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Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion—part I

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Abstract

Solid dispersions containing different ratios of itraconazole and hydroxypropylmethylcellulose (HPMC) were prepared by solvent casting. Based on dose, differential scanning calorimetry and dissolution results, a drug/polymer ratio of 40/60 w/w was selected in order to prepare dispersions by melt extrusion. The melt extrusion process was characterized using a design of experiments (DOE) approach. All parameter settings resulted in the formation of an amorphous solid dispersion whereby HPMC 2910 5 mPa s prevents re-crystallization of the drug during cooling. Dissolution measurements demonstrated that a significantly increased dissolution rate was obtained with the amorphous solid dispersion compared to the physical mixture. The outcome of DOE further indicated that melt extrusion is very robust with regard to the itraconazole/HPMC melt extrudate characteristics. Stability studies demonstrated that the itraconazole/HPMC 40/60 w/w milled melt extrudate formulation is chemically and physically stable for periods in excess of 6 months as indicated by the absence of degradation products or re-crystallization of the drug.

Keywords: Solid dispersion; Itraconazole; Melt extrusion

1. Introduction

Itraconazole is a potent broad-spectrum triazole antifungal drug with activity against histoplasmosis, blastomycosis and onychomycosis (Grant and Clissold, 1989; De Beule and Van Gestel, 2001). This compound was the first orally available drug

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with activity against *Candida* species such as *Candida albicans*, *parapsilosis*, *tropicalis*, *glabrata* and *krusie* and against *Aspergillus* species such as *Aspergillus flavus* and *fumigatus*. *Candida* sp. and *Aspergillus* sp. are the two most common human fungal pathogens (Jain and Sehgal, 2001). The compound is insoluble in water ($S \sim 1$ ng/ml at neutral pH and $S = 6$ μg/ml in 0.1 N HCl at pH 1), has an ionization constant of 4.0 and a very high octanol–water partition coefficient ($\log P > 5$) (Peeters et al., 2002). The chemical structure is shown in Fig. 1.

According to the biopharmaceuticals classification system, itraconazole is an extreme example of a class II compound meaning that its oral bioavailability is determined by dissolution rate in the GI tract (Amidon et al., 1995; Dressman et al., 1998, 2001). In assessing methods to provide for an orally bioavailable formulation of poorly water soluble drug candidates, a useful starting point is the Noyes–Whitney equation which describes the dissolution rate of a solid:

$$\frac{dC}{dt} = \frac{D \times A \times (C_s - C_t)}{h \times V} \quad (1)$$

where the dissolution rate (dC/dt) is determined by D, the diffusion coefficient, h, the diffusion layer thickness at the solid–liquid interface, A, the surface area of drug exposed to the dissolution media, V, the volume of the dissolution media, C_s, the saturation solubility of the drug and C_t, the drug concentration at time, t.

Preliminary studies showed that increased dispersibility and/or wettability as well as particle size reduction (even to dimensions smaller than 200 nm) did not provide for useful oral bioavailability of itraconazole. The formulation of solid dispersions was thus considered as a possible method to enhance the dissolution characteristics of this class II drug (Gruenhagen, 1995; Sheen et al., 1995; Serajuddin, 1999; Leuner and Dressman, 2000; Erkoboni and Andersen, 2000, WO 0056726; Baert et al., 1997, WO 9744014). The distribution of the drug in the carrier, in some cases at the molecular level (i.e., a true solid solution), as well as the avoidance of the phase-to-phase transition for the crystalline to solubilized state may increase the dissolution rate and apparent solubility. As a consequence this may result in enhanced bioavailability. As reviewed by Dressman, a solid solution/dispersion can be prepared in two main ways: solvent casting and melt extrusion (Leuner and Dressman, 2000). We have used both methods herein with solvent casting providing useful screening data and melt extrusion giving a pharmaceutically relevant technique. The purpose of the present study is to develop a solid dispersion prepared by melt extrusion which results in an improved dissolution rate for itraconazole, provides for sufficient physical and chemical stability and serves as an alternative for the currently marketed Sporanox oral capsule (a solid solution-based system wherein drug and hydroxypropylmethylcellulose (HPMC) in solution are sprayed on an inert sugar sphere) (Gilis et al.,

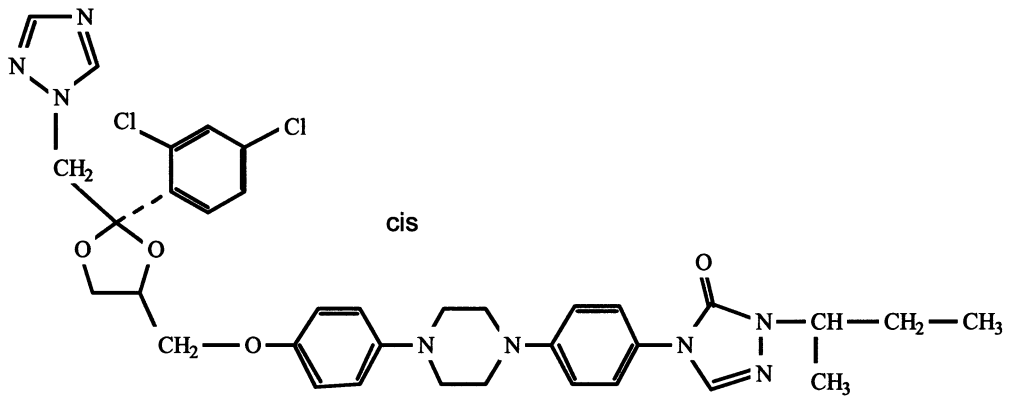

Fig. 1. Chemical structure of itraconazole.

1995, US 5633015). Also, the characterization of the melt extrusion process by means of a design of experiments (DOE) is described.

2. Materials and methods

2.1. Materials

Itraconazole (purity more than 99%) was synthesized by Janssen Pharmaceutica (Beerse, Belgium) and HPMC 2910 5 mPa s was obtained from Aqualon, Hercules (Zwijndrecht, the Netherlands).

2.2. Preparation of drug/polymer films

To select the optimal ratio, drug/polymer films were prepared by solvent casting. Itraconazole and HPMC were dissolved in a mixture of dichloromethane and ethanol 80/20 v/v in drug/polymer ratios ranging between 67/33 w/w and 40/60 w/w. The solvent was evaporated in a vacuum oven at 80 °C for 1 h. The residual films were analyzed using differential scanning calorimetry (DSC) and dissolution measurements.

2.3. Preparation of physical mixture

The physical mixture of itraconazole and HPMC in a ratio 40/60 w/w was prepared by mixing both components in a planetary blender (Collette MP20, Collette, Belgium) for 30 min.

2.4. Hot melt extrusion

The hot melt extrusion was performed with a co-rotating twin-screw extruder APV MP19 PH 25:1 (APV, UK). The screw configuration consisted of two mixing zones and three transporting zones over the barrel length. The barrel consisted of five heating zones. The first heating zone was water-cooled. The physical mixture was fed into the extruder by a gravimetric feeder (K-Tron, UK) and was melted throughout the barrel. At the exit of the barrel, a die plate was installed containing one orifice (diameter 3 mm). The extrudate strands were cooled at ambient temperature on a belt conveyer.

To characterize the melt extrusion process, a DOE was used. Table 1 gives on overview of the parameters and settings that were selected to perform the DOE. For each temperature setting, the four heating zones were set at the same temperature throughout the barrel. A full factorial design ($a = 3$) with two center-points was selected (Montgomery, 1991). The following independent, continuous parameters were investigated in ten runs ($m = 10$) in random order: temperature, feed rate and screw speed. These parameters are considered to be critical for the extrusion process (White, 1990). Other critical process parameters, such as screw configuration, orifice diameter and cooling conditions were kept constant throughout the DOE. The DOE provides sufficient degrees of freedom to estimate main effects, two parameter interactions and total error. The glass transition, the itraconazole melting point and the intrinsic dissolution were selected as response variables. The graphic software STATGRAPHICS PLUS version 2.1 (STSC Inc., Rockville, MD) was used to develop the DOE and analyze the results. Prior to analysis, all samples were milled with an IKA M20 universal laboratory mill (IKA-Werke GmbH&Co, Staufen, Germany) and sieved to obtain a fraction below 150 μm. The milled melt

Table 1
DOE parameter settings including temperature, feed rate and screw speed for melt extrusion of itraconazole and HPMC 40/60 w/w

Run	T (°C)	Feed rate (kg/h)	Screw speed (rpm)
1	150	1.0	200
2	220	2.0	200
3	185	1.5	300
4	220	2.0	400
5	220	1.0	200
6	150	2.0	200
7	150	2.0	400
8	185	1.5	300
9	150	1.0	400
10	220	1.0	400

A full factorial design with two center-points was selected as the model.

extrudate resulting from these experiments was analyzed using DSC and intrinsic dissolution.

2.5. Differential scanning calorimetry

The DSC measurements were performed using a Perkin–Elmer DSC-7 DSC with a TAC7/DX thermal analysis controller. Cooling was provided with a Perkin–Elmer refrigerated cooling device (FC-60-PED). Data were treated mathematically using the resident PYRIS Software. Calibration was carried out using indium and zinc as reference materials. The samples were analyzed in 30 μl perforated and covered aluminum Perkin–Elmer pans under a nitrogen purge.

Approximately 5 mg crystalline itraconazole was heated from 25 to 200 °C with a heating rate of 20 °C/min, and afterwards cooled with a cooling rate of 20 °C/min to room temperature. A second heating cycle is then applied on the sample starting at room temperature up to 200 °C with a heating rate of 20 °C/min. Approximately 10 mg HPMC 2910 5 mPa s was heated from 25 to 200 °C with a heating rate of 20 °C/min. Approximately 5 mg of the itraconazole/HPMC solvent films were heated from 40 to 260 °C with a heating rate of 20 °C/min. Approximately 10 mg of the itraconazole/HPMC 2910 5 mPa s 40/60 w/w milled melt extrudate samples were heated from 25 to 200 °C with a heating rate of 40 °C/min. Three samples were measured for each run of the DOE ($a = 3$).

2.6. Powder X-ray diffraction

Powder X-ray diffraction was performed with a Siemens D5000 Diffractometer (Madison, WI). Monochromatic CuKα1 radiation was used as X-ray source. Parallel beam optics was used with 1 mm entrance slit, Goebel mirrors, 0.6 mm mirror exit slits and vertical soller slits between mirrors and sample. The diffraction pattern was measured with a voltage of 40 kV and a current of 35 mA in the area of $3 < 2\theta < 35$ in a continuous scan mode of $1°2\theta$/min. Both pure itraconazole and HPMC as well as itraconazole/HPMC 40/60 w/w melt extrudate were measured.

2.7. HPLC analysis

The analysis was performed using a Waters HPLC (Waters, Milford, MA) with MILLENNIUM 32 Software. The column used was a Hypersil BDS-C18, 3 μm, 10 cm × 4.6 mm ID. The mobile phase consisted of 0.01 M tetrabutylammonium hydrogen sulphate in water and acetonitrile using a gradient elution at a flow rate of 1.5 ml/min. Concentration determination was performed using UV detection at a wavelength of 250 and 225 nm.

2.8. Dissolution testing

The in vitro drug release of the different drug/polymer films was measured in order to select the optimal ratio. Samples with a 100 mg dose were directly added to 300 ml of simulated gastric fluid (without pepsin) (37 °C). From clinical absorption experiments, the effective dose for itraconazole was set at 200 mg/day (De Beule and Van Gestel, 2001). Therefore, a dose of 100 mg was selected for these screening experiments. Dissolution was assessed using a paddle rotating at 100 rpm (USP II apparatus). The release was followed for 1 h and samples were taken after 15, 30, 45 and 60 min. An aliquot of 3 ml was filtered through a Millex HV 0.45 μm filter (Millipore SLHV R04 NL). The sample was not replaced with fresh solvent. The concentration of itraconazole was quantified with UV at the maximum wavelength of 254 nm.

Dissolution testing was also performed on itraconazole/HPMC 40/60 w/w melt extrudate and compared with physical mixture containing crystalline itraconazole. Samples with a 200 mg dose were directly added to 900 ml of 0.1 N HCl (37 °C) and dissolution was assessed using a paddle rotating at 150 rpm (USP II apparatus). Dissolution was followed for 2 h and samples were taken after 5, 15, 30, 45, 60 and 120 min. Filtration and determination of the concentration on itraconazole is performed as described above.

2.9. Intrinsic dissolution measurement of the melt extrudate samples

The intrinsic dissolution of the different melt extrudate samples was measured to compare the influence of the different parameter settings used in the DOE. The sieved fraction (120 mg) of the melt extrudate was compressed to a tablet using a manual hand press at a compression pressure of 1.52 MPa. Milling was performed as described in Section 2.4. The tablets had a diameter of 8 mm and a thickness of 2 mm. The tablet was fixed in a PFTE holder, such that only the tablet surface came into contact with the dissolution medium. The PFTE loaded holder was placed in the dissolution vessel containing 500 ml 0.1 N HCl (37 °C). Two tablets were measured for each run of the DOE ($a = 2$). Stirring was performed with a paddle rotating at 150 rpm (USP II apparatus). The dissolution was followed up to 90 min and samples of 3 ml were taken every 10 min. The concentration of itraconazole was quantified with UV at a maximum wavelength of 254 nm. After analysis the measured sample was returned to the dissolution vessel. The percentage of itraconazole released was plotted against time. The intrinsic dissolution rate was derived from the slope of this curve.

2.10. Stability testing

To assess the chemical and physical stability of the milled melt extrudate, a stability study was conducted for 6 months in different storage conditions of temperature and relative humidity (4 °C, 25 °C/60%RH, 30 °C,70%RH, 40 °C/75%RH, 50 °C). The samples were stored in closed aluminum–polyethylene laminated bags. The chemical stability (degradation of drug substance) was assessed by HPLC (sample size = 312.5 mg, $n = 1$) and the physical stability (recrystallization of the drug substance) by the DSC methods, both performed as described above. Samples were analyzed after 1, 3 and 6 months. The stability study was performed on the sample of run 4 of the DOE (Table 2). This sample was produced at the highest temperature (thermal degradation), highest screw speed (i.e. highest frictional energy) and at an acceptable feed rate.

Table 2
Effect of processing parameters on glass transition temperature ($n = 3$, mean ± RSD) and intrinsic dissolution rate (duplicate values are given) for a series of melt extrudate samples according to the DOE

Run	T_g[a] (°C)	Intrinsic dissolution rate[b] (kg/(s.m^2))	
1	62.19 ± 3.71	65.66	60.34
2	59.16 ± 3.18	67.66	61.66
3	58.51 ± 1.87	57.66	71.66
4	65.91 ± 2.85	67.00	65.00
5	63.44 ± 6.79	69.66	66.34
6	65.52 ± 1.30	65.00	51.66
7	61.63 ± 8.67	65.66	59.66
8	63.39 ± 4.62	69.00	57.66
9	66.11 ± 1.36	55.00	56.34
10	66.22 ± 3.32	60.34	66.34

[a] Glass transition temperature.
[b] Intrinsic dissolution rate in mass per surface area and per unit of time.

3. Results and discussion

The DSC results of itraconazole are presented in Fig. 2 and Fig. 4. The first heating run shows an endothermic melting peak with its maximum at 172 °C and an enthalpy (ΔH) of about 85 J/g. During cooling of the melt, two exothermic peaks are observed at 87 °C ($\Delta H = -1.2$ J/g) and 69 °C ($\Delta H = -0.7$ J/g), respectively. Reheating results in a glass transition at 60 °C and two endothermic peaks at 76 °C ($\Delta H = 0.7$ J/g) and 92 °C ($\Delta H = 1.0$ J/g), respectively. Previous experiments have shown that these observations occur irrespective of the heating and cooling rate used for the DSC experiments (within a range of 1–50 °C/min). Also Six et al. observed the formation of glassy itraconazole irrespective of the cooling rate (Six et al., 2001a,b). It was concluded by the same authors that the transitions observed during the cooling and the second heating run of itraconazole represent the formation of glassy itraconazole and a monotropic mesophase upon cooling from the melt (Six et al., 2001b).

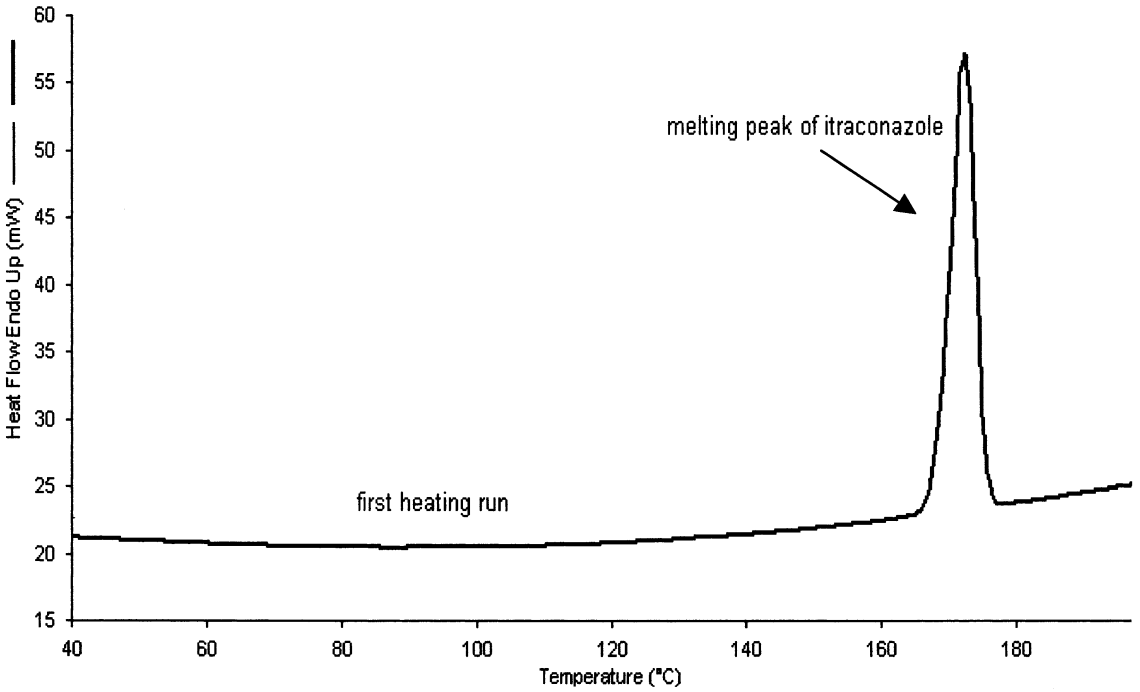

Fig. 2. DSC profile of the first heating run of crystalline itraconazole. Approximately 5 mg of crystalline itraconazole was analyzed in perforated and covered aluminum pans under a nitrogen purge. The sample was heated from 25 to 200 °C with a heating rate of 20 °C/min.

The carrier HPMC 2910 5 mPa s has a glass transition at 141 °C (DSC profile not shown).

In order to select the optimal ratio, different drug/polymer films were prepared by solvent casting and analyzed by DSC and dissolution measurement. The DSC profiles of the drug/polymer films lack melting endotherms (meaning absence of monotropic mesophase as well as crystalline itraconazole), indicating that solvent casting results in the formation of an amorphous solid dispersion of itraconazole and HPMC within the investigated range of ratios. The dissolution profiles of the different films are shown in Fig. 3. These results indicate that the dissolution rate increases as a function of the polymer content in the solid dispersion. Complete drug release was obtained within 60 min with a drug/polymer ratio of 40/60 w/w.

The size of a potential dosage form with a 200 mg dose was considered in these assessments by choosing the lowest polymer/drug ratio that gave adequate dissolution and physicochemical properties. Since adequate dissolution rate was observed for the 40/60 drug/polymer ratio, this system was selected for further characterization and development.

The solid dispersion of itraconazole/HPMC 40/60 w/w was then prepared and characterized by melt extrusion using a DOE approach. The results of the DOE are listed in Table 2.

To investigate the effect of the parameters on the response variables, the variance associated with the parameters and that related to the measurement had to be determined. Only when the variance caused by the parameters is significantly larger than the variance caused by the measurement, will the analysis of the DOE be meaningful. This comparison was done by a variance analysis (Minkkinen, 1995):

The response of a design with m runs is measured a times.

The total variance of the design can be divided in:

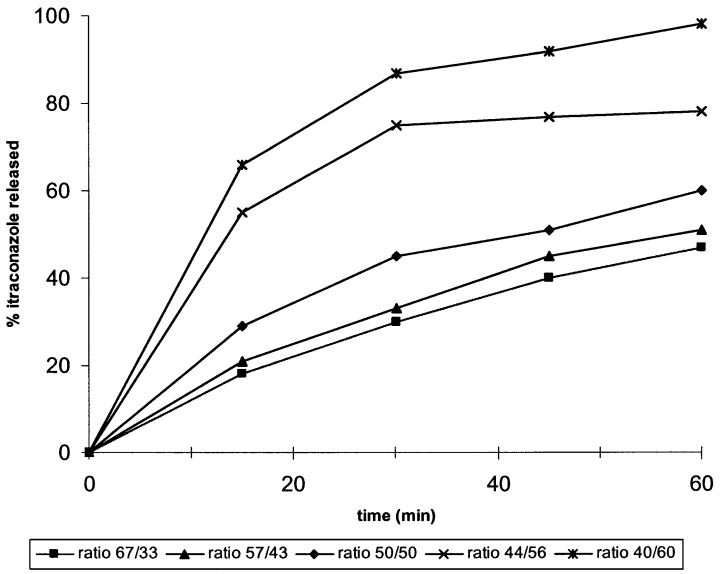

Fig. 3. Effect of the ratio itraconazole/HPMC on the in vitro release characteristics of the drug/polymer films. Samples with a 100 mg dose were directly added to 300 ml of simulated gastric fluid (without pepsin) (37 °C) and dissolution was assessed using a paddle rotating at 100 rpm (USP II apparatus).

– the variance caused by random variance of the process and the measurement: S_e
– the variance caused at the level of the different parameters: S_p

S_e is further broken into:

$$S_e^2 = S_{exp}^2 + S_{meas}^2/a \quad (2)$$

S_{exp} is the variance of k replicas of the runs. This is the random variance caused by the process. S_{meas} is the random variance of the a measurements of the response variable.

The total variance caused by the parameters is:

$$S_{tp}^2 = S_p^2 + S_e^2/k \quad (3)$$

When the measurement of the response variable is not under control, then is $S_{exp} \ll S_{meas}$, and thus $S_e \approx S_{meas}/a$.

Eq. (3) then becomes:

$$S_{tp}^2 = S_p^2 + S_{meas}^2/a \quad (4)$$

In order to test for significant effects, S_p needs to be significant larger then S_{meas}.

The F-test becomes:

$$F = aS_{tp}^2/S_{meas}^2 \approx (aS_p^2 + S_{meas}^2)/S_{meas}^2 \quad (5)$$

So that S_{tp}, $(m-1)$ and S_{meas} have $m(a-1)$ degrees of freedom.

Tables 3 and 4 show this analysis for the glass transition and intrinsic dissolution rate, respectively. Since the calculated F-value is higher than the theoretical F-value on a 95% confidence

Table 3
Analysis of variance for the glass transition temperature

Source	Sum of squares	Mean squares
S_{meas}^2	152.1	7.6
S_{tp}^2	72.5	8.1
F-value		3.18
$F_{9,20}(0.95)$[a]		2.39

[a] Value from Montgomery (1991).

Table 4
Analysis of variance for the intrinsic dissolution rate

Source	Sum of squares	Mean squares
S_{meas}^2	163.9	8.2
S_{tp}^2	28.8	3.2
F-value		0.78
$F_{9,10}(0.95)$[a]		3.02

[a] Value from Montgomery (1991).

Table 5
Analysis of variance to estimate the effect of the process parameters on the glass transition temperature

Source	Sum of squares	Degrees of freedom	Mean squares	F	P-value[a]
A: temperature	0.0631901	1	0.0631901	0.00	0.9523
B: feed rate	4.12563	1	4.12563	0.28	0.6357
C: screw speed	11.4123	1	11.4123	0.76	0.4466
AB	1.48006	1	1.48006	0.10	0.7737
AC	11.2884	1	11.2884	0.75	0.4488
BC	1.8384	1	1.8384	0.12	0.7490
Total error	44.8551	3	14.9517		
Total	75.063	9			

[a] 95% confidence interval.

interval, the DOE can be further analyzed (ANOVA) for the glass transition (Table 5). The results of this ANOVA show that none of the parameters has a significant influence on the position of the glass transition within a 95% confidence interval (all P-values > 0.05).

Since the calculated F-value for the intrinsic dissolution rate is lower than the theoretical F-value on a 95% confidence interval, the DOE can not be further analyzed. However, Table 2 shows that within the parameter settings of the DOE, no outliers are observed for the intrinsic dissolution

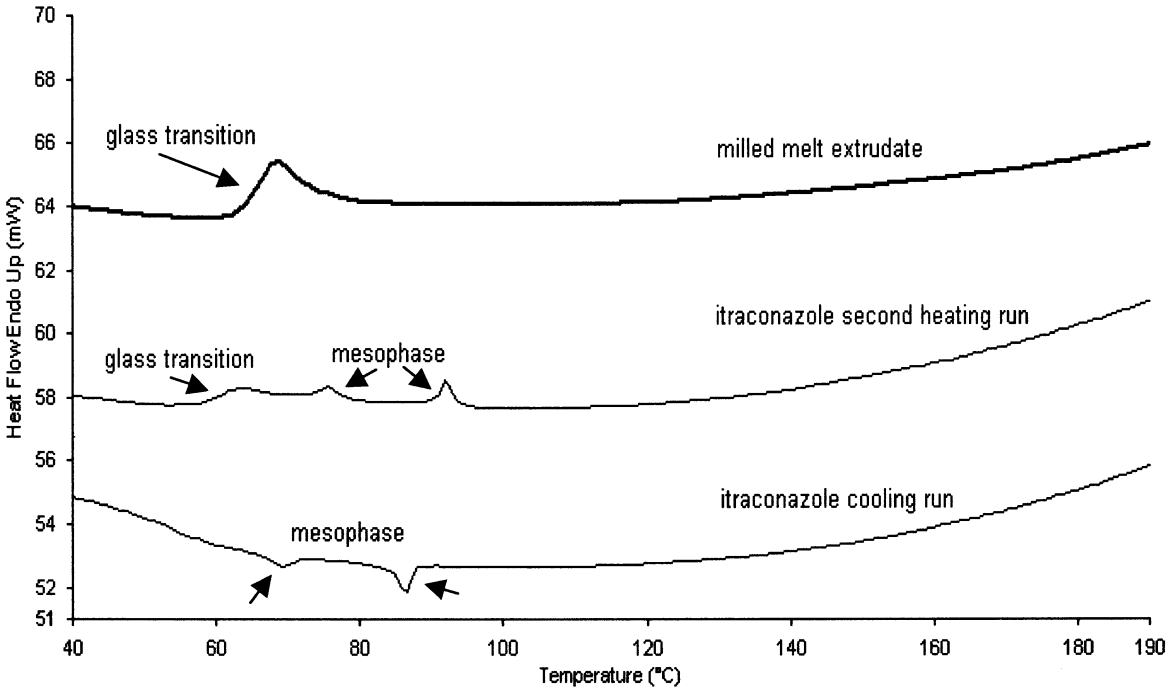

Fig. 4. DSC profile of the cooling and second heating run of crystalline itraconazole. Approximately 5 mg of crystalline itraconazole was analyzed in perforated and covered aluminum pans under a nitrogen purge. The sample cooled with a cooling rate of 20 °C/min to room temperature and again heated to 200 °C with a heating rate of 20 °C/min. DSC profile of itraconazole/HPMC 2910 5 mPa s 40/60 w/w milled melt extrudate. A sample of approximately 10 mg was analyzed in perforated and covered aluminum pans under a nitrogen purge. The sample was heated from 25 to 200 °C with a heating rate of 40 °C/min.

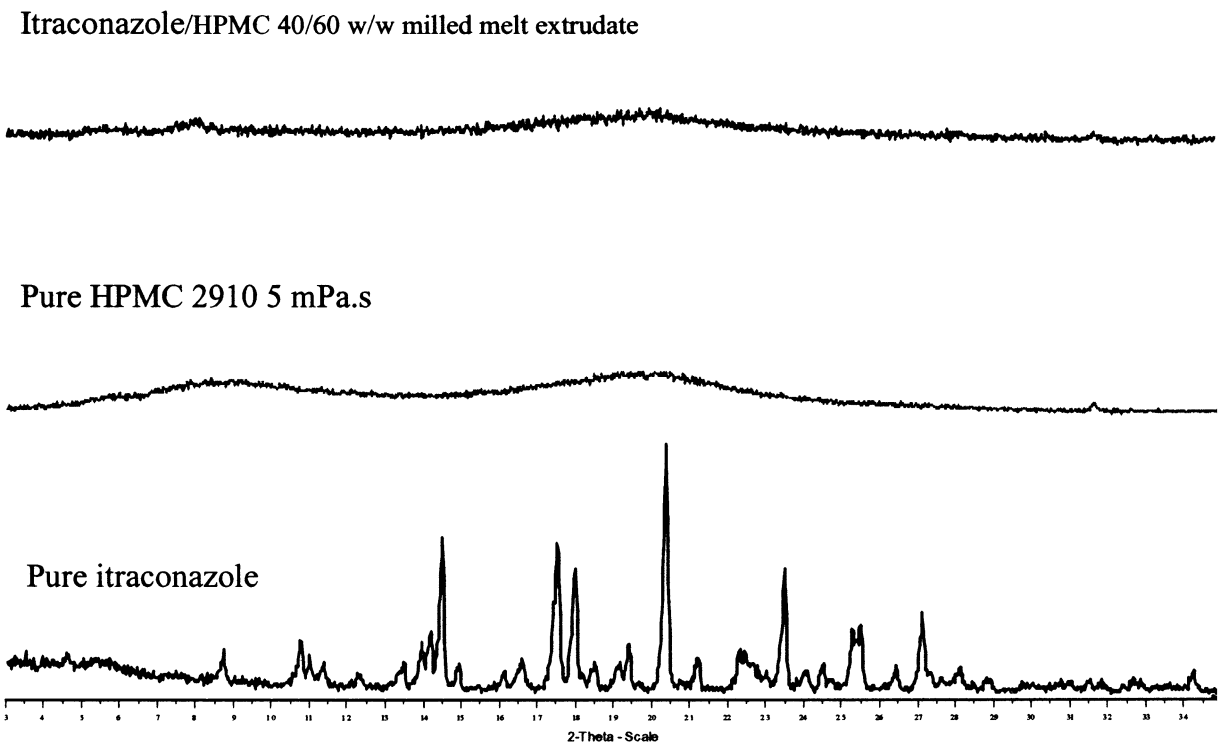

Fig. 5. Powder X-ray diffraction pattern for itraconazole, HPMC and itraconazole/HPMC 40/60 w/w milled melt extrudate (monochromatic CuKα1 radiation, parallel beam optics with 1 mm entrance slit, Goebel mirrors, 0.6 mm mirror exit slits and vertical soller slits between mirrors and sample, 40 kV, 35 mA, $3 < 2\theta < 35$, continuous scan mode of $1°2\theta$/min).

rate and the values are comparable for all different samples.

The third response variable, the melting point of itraconazole, could not be detected in any of the runs. Fig. 4 shows the DSC profile of melt extrudate sample four from the DOE. This DSC curve lacks the two small endothermic peaks compared to the second heating run of itraconazole. This means that the carrier HPMC 2910 5 mPa s prevents the formation of the monotropic mesophase of itraconazole during melt extrusion and thus forms an amorphous solid dispersion within the parameter settings of the DOE.

Also milling of the extrudate does not seem to induce re-crystallization. Powder X-ray diffraction (Fig. 5) confirms the absence of any crystalline material in the milled melt extrudate.

In order to evaluate the in vitro release characteristics of the itraconazole/HPMC 40/60 w/w milled melt extrudate, the release of sample four of the DOE was compared to a physical mixture

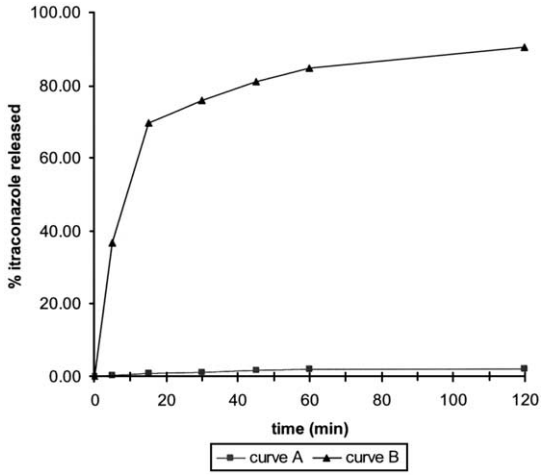

Fig. 6. In vitro drug release of itraconazole/HPMC 2910 5 mPa s 40/60 w/w physical mixture (curve A) and milled melt extrudate (curve B). Samples with a 200 mg dose were directly added to 900 ml of 0.1 N HCl (37 °C) and dissolution was assessed using a paddle rotating at 150 rpm (USP II apparatus).

containing crystalline itraconazole. Fig. 6 shows that the melt extrudate releases 90% of itraconazole after 120 min, while the physical mixture only releases 2% after 120 min.

HPLC analysis showed that no degradation products were formed, indicating that the drug substance is thermally stable under the processing conditions used to prepare this sample.

During the stability investigation, the assay of itraconazole did not decrease and no significant increase in degradation products was observed up to 6 months under the different storage conditions. Also no re-crystallization of the drug substance was observed in this time period. These observations indicate that the solid dispersion prepared by melt extrusion of itraconazole and HPMC 40/60 w/w is chemically and physically stable up to 6 months under the storage conditions tested.

4. Conclusions

The results obtained in this study indicate that melt extrusion of itraconazole and HPMC 2910 5 mPa s 40/60 w/w, results in an amorphous solid dispersion whereby the polymeric carrier prevents crystallization of the drug substance during cooling. This result in enhanced in vitro dissolution compared to the physical mixture containing the crystalline drug substance. The results of the DOE demonstrated that melt extrusion is a robust process towards the product characteristics of the milled melt extrudate. The stability results show that the formulation is stable up to 6 months when packed in aluminum bags. Based on these results it was decided to select the itraconazole/HPMC 40/60 w/w milled melt extrudate for further development as an alternative for the currently marketed Sporanox oral capsule. This is the subject of an ongoing study.

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 bioavailability. Pharm. Res. 12, 413–420.

Baert, L., Thone, D., Verreck, G. 1997. Antifungal compositions with improved bioavailability. PCT Patent Application WO 9744014.

De Beule, K., Van Gestel, J., 2001. Pharmacology of itraconazole. Drugs 61 (Suppl. 1), 27–33.

Dressman, J.B., Amidon, G., Reppas, C., Shah, V.P., 1998. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm. Res. 15, 11–22.

Dressman, J., Butler, J., Hempenstall, J., Reppas, C., 2001. The BCS: where do we go from here? Pharm. Tech. 25, 68–76.

Erkoboni, D., Andersen, R. 2000. Improved aqueous solubility pharmaceutical formulation. PCT Patent Application WO 0056726.

Gilis, P.A., De Conde, V., Vandecruys, R. Beads having a core coated with an antifungal and a polymer. US Patent 5633015.

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

Gruenhagen, H.H., 1995. Melt extrusion technology. Pharm. Manuf. Int. 2, 167–170.

Jain, S., Sehgal, V., 2001. Itraconazole: an effective oral antifungal for onchomychosis. Int. J. Dermatol. 40, 1–5.

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

Minkkinen, P., 1995. Estimation of variance components of interlaboratory comparisons. Chemometr. Intell. Lab. Syst. 29, 263–270.

Montgomery, D.C., 1991. Design and Analysis of Experiments, third ed.. Wiley, New York.

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

Sheen, P., Khetarpal, V., Cariola, C., Rowlings, C., 1995. Formulation of a poorly water-soluble drug in solid dispersions to improve bioavailability. Int. J. Pharm. 118, 221–227.

Six, K., Verreck, G., Peeters, J., Augustijns, P., Kinget, R., Van den Mooter, G., 2001a. Characterization of glassy itraconazole: a comparative study of its molecular mobility below T_g with that of structural analogues using MTDSC. Int. J. Pharm. 213, 163–173.

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

White, J.L., 1990. Twin Screw Extrusion, Technology and Principles. Hanser Publishers, New York.