1 (□), 40% itraconazole in 1/2 w/w PVPVA 64/Inutec SP1 (♦), 40% itraconazole in PVPVA 64 (▲), (n = 3, error bars indicate SD).

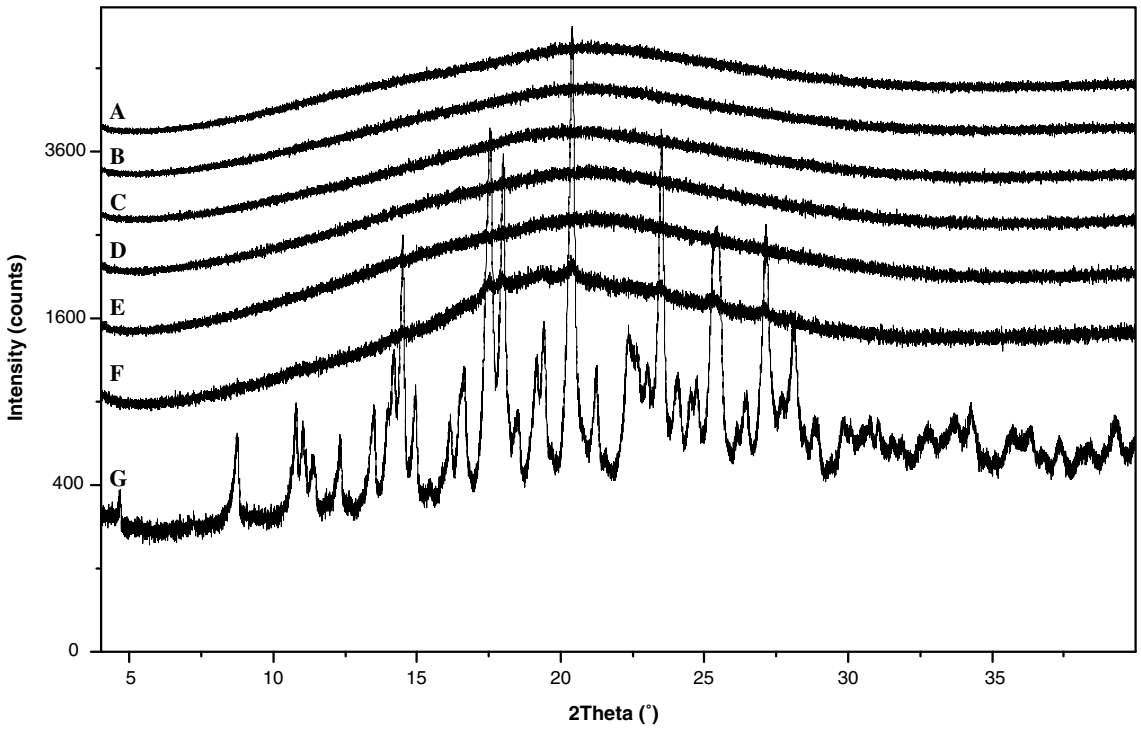

Fig. 4. X-ray diffraction profiles of all ternary solid dispersions and crystalline itraconazole with from top to bottom; 20% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (A), 30% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (B), 40% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (C), 40% itraconazole in 3/1 w/w PVPVA 64/Inutec SP1 (D), 40% itraconazole in 4/1 w/w PVPVA 64/Inutec SP1 (E), 40% itraconazole in 1/2 w/w PVPVA 64/Inutec SP1 (F) and crystalline itraconazole (G).

3.3.2. Modulated differential scanning calorimetry

As shown in Table 2 only two compositions have a crystalline itraconazole phase, 40% itraconazole in 2/1 and 1/2 w/w PVPVA 64/Inutec SP1. These samples were the first compositions that were investigated. Evaluation of the thermograms made clear that a sufficient amount of PVPVA 64 was needed in order to keep itraconazole molecularly dispersed. In order to keep the Inutec SP1 fraction as high as possible, the PVPVA 64 amount was increased in steps, 3/1 w/w and 4/1 w/w, respectively. Also, starting from the formulation with the smallest crystalline drug phase, 40% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1, the drug load was decreased to 30% and 20%. All these compositions led to the formation of amorphous solid solutions. Indeed, none of these samples showed an itraconazole melting peak (Table 2). A closer inspection of the reversing heat flow revealed the presence of glass transitions. The reference glass transitions of itraconazole, PVPVA 64 [7] and Inutec SP1 [3] are 59.4, 107, and 143 °C, respectively. Depending on the composition, either an itraconazole rich amorphous phase with a glass transition temperature around 58 ± 1 °C, a mixed phase with a glass transition temperature ranging from 82 to 93 °C, or an Inutec SP1 phase with a glass transition temperature around 141–145 °C was found (Table 2). Interestingly, no endotherms at 70.3 and 90 °C due to the formation of a nematic mesophase, typical for glassy itraconazole were observed [15]. Therefore, the itraconazole rich amorphous phases must still contain a small amount of carrier, impeding the formation of a structured mesophase.

In order to elucidate the nature of the mixed phase, the experimentally obtained glass transitions ranging from 82 to 93 °C were compared to theoretical glass transitions for itraconazole/PVPVA 64 solid solutions according to the Gordon-Taylor/Kelly-Bueche equation (Eq. (1)) in combination with the Simha-Boyer rule (Eq. (2)) [16–18].

$$T_{gmix} = (T_g1w1 + T_g2K1w2)/(w1 + K1w2) \quad (2)$$

$$K \cong (\rho 1 T_g 1)/(\rho 2 T_g 2) \quad (3)$$

In the Gordon-Taylor equation $w1$ and T_g1 are the weight fraction and the glass transition temperature (59.4 °C) of itraconazole, respectively, $w2$ and T_g2 are the weight fraction and the glass transition temperature (107 °C) of spray-dried PVPVA 64, respectively, $K1$ is a constant that is calculated with the Simha-Boyer rule in which ρ_1 and T_g1 are, respectively, the density and the glass transition temper-

Table 2
MDSC data of spray-dried Itraconazole/PVPVA 64/Inutec SP1 solid dispersions

Itraconazole % in w/w PVPVA 64/Inutec SP1	T_m (°C)[a]	ΔHf_{in} (J/g)[b]	Crystallinity degree (%)[c]	T_g1 (°C)	T_g2 (°C)	T_g3 (°C)
20% in 2/1	/	/	/	/	93.8 ± 0.9	142.4 ± 0.7
30% in 2/1	/	/	/	/	88.4 ± 1	142.6 ± 0.3
40% in 2/1	152.4 ± 0.4	1 ± 0.1	3.2 ± 0.4	58.7 ± 0.6	93.8 ± 7.2	141.4 ± 0.6
40% in 3/1	/	/	/	/	82.8 ± 0.4	143.5 ± 4.5
40% in 4/1	/	/	/	/	83.6 ± 3.3	144.9 ± 1.8
40% in ½	158.5 ± 0.1	9.0 ± 2.4	28 ± 7	57.7 ± 0.6	/	/

[a] Itraconazole melting temperature.
[b] Itraconazole melting enthalpy minus Itraconazole recrystallization enthalpy.
[c] Initial crystallinity degree of Itraconazole calculated using ΔHf_{in} according to the following formula: $\text{Crystallinity}(\%) = \frac{\Delta Hf_{in}}{\Delta Hf \times w\%) \times 100}$ with ΔHf = 80.3 J/g.

Table 3
Comparison between the Itraconazole/PVPVA 64 ratio based on Gordon-Taylor analysis of the mixed phase glass transition, and the Itraconazole/PVPVA 64 ratio based on the Itraconazole content and the theoretical PVPVA 64/Inutec SP1 ratio

Itraconazole % in w/w PVPVA 64/Inutec SP1	Itraconazole (%)[a]	Crystallinity degree (%)[b]	Mixing T_g (°C)	Itraconazole/PVPVA 64[c]	Itraconazole/PVPVA 64[d]	Δ[e]
20% in 2/1	19.3 ± 0.1	/	93.8 ± 0.9	0.269 ± 0.002	0.264 ± 0.001	0.004 ± 0.002
30% in 2/1	28.9 ± 0.1	/	88.4 ± 1.0	0.382 ± 0.002	0.378 ± 0.001	0.004 ± 0.002
40% in 2/1	39.6 ± 0.5	3.2 ± 0.4	93.8 ± 7.2	0.269 ± 0.01	0.495 ± 0.006	−0.226 ± 0.012
40% in 3/1	40.8 ± 0.2	/	82.8 ± 0.4	0.499 ± 0.004	0.479 ± 0.002	0.020 ± 0.005
40% in 4/1	42.7 ± 0.1	/	83.6 ± 3.3	0.483 ± 0.002	0.482 ± 0.001	0.0003 ± 0.002

[a] Itraconazole content (weight percentage) obtained by HPLC analysis.
[b] Itraconazole crystallinity degree.
[c] Itraconazole/PVPVA 64 w/w ratio based on Gordon-Taylor analysis of the mixed phase glass transition.
[d] Itraconazole/PVPVA 64 w/w ratio based on the Itraconazole content and the theoretical PVPVA 64/Inutec SP1 w/w ratio.
[e] Difference between c and d.

ature of the amorphous component with the lowest glass transition temperature, and ρ_2 and T_g2 are, respectively, the density and glass transition temperature of the amorphous component with the highest glass transition temperature. The densities of itraconazole and PVPVA 64 are 1.270 and 1.190 g/cm^3, respectively [7].

In an earlier publication it has been demonstrated that up to 80% of itraconazole can be molecularly dispersed in PVPVA 64 [7]. Moreover, the position of the glass transition temperature as a function of the itraconazole/PVPVA 64 ratio corresponded to the values obtained with the Gordon-Taylor equation, indicating volume additivity and absence of strong heteromolecular forces. Therefore, the linear relationship between the glass transition temperature and the itraconazole/PVPVA 64 weight ratio can be used to estimate the itraconazole content from the glass transition temperature of an itraconazole/PVPVA 64 phase with an unknown composition. In order to elucidate whether Inutec SP1 was present in the mixed phase or not, it was assumed that the mixed phase consisted of itraconazole and PVPVA 64. In Table 3 the difference between the itraconazole content in the mixed amorphous phase, based on either the Gordon-Taylor equation, or the HPLC experiments and the theoretical PVPVA 64/Inutec SP1 ratios is compared. Except for the 40% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 sample, the Δ-values obtained from the differences between the values of the itraconazole fractions were found to be close to zero. Hence, the mixed amorphous phase can be considered as an itraconazole/PVPVA 64 phase. The aberrant Δ-value for the 40% itraconazole in 2/1w/w PVPVA 64/Inutec SP1 sample can be ascribed to the presence of a crystalline itraconazole phase and the presence of an itraconazole rich amorphous phase, leaving an itraconazole/PVPVA 64 phase with a lower itraconazole content. There is no obvious reason for the slightly increased Δ-value of the 40% itraconazole in 3/1 w/w PVPVA 64/Inutec SP1 sample. Based on this good agreement, it can be stated that itraconazole resides predominantly in the PVPVA 64 phase. However, the decreased melting temperature of itraconazole in the 40% in 2/1 and 1/2 w/w PVPVA 64/Inutec SP1 samples, 152 ± 0.4 and 158.5 ± 0.4 °C, respectively instead of 165.2 ± 0.2 °C, indicates that there is some interaction between the crystalline itraconazole phase and the surrounding polymers.

3.3.3. Environmental scanning electron microscopy

Fig. 5 depicts ESEM images of Inutec SP1 and all ternary solid dispersions. The bar on the pictures indicates the degree of magnification (50 μm in picture A and 20 μm in all other pictures). On pictures A and B the spherical porous structure of Inutec SP1 is visible, the particle size varies from ca. 20 to ca. 100 μm. On picture C, D, E, F, G, and H, the solid dispersions with itraconazole, PVPVA 64 and Inutec SP1 are depicted. As the amount of PVPVA 64 increases a fine powder consisting of spherical particles with a diameter ranging from less than 1 μm up to 5 μm appears. This fine powder is either loose or aggregated with the separate Inutec SP1 particles.

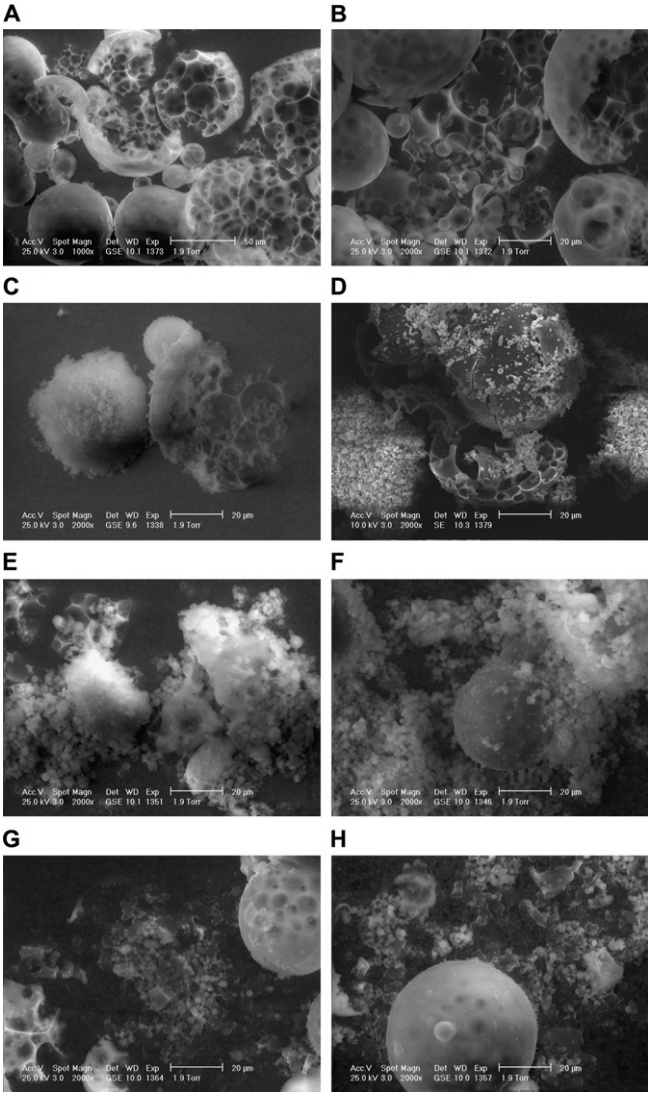

Fig. 5. ESEM images of Inutec SP1 (A and B), 40% itraconazole in 1/2 w/w PVPVA 64/Inutec SP1 (C), 40% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (D), 40% itraconazole in 3/1 w/w PVPVA 64/Inutec SP1 (E), 40% itraconazole in 4/1 w/w PVPVA 64/Inutec SP1 (F), 20% itraconazole in 2/1 w/w PVPVA 64/Inutec SP1 (G), 30% itraconazole in 2/1 PVPVA 64/Inutec SP1 w/w (H).

Based on these images and on the conclusions that were drawn from the MDSC experiments, e.g., the fact that itraconazole was either molecularly dispersed in PVPVA 64, or present as a separate amorphous or crystalline phase, it can be concluded that itraconazole or PVPVA 64 and Inutec SP1 were not mixed on a molecular level.

4. Conclusion

Based on Gordon-Taylor analysis it could be concluded that all the molecularly dispersed itraconazole resided in the PVPVA phase and that Inutec SP1 did not interact with any of the components on a molecular level. These findings were in agreement with the morphological properties of the powder. Indeed, ESEM images revealed the presence of small itraconazole/PVPVA 64 particles and large Inutec SP1 spheres. This outcome is rather consistent with the fact that Inutec SP1 was suspended in the spray drying solution. The presence of a considerably large crystalline itraconazole phase gave rise to a rather low extent of dissolution for the 40% itraconazole in 1/2 w/w PVPVA 64/Inutec SP1 sample. Therefore, the PVPVA 64 weight fraction was increased in the other formulations in order to keep the drug molecularly dispersed. Compared to the binary itraconazole/PVPVA 64 dispersions that were used for comparison, the ternary compositions had a much higher itraconazole/PVPVA 64 weight ratio which, in general, causes a decrease in the extent and the rate of dissolution [14]. On the other hand, the presence of Inutec SP1 in the ternary systems promoted dissolution by maintaining a higher saturation solubility and hence increasing the dissolution driving force [15]. Therefore, the improvement of the ternary solid dispersions over the binary itraconazole/PVPVA 64 solid dispersions is composition dependent. It is noteworthy; however, that adding PVPVA 64 to spray-dried itraconazole/Inutec SP1 binary solid dispersions, as reported earlier by Van den Mooter [3], did lead to a significant improvement in terms of dissolution. Also, the formation of a molecular dispersion of itraconazole will most probably improve stability.

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