Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 316 (2006) 1–6
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs

Guy Van den Mooter[a,*], Ilse Weuts[a], Thomas De Ridder[a], Norbert Blaton[b]

[a] *Laboratorium voor Farmacotechnologie en Biofarmacie, K.U.Leuven, Leuven, Belgium*
[b] *Laboratorium voor Analytische Chemie en Medicinale Fysicochemie, K.U.Leuven, Leuven, Belgium*

Received 23 June 2005; received in revised form 31 January 2006; accepted 13 February 2006
Available online 6 March 2006

Abstract

Solid dispersions made up of itraconazole and Inutec SP1, a new polymeric surfactant, were prepared by spray drying and hot-stage extrusion. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD) were used to evaluate the miscibility of the components of the dispersions, and dissolution experiments were performed in simulated gastric fluid without pepsin (SGF_{sp}) to evaluate the pharmaceutical performance of itraconazole from the solid dispersions. DSC analysis showed that the solid dispersions are phase separated systems made up of glassy and crystalline itraconazole and amorphous Inutec SP1. The amount of crystalline drug substance was higher in the dispersions prepared by hot-stage extrusion and was clearly a function of the drug concentration. Since no crystallinity could be detected by XRD points to the fact that the crystallites formed are very small in size. Despite the presence of glassy and crystalline clusters, the dissolution properties of the solid dispersions were significantly improved in comparison to pure itraconazole (glassy or crystalline) or physical mixtures with Inutec SP1. This study proves the potential of the new polymeric surfactant as a carrier in the formulation of solid dispersions for poorly soluble drugs.

Keywords: Itraconazole; Solid dispersions; Inutec SP1; Spray drying; Hot-stage extrusion

1. Introduction

Today, 35–40% of all new chemical entities suffer from poor aqueous solubility (Report by Technology Catalysts International, 2002). Hence the enhancement of the solubility of poorly water-soluble drugs is one of the most challenging aspects of modern drug development. The use of solid dispersions has been recognized for many years as a strategy that can increase the solubility and dissolution rate of drugs (Serajuddin, 1999; Leuner and Dressman, 2000). Notwithstanding the early promises and high research efforts, very few products relying on this technology have reached the market. The main reason for this discrepancy is the fact that the structures formed can be metastable from a thermodynamical point of view. Phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage, inevitably results in decreased solubility and dissolution rate. Hence variability in oral bioavailability results for drugs showing dissolution limited absorption.

Despite the continuous interest in solid dispersions, the number of different polymeric carriers that have been used during the past 40 years is still rather limited. Indeed, the majority of studies that have been published so far report on the use of polyethylene glycol or polyvinylpyrrolidone. Although combinations of polymers or polymers and surfactants have been proposed in an attempt to tailor the physicochemical properties of the polymeric carriers to those of the dispersed drugs, there is definitely a need to explore new carrier materials (Six et al., 2004; Dannenfelser et al., 2004).

One such potential material is Inutec SP1. It is a derivative of inulin prepared by the reaction between isocyanates and the polyfructose backbone in the presence of a basic catalyst such as a tertiary amine or a Lewis acid (Stevens et al., 2001a, 2001b). In this way alkyl groups are introduced which are randomly distributed on the polysaccharide backbone. The structure of Inutec SP1 is depicted in Fig. 1. The resulting inulin carbamates pos-

* Corresponding author at: Laboratorium voor Farmacotechnologie en Biofarmacie, Campus Gasthuisberg O + N2, 49 Herestraat, B-3000 Leuven, Belgium. Tel.: +32 16330300; fax: +32 16330305.
E-mail address: guy.vandenmooter@pharm.kuleuven.be (G. Van den Mooter).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.02.025

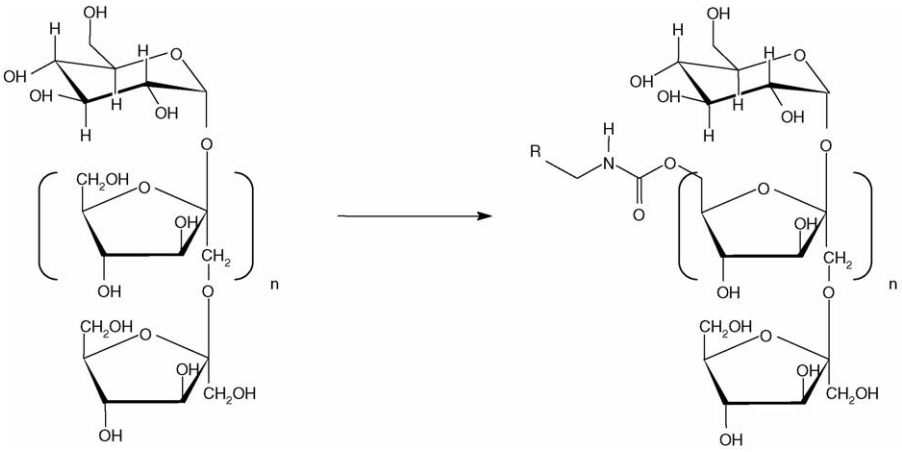

Fig. 1. Synthesis of Inutec SP1 from inulin.

sess tensioactive properties and can be used as an emulsifier in pharmaceutical formulations. It has been shown that in a two phase system like an oil-in-water emulsion, the alkyl groups become strongly adsorbed on the oil droplets, while the inulin chain is the stabilizing part of the molecule, forming loops dangling in solution (Booten and Levecke, 2003). Other advantages of Inutec SP1 are a low viscosity and preservation of its stabilizing effect on emulsions and suspensions with high electrolyte concentrations.

The aim of the present study was to evaluate the potential of this new polymeric surfactant as a carrier in the formulation of solid dispersions of itraconazole. Itraconazole is a potent antifungal drug of the triazole class. It has an extremely low aqueous solubility ($S < 1$ μg/ml) and poor dissolution rate in the GI tract and is therefore selected as model drug in this study. As a consequence of its poor solubility profile, it shows large interindividual differences in bioavailability after oral administration (Peeters et al., 2002; Grant and Clissold, 1989). According to the Biopharmaceutics Classification System, itraconazole is classified as a class II compound (Amidon et al., 1995).

2. Materials and methods

2.1. Materials

Itraconazole (<355 μm, purity more than 99%) was kindly donated by Janssen Pharmaceutica (Beerse, Belgium). Inutec SP1 was generously provided by Orafti Non-Food (Tienen, Belgium).

2.2. Methods

2.2.1. Preparation of physical mixture

The physical mixtures of itraconazole and Inutec SP1 were prepared by mixing both components in a mortar for 5 min followed by sieving (<355 μm). The following ratios itraconazole/Inutec SP1 (w/w) were prepared: 5/95; 10/90; 15/85; 20/80; 30/70.

2.2.2. Hot-stage extrusion

Hot-stage extrusion was performed with a mini-extruder (5 ml set up; DSM Research, Geleen, The Netherlands) at 170 °C and 100 rpm. Physical mixtures of Inutec SP1 and itraconazole were put in the extruder and processed during 5 min. The resulting extrudates were collected after cooling at ambient temperature and milled for 2 min with a laboratory cutting mill IKA-Werke (Staufen, Germany) and sieved to exclude particles >355 μm. All samples were stored in a desiccator (P_2O_5) at −40 °C and analyzed within 3 weeks. The following ratios itraconazole/Inutec SP1 (w/w) were prepared: 5/95; 10/90; 15/85; 20/80; 30/70.

2.2.3. Spray drying

Spray drying was performed with a Büchi Mini Spray Dryer B191 (Flawil, Switzerland). Solutions of itraconazole were prepared in 50 ml of a 50/50 (v/v) dichloromethane/methanol mixture. To this solution Inutec SP1 was added and the resulting suspension was stirred for 15 min and subsequently during 1 min further homogenized with a laboratory homogenizer at 22,000 rpm (Polytron PT-MR 2100; Kinematica AG, Switzerland). The resulting suspension was spray dried using the following process parameters: the inlet temperature was 80 °C, the aspirator and air flow were set at 100%; the pump speed was 6 ml/min. During spray drying the suspension was continuously stirred with a magnetic stirrer. The spray dried solid dispersion was isolated and subsequently dried in a vacuum-oven at 40 °C (Mazzazi Systems, Italy) till constant mass. All samples were stored in a desiccator (P_2O_5) at −40 °C and analyzed within 3 weeks. The ratio itraconazole/Inutec SP1 (w/w) was 20/80.

2.2.4. HPLC analysis

The exact drug content in the dispersions was determined using an appropriate HPLC method. HPLC (Merck-Hitachi, Darmstadt, Germany) analysis was performed by using an L-7100 Lachrom pump, an L-7200 Lachrom auto sampler 728, an L-7400 Lachrom UV-detector and a D-7000 HPLC System Manager. The column used was Chromolith Performance RP-18 (100 mm × 4.6 mm, Merck, Darmstadt, Germany);

the pre-column was a Chromolith guard Cartridge RP-18 (5 mm × 4.6 mm, Merck, Darmstadt, Germany). Acetonitrile/tetrabutyl ammonium hydrogen sulphate 0.01N (55/45, v/v) was used as mobile phase at a flow rate of 1 ml/min. The injection volume was 10 μl and the detection wavelength was 260 nm. These conditions resulted in a typical elution time for itraconazole of 4.8 min.

2.2.5. Dissolution testing

Dissolution experiments were performed using the SR8 Plus, Hanson Research dissolution testing system (California, USA). Binary solid dispersions (equivalent dose of 100 mg of itraconazole) were directly added to 1000 ml of simulated gastric fluid sine pepsin (USP XXIV) at 37 °C. Dissolution was assessed using the paddle method at 100 rpm (USP XXIV). The dissolution process was monitored for 2 h. The concentration of itraconazole was quantified at pre-determined time intervals. Two milliliters of sample was removed from the dissolution vessel and replaced by fresh dissolution medium. The samples were filtered with a Teflon membrane filter of 0.45 μm (Acrodisc, Pall Life Sciences, Ann Arbor, MI, USA). The amount of drug was determined using the HPLC method described in the previous paragraph. All experiments were performed in triplicate.

2.2.6. Differential scanning calorimetry

The DSC measurements were performed using a DSC 822^e Mettler-Toledo (Mettler Toledo, Switzerland). Cooling was provided with an intercooler. Data were treated mathematically using the resident STARe Software v.6.10 (Mettler Toledo, Switzerland). Calibration was carried out using indium and mercury as reference materials. The samples were analyzed in 40 μl covered and perforated aluminium Mettler-Toledo pans under a nitrogen purge. The samples were heated from 25 to 180 °C at a heating rate of 20 °C/min. Cooling was performed at 20 °C/min.

All measurements were performed in triplicate.

2.2.7. Powder X-ray diffraction

Powder X-ray diffraction was performed with a Philips PW 1050 diffractometer (Philips, Eindhoven, The Netherlands). Monochromatic Cu Kα radiation (λ = 1.54184 Å) was Ni filtrated. Parallel beam optics was used with 1/4° entrance and anti-scatter slit, 0.2 mm exit slit. The diffraction pattern was measured with a voltage of 32 kV and a current of 40 mA in the range of $4° < 2\Theta < 60°$ in a step scan mode (step interval of 0.02° and 1 s/step).

3. Results and discussion

The aqueous solubility of itraconazole is estimated at 1 ng/ml at neutral pH and approximately 4 μg/ml at pH 1 (Peeters et al., 2002), therefore it was used as a model drug. Several types of solid dispersions of itraconazole have been described previously by our research group in order to improve its dissolution characteristics: one phase glass solutions and multiple phase systems using hydrophilic polymers (Six et al., 2003, 2004, 2005; Verreck et al., 2003; Wang et al., 2004). The performance of these systems was optimal when itraconazole was truly molecularly dispersed in the polymeric carrier. On the other hand a significant advantage with respect to dissolution properties was observed for the pure glassy state compared to the crystalline state; the amount of crystalline itraconazole that dissolved after 2 h in simulated gastric fluid was approximately 3%, while it increased up to 9% in the case of the pure glassy state. However, a significant improvement of the dissolution properties was only observed (up to 90% dissolved in simulated gastric fluid) when the drug was truly molecularly dispersed in a polymeric carrier.

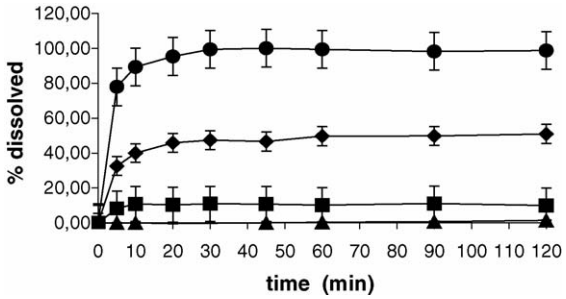

Fig. 2. Dissolution profiles of crystalline itraconazole (▲) and the physical mixture in a 20/80 drug/polymer ratio (■) compared to itraconazole formulated in a 20% spray dried (♦) and extruded solid dispersion (●) in simulated gastric fluid without pepsin.

In the present study, solid dispersions were prepared with the surface-active polymeric carrier Inutec SP1 by spray drying and hot-stage extrusion. Fig. 2 shows the dissolution profile of crystalline itraconazole and the physical mixture of crystalline itraconazole and Inutec SP1 (20:80) in comparison to that of itraconazole formulated in the two types of solid dispersion (20:80). The results show that the physical mixture already has a higher dissolution than the pure crystalline drug. The performance of the solid dispersions is striking: more than 47% of the drug is dissolved within 30 min for the spray dried dispersion while for the extruded dispersion approximately 99% of itraconazole is dissolved within 30 min. In order to evaluate the influence of drug loading, solid dispersions containing 5–30% of itraconazole were prepared by hot-stage extrusion. The dissolution curves are presented in Fig. 3. Due to the relatively high scatter of the results, no clear trend could be observed, but the amount dissolved after 60 min was always more than 80% of

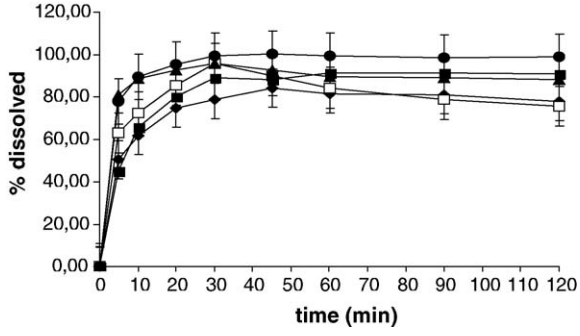

Fig. 3. Dissolution profiles of itraconazole in solid dispersions prepared by hot-stage extrusion in different drug/polymer ratios: 5/95 (♦), 10/90 (□), 15/85 (▲), 20/80 (●) and 30/70 (■) (w/w) drug/polymer ratio in simulated gastric fluid without pepsin.

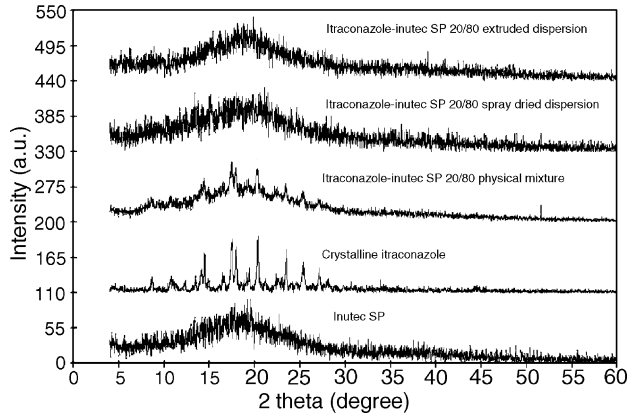

Fig. 4. X-ray powder diffraction pattern of the 20% physical mixture, the 20% spray dried and extruded solid dispersions, crystalline itraconazole and pure Inutec SP1.

the administered dose showing the potential of Inutec SP1 as a carrier.

In order to explain the dissolution behaviour of itraconazole from solid dispersions with Inutec SP1 and to explain the difference between the spray dried and extruded dispersions, we investigated the physical structure by DSC and X-ray powder diffraction. Fig. 4 shows that itraconazole remains in the crystalline state when formulated as a physical mixture with Inutec SP1. On the other hand, both solid dispersions show the absence of diffraction peaks pointing to the loss of crystallinity as a consequence of the preparation procedure. However, based on diffraction data no distinction can be made between both dispersions with respect to their dissolution behaviour.

Fig. 5 shows the DSC curves of pure Inutec SP1 and crystalline itraconazole. Itraconazole shows a melting peak at 165.9(±0.2) °C (enthalpy of fusion 85.1 ± 0.3 J/g) and Inutec SP1 is characterized by a small endothermic signal with an onset at 103.4(±0.2) °C (enthalpy of fusion 0.5 ± 0.1 J/g) and a glass transition at 143.2(±1.7) °C. This glass transition is obscured in the first heating due to the large water evaporation endotherm (curve c). It has been shown that inulin is a semi-crystalline oligosaccharide (Hebbette, 2002) and the small endothermic peak can probably be attributed to a crystalline fraction of Inutec

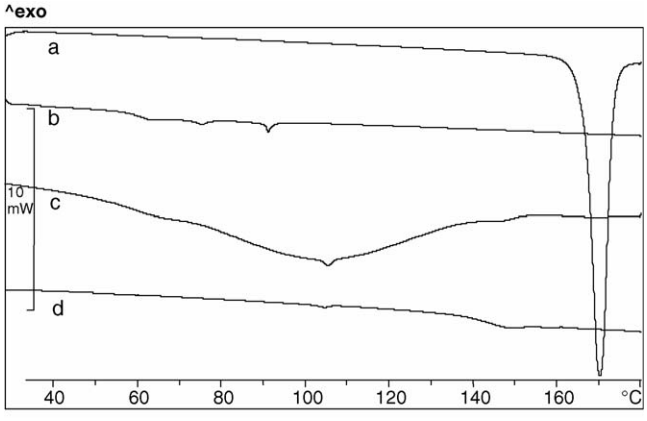

Fig. 5. DSC curves of itraconazole (a: first heating; b: second heating) and Inutec SP1 (c: first heating; d: second heating).

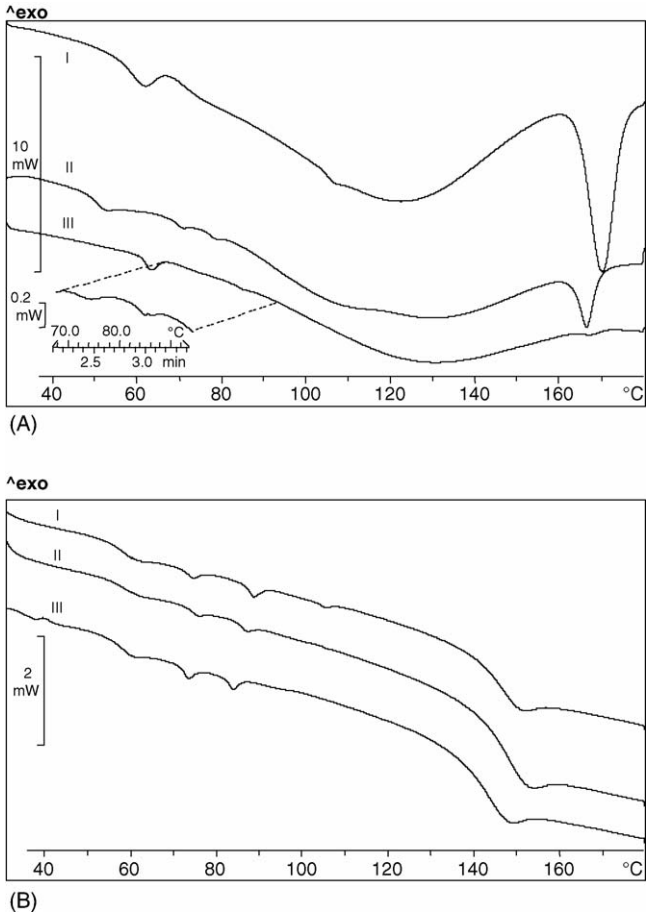

Fig. 6. (A) DSC curves (first heating) of the physical mixture (I) and the solid dispersions prepared by hot-stage extrusion (II) and spray drying (III). The concentration of itraconazole is always 20% (w/w). A blow up of curve III shows the details of the transitions. (B) DSC curves (second heating) of the physical mixture (I) and the solid dispersions prepared by hot-stage extrusion (II) and spray drying (III). The concentration of itraconazole is always 20% (w/w).

SP1. Fig. 6 shows the DSC curves of the physical mixture and the solid dispersions all containing 20% of drug. Five different thermal events can be distinguished in the spray dried solid dispersion. At 56.9(±0.3) °C a glass transition is observed and at 67.9(±0.6) and 79.3(±0.6) °C two small endothermic peaks appear. These three transitions indicate the presence of a separate glassy itraconazole phase. We previously described the structure of glassy itraconazole (Six et al., 2001). When cooled from the melt or after spray drying, itraconazole does not readily crystallize but transforms into a chiral nematic mesophase, characterized by two additional thermal events besides the glass transition. The transition at approximately 80 °C is the transition from the chiral nematic mesophase to an isotropic liquid while that at approximately 68 °C is the consequence of rotational restriction of the molecules. At lower temperature, the material is frozen into a glass. Compared to pure glassy itraconazole, the transitions belonging to the mesophase are slightly lower (74 and 90 °C, respectively, for pure glassy itraconazole; see Fig. 5, curve b). This was observed also previously in other solid dispersions with itraconazole (Six et al., 2002, 2004) and indicates that Inutec SP1 influences the two-dimensional struc-

Table 1
DSC data of hot-stage extruded solid dispersions Inutec SP1–itraconazole

% Itraconazole	First heating						Second heating			
	T_m (°C), itraconazole	ΔH_{fusion} (J/g)	T_g (°C), itraconazole	T_g (°C), Inutec SP1	Peak 1 (°C), mesophase	Peak 2 (°C), mesophase	T_g (°C), itraconazole	T_g (°C), Inutec SP1	Peak 1 (°C), mesophase	Peak 2 (°C), mesophase
5	ND	ND	52.7 ± 2.0	ND	64.6	68.0	57.1 ± 0.5	143.6 ± 0.8	68.6 ± 0.2	75.9 ± 0.4
10	ND	ND	49.3 ± 1.3	ND	64.8 ± 1.2	73.9 ± 0.6	57.8 ± 0.1	143.0 ± 0.4	69.9 ± 0.5	78.8 ± 0.7
15	160.6 ± 0.1	7.2 ± 0.1	48.3 ± 0.1	ND	65.1 ± 0.2	74.6 ± 0.1	57.5 ± 0.7	140.5 ± 0.5	71.0 ± 0.1	79.4 ± 0.1
20	162.4 ± 0.1	10.9 ± 0.5	50.4 ± 0.1	ND	67.5 ± 0.4	75.5 ± 0.5	57.1 ± 0.5	142.3 ± 1.9	71.2 ± 0.2	81.6 ± 0.2
30	162.2 ± 0.1	12.1 ± 1.0	51.5 ± 0.2	ND	68.8 ± 0.12	78.1 ± 0.1	59.4 ± 0.5	144.7 ± 0.3	72.3 ± 0.1	84.5 ± 0.1

ND = not detectable.

ture (chiral nematic mesophase) formation of the material. The fourth thermal event in the DSC curve of the spray dried solid dispersion corresponds to the melting of crystalline itraconazole (164.8 ± 1.4 °C). The initial crystallinity was estimated as described in an earlier publication and was found to be less than 2.0% (Van den Mooter et al., 2001). This low value explains why no diffraction peaks were observed during X-ray powder diffraction. Finally a broad endotherm indicating the evaporation of residual solvent and sorbed water is observed as well. The small endothermic peak due to the presence of a crystalline fraction of Inutec SP1 is no longer present in the spray dried solid dispersion. The broad solvent evaporation endotherm may mask some thermal events, therefore all samples were subjected to a second heating run. The glass transition and the two small endothermic peaks originating from the presence of the chiral nematic mesophase are still present, although they all shifted to a slightly higher temperature (58.3 ± 1.9, 72.7 ± 0.2 and 84.4 ± 0.2 °C for the glass transition and the mesophase transitions, respectively). An additional glass transition was observed in the second heating, that of Inutec SP1 at 145.0 ± 0.3 °C. These results clearly show that the spray dried solid dispersion is composed of at least three phases: glassy itraconazole, crystalline itraconazole and amorphous Inutec SP1 (water is not considered here as a separate phase). After the second heating, itraconazole is only present in the glassy state. The same observations largely hold for the physical mixture and the solid dispersion prepared by hot-stage extrusion. However, the latter shows a much larger melting endotherm of itraconazole as well as an exotherm (ranging from approximately 110 to 130 °C) due to cold crystallization of the drug during the heating run. Taking into account the cold crystallization, the normalized melting enthalpy due to initial crystallinity was 10.9 ± 2.0 J/g (corresponding to 12.8% initial crystallinity), while only 1.7 ± 0.1 J/g for the spray dried dispersion which shows a slightly higher crystalline fraction in the extruded solid dispersion.

Table 1 shows DSC data of solid dispersions prepared by hot-stage extrusion with variable itraconazole concentration. The data indicate that at 5% drug loading, itraconazole is forming clusters of glassy material, hence two phases are present. From 15% on, a third phase (crystalline itraconazole) exists next to the Inutec SP1 and the glassy drug phase.

Contrary to previously obtained results, the present data show that solid dispersions in which itraconazole is forming a separate phase (glass or crystalline clusters) yield improved dissolution properties. Since from a qualitative point of view the physical state of the drug is not significantly different in the 20% solid dispersions prepared by spray drying or hot-stage extrusion, the explanation of the dissolution behaviour can probably be ascribed to the action of Inutec SP1 itself. It is a polymeric surfactant with a high HLB value, hence its solubility in a lipophilic or a hydrophobic phase is extremely low. Due to the polymeric character, this type of surfactant tends to form aggregates when dispersed in water, resulting in a slightly turbid solution (Booten and Levecke, 2003). However, this means that when an oil or hydrophobic particles are added to an aqueous dispersion of Inutec SP1, the polymeric surfactant will concentrate on the interface between the hydrophobic particles and water, leading to improved wetting and hence dissolution. The excellent surface-active properties of this new polymeric surfactant can be best illustrated by the fact that due to its special configuration on the interface between a hydrophobic particle and water, only partial coverage of this interface is required to obtain extremely high stabilizing properties in terms of flocculation (Booten and Levecke, 2003).

Finally, besides the action of the surfactant, our results also show a significant difference of dissolution properties between the spray dried and hot stage extruded solid dispersions. Since the contact between the drug particles and those of the polymeric surfactant are important with respect to wetting, it is not surprising that hot-stage extrusion yields in this case materials with better dissolution properties. Indeed the high shear forces exerted by the screw in the extruder force the particles to make more intense contacts compared to those in a powder obtained by spray drying.

Acknowledgment

The authors acknowledge the support from Onderzoeksraad K.U.Leuven for financial support.

References

Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. Theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bio-availability. Pharm. Res. 12, 413–420.

Booten, K., Levecke, B., 2003. Inutec® surfactants: the properties of a new type of surfactants. Household Pers. Care Today 1, 26–28.

Dannenfelser, R.-M., He, H., Joshi, Y., Bateman, S., Serajuddin, A., 2004. Development of clinical dosage forms for a poorly water soluble drug. I. Application of polyethylene glycol–polysorbate 80 solid dispersion carrier system. J. Pharm. Sci. 93, 1165–1175.

Grant, S.M., Clissold, S.P., 1989. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs 37, 310–344.

Hebbette, C., 2002. Crystallisation, melting and gel formation of concentrated inulin-water systems. Ph.D. Thesis. K.U.Leuven.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.

Peeters, J., Neeskens, P., Tollenaere, J.P., Van Remoortere, P., Brewster, M., 2002. Characterization of the interaction of 2-hydroxypropyl-β-cyclodextrin with itraconazole at pH 2, 4 and 7. J. Pharm. Sci. 91, 1414–1422.

Serajuddin, A., 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. 88, 1058–1066.

Six, K., Verreck, G., Peeters, J., Binnemans, K., Berghmans, H., Augustijns, P., Kinget, R., Van den Mooter, G., 2001. Investigation of thermal properties of glassy itraconazole: identification of a monotropic mesophase. Thermochim. Acta 376, 175–181.

Six, K., Leuner, C., Dressman, J., Verreck, G., Peeters, J., Blaton, N., Augustijns, P., Kinget, R., Van den Mooter, G., 2002. Thermal properties of hot-stage extrudates of itraconazole and Eudragit E 100 phase separation and polymorphism. J. Therm. Anal. Calorim. 68, 91–601.

Six, K., Berghmans, H., Leuner, C., Dressman, J., Van Werde, K., Mullens, J., Benoist, L., Thimon, M., Meublat, L., Verreck, G., Peeters, J., Brewster, M.E., Van den Mooter, G., 2003. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion Part II. Pharm. Res. 20, 1047–1054.

Six, K., Verreck, G., Peeters, J., Brewster, M., Van den Mooter, G., 2004. Increased physical stability and improved dissolution properties of itraconazole, a class II drug, by solid dispersions that combine fast and slow dissolving polymers. J. Pharm. Sci. 93, 124–131.

Six, K., Daems, T., de Hoon, J., Van Hecken, A., Depre, M., Bouche, M.-P., Prinsen, P., Verreck, G., Peeters, J., Brewster, M.E., Van den Mooter, G., 2005. Clinical study of solid dispersions of itraconazole prepared by hot-stage extrusion. Eur. J. Pharm. Sci. 24, 179–186.

Stevens, C.V., Meriggi, A., Booten, K., 2001a. Chemical modification of inulin, a valuable renewable resource, and its industrial applications. Biomacromolecules 2, 1–16.

Stevens, C.V., Meriggi, A., Peristeropoulou, M., Christov, P.P., Booten, K., Levecke, B., Vandamme, A., Pittevils, N., Tadros, T.F., 2001b. Polymeric surfactants based on inulin, a polysaccharide extracted from chicory. 1. Synthesis and interfacial properties. Biomacromolecules 2, 1256–1259.

Van den Mooter, G., Wuyts, M., Blaton, N., Busson, R., Grobet, P., Augustijns, P., Kinget, R., 2001. Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. Eur. J. Pharm. Sci. 12, 261–269.

Verreck, G., Six, K., Van den Mooter, G., Baert, L., Peeters, J., Brewster, M.E., 2003. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion, Part I. Int. J. Pharm. 251, 165–174.

Wang, X., Michoel, A., Van den Mooter, G., 2004. Study of the phase behaviour of polyethylene glycol 6000–itraconazole solid dispersions using DSC. Int. J. Pharm. 272, 181–187.