Characterization of Solid Dispersions of Itraconazole and Hydroxypropylmethylcellulose Prepared by Melt Extrusion, Part II

Karel Six,[1] Hugo Berghmans,[2] Christian Leuner,[3] Jennifer Dressman,[3] Kristof Van Werde,[4] Jules Mullens,[4] Luc Benoist,[5] Mireille Thimon,[5] Laurent Meublat,[5] Geert Verreck,[6] Jef Peeters,[6] Marcus Brewster,[6] and Guy Van den Mooter[1,7]

Received February 11, 2003; accepted April 2, 2003

Purpose. This study was done to elucidate the physical and pharmaceutical properties of itraconazole–HPMC dispersions and the influence of water on the phase separation.

Methods. Extrudates were prepared using a corotating twin-screw hot-stage extruder with fixed process parameters. Modulated-temperature differential scanning calorimetry (MTDSC) and DSC 111 were used to examine the mixing behavior of itraconazole and the carrier by evaluation of the glass transition region. High temperature diffuse reflectance infrared transform spectroscopy (HT-DRIFT) was performed to reveal interactions between itraconazole and HPMC. Dissolution was performed to investigate the pharmaceutical performance of the dispersions.

Results. Although the dissolution rate of itraconazole significantly increased, we found that the solid dispersions do not form a homogeneous system. A different picture was obtained depending on the way MTDSC analysis was performed, i.e., using open or closed sample pans. Water can evaporate in open pans, which allows itraconazole to interact with HPMC and leads to a partially mixed phase. Analysis in hermetically closed pans revealed a further phase separation as water remains on the sample and impedes the interaction between drug and polymer.

Conclusions. Solid dispersions of itraconazole and HPMC do not form a homogeneous phase.

KEY WORDS: itraconazole; solid dispersions; phase separation; MTDSC; dissolution.

INTRODUCTION

Itraconazole is a potent antifungal drug of the triazole group with activity against histoplasmosis, blastomycosis, and onychomycosis. The pharmacologic mechanism is the same as that of the structural analogues ketoconazole and miconazole, which interfere with the synthesis of ergosterol of the fungal membrane by inhibiting 14α-demethylase, a CYP 450 isoenzyme (1). Because of its very low aqueous solubility (S < 1 μg/ml) and poor dissolution rate, itraconazole shows large interindividual differences in bioavailability after oral administration (2). According to the Biopharmaceutics Classification System (3), it can be classified as a class II compound.

The formulation of solid dispersions is generally accepted as a method to enhance the dissolution characteristics of poorly soluble drugs. The distribution of the drug in the carrier, sometimes at the molecular level, together with the enhanced wettability and microenvironment created by the carrier may increase both the solubility and dissolution rate. The interested reader is referred to two recent papers reviewing the use of solid dispersions for poorly soluble drugs (4,5).

Several formulations have been developed in order to overcome the dissolution rate–limited oral absorption of itraconazole (6,7). In these formulations, the physical state of the drug is changed from the crystalline to the amorphous state. The presence of the amorphous state leads to improved dissolution properties because of the absence of a crystalline lattice. The drawback of this high-energy state lies in its inherent physical metastability.

In a previous paper we reported that pure glassy itraconazole showed good shelf life stability if stored at 40°C or more below its Tg (Tg = 59.9°C) because of the extremely small molecular mobility (8). In contrast to its structural analogues miconazole and ketoconazole, liquid itraconazole undergoes an isotropic liquid to chiral nematic mesophase transition at 90°C, followed by a second transition at 74°C, which is caused by rotational restriction of the molecules. Finally, this structure is frozen into a glass at approximately 59.9°C (9).

The marketed form of itraconazole, Sporanox®, is prepared by spraying the drug and HPMC onto neutral pellets using organic solvents. In order to eliminate the use of solvents, a new process based on hot-stage extrusion is being explored. The aim of the present study was to investigate the phase behavior of solid dispersions of itraconazole and HPMC prepared by hot-stage extrusion by studying the glass transition region. Different viscosity types of HPMC were used (HPMC 603, E5, 615) to investigate the influence on physical and pharmaceutical properties of the dispersions. HPMC absorbs moisture from the atmosphere, the amount of water depending on the initial moisture content and the temperature and relative humidity of the surrounding air. This prompted us to investigate the glass transition region by temperature modulated and conventional differential scanning calorimetry (DSC) using both open and closed sample pans.

EXPERIMENTAL AND METHODS

Materials

Itraconazole (purity more than 99%), hydroxypropylmethylcellulose type 2910 E5 (viscosity 5 mPas; Methocel, Dow) was kindly provided by Janssen Pharmaceutica (Beerse, Belgium). Hydroxypropylmethylcellulose (HPMC) trade name, Pharmacoat® 603 and 615 (vicosity 3 and 15 mPas, respectively) were donated by Syntapharm GmbH (Mülheim-Ruhr, Germany).

[1] Laboratorium voor Farmacotechnologie en Biofarmacie, K.U.Leuven, Leuven, Belgium.
[2] Laboratorium voor Polymeerchemie, K.U.Leuven, Leuven, Belgium.
[3] Department of Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt, Germany.
[4] Laboratorium voor anorganische en fysische scheikunde, LUC, Diepenbeek, Belgium.
[5] Setaram-Groupe KEP, Laboratoire d'Applications, 69300 Caluire, France.
[6] Johnson and Johnson Pharmaceutical Research and Development, Beerse, Belgium.
[7] To whom correspondence should be addressed. (e-mail: Guy.vandenmooter@pharm.kuleuven.ac.be)

0724-8741/03/0700-1047/0 © 2003 Plenum Publishing Corporation

Modulated-Temperature DSC

Modulated-temperature DSC (MTDSC) measurements were carried out using a 2920 modulated DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system (RCS). Data were treated mathematically using universal analysis software (TA Instruments, Leatherhead, UK). A flow rate of 40 ml/min of helium was used in the DSC cell while the RCS unit was purged with nitrogen at a rate of 150 ml/min. Samples (approximately 9.00 mg, accurately weighed) were scanned using hermetically sealed and open aluminum pans (TA Instruments, Brussels, Belgium). The amplitude used was ± 0.212°C, the period 40 s, and the underlying heating rate 2°C/min.

Octadecane, benzoic acid, cyclohexane, and indium standards were used to calibrate the DSC temperature scale; enthalpic response was calibrated with indium. The heat capacity signal was calibrated by comparing the response of dry, powdered aluminum oxide to the equivalent literature value, which lies in the glass transition region of itraconazole. Validation of temperature, enthalpy, and heat capacity measurement using the same standard materials showed that deviation of the experimental from the theoretical value was less than 0.5°C for temperature measurement, less than 0.1% for enthalpy measurement and less than 0.75, 1 and 1.25% for measurement of the heat capacity at 56.85, 26.85 and 6.85°C, respectively.

Conventional DSC

DSC experiments were performed on a setaram DSC 111 with a CS 32 controller (Setaram, Caluire, France). The equipment was calibrated according to the user's guide using indium and octadecane as reference materials. About 100 mg of sample is introduced in an aluminum crucible and hermetically closed. The sample is heated at 1°C/min from 25°C to 160°C.

Hot-Stage Extrusion

Solid dispersions of itraconazole and HPMC were prepared by hot-stage extrusion with a corotating twin-screw extruder MP19 PH 25:1 (APV, UK). The concentration of drug in the dispersions was either 10, 20, 25, 40, 60, or 80% w/w. The screw configuration consisted of two mixing zones and three transport zones distributed over the entire barrel length; the feeding rate was fixed at 1 kg/h, and the screw rate at 300 rpm. The five temperature zones were set at 100, 130, 170, 180, and 185°C from feeder to die. The extrudates were collected after cooling at ambient temperature on a conveyor belt. Samples were milled for 1 min with a laboratory cutting mill (IKA A10, IKA Labortechnik, Staufen, Germany) and sieved to exclude particles >355 μm.

All samples were stored in a desiccator at room temperature and analyzed within 3 weeks after preparation.

High-Temperature DRIFT

High-temperature (HT)-DRIFT measurements were performed on a Bruker IFS 66 spectrometer equipped with a high-temperature–high-pressure chamber with parabolic ZnSe windows (0030-011 Spectratech Inc.). A DTGS detector was used for which a resolution of 4 cm^{-1} was selected. Investigated samples were mixed with KBr at 2% (w/w). The samples were continuously flushed with nitrogen. Heating was controlled with a Eurotherm digital temperature controller (model 808). A heating rate of 5°C min^{-1} from 25 to 200°C was chosen for every HT-DRIFT experiment.

Dissolution Testing

Dissolution experiments were performed using the USP 24 method 2 (paddle method) in a calibrated Erweka DT 700 (Heusenstamm, Germany). In order to compare the dissolution properties of the extrudates, physical mixtures and pure itraconazole, 500 ml of simulated gastric fluid without pepsin (USP 24) was used as dissolution medium at a temperature of 37°C and a paddle speed of 100 rpm. Powdered extrudates and physical mixtures (always containing 200 mg itraconazole; nonsink conditions) or pure glassy itraconazole was added to the dissolution medium. In all cases the size was smaller than 355μm. Samples of 5 ml were taken and immediately replaced with fresh dissolution medium at 5, 10, 15, 30, 45, 60, 120, 180, and 240 min and filtered with a Teflon filter of 0.45 μm (Schleicher & Schüll Rezist® 30/0.45 PTFE). After the first 2 ml was discarded, the filtrates were diluted (see below) 1 to 10 with mobile phase and analyzed using HPLC.

HPLC Analysis

HPLC analysis was performed using a Merck Hitachi pump L7110, a Bischoff autosampler 728, and Bischoff Lambda 1000 UV-VIS detector, and the peak areas were calculated using Borwin integration software. The column used was Lichrospher 100 RP-18 12.5 × 4 (5 μm) (Merck, Darmstadt, Germany); acetonitrile/tetrabutyl ammonium hydrogen sulfate 0.01 N (55:45 v/v) was used as mobile phase at a flow rate of 1.0 ml/min; UV detection was used at a wavelength of 260 nm. These conditions resulted in a typical elution time for itraconazole of 4.8 min.

RESULTS AND DISCUSSION

The primary aim of formulating sparingly soluble drugs in solid dispersions is to enhance their dissolution rate. Figure 1 shows the dissolution profile of crystalline and glassy itraconazole in comparison to that of itraconazole formulated in a solid dispersion with HPMC E5. The results show that glassy itraconazole has a higher dissolution rate than the crystalline form. However, the performance of the solid dispersion is outstanding: more than 80% of the drug is dissolved within 30 min. The physical structure of the dispersions is responsible for this (see below), but the polymer itself can also be thought to contribute significantly to the increased dissolution rate by creating a favorable microenvironment for the drug at the dissolving surface. Indeed, Craig reported that the dissolved polymer forms a layer around the formulation, in which the drug has to dissolve before being released (4).

In a solid dispersion with HPMC there are several possibilities for the distribution of itraconazole: the drug can be homogeneously dispersed and, depending on the solid-state solubility in the polymer, a molecular dispersion or a suspension can result. The latter can give rise to clusters of either glassy or crystalline itraconazole; hence, a phase-separated system will result. Preliminary experiments showed that ther-

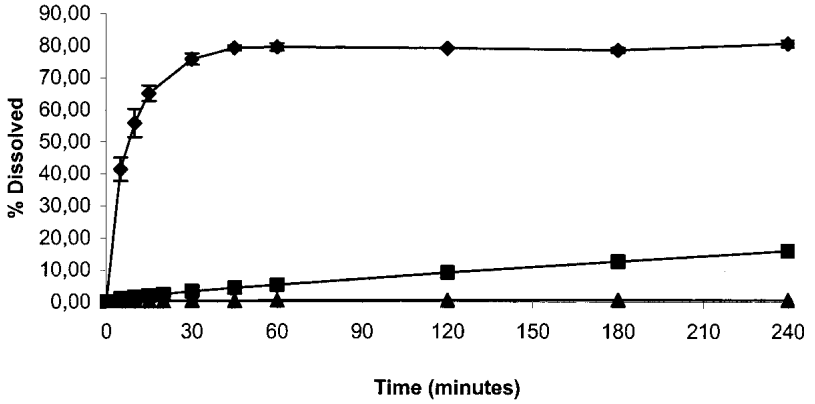

Fig. 1. Dissolution profiles of crystalline (▲) and glassy itraconazole (■) compared to itraconazole formulated in a 25% solid dispersion (♦).

mal analysis is a suitable method for gaining insight into the physical structure of the current dispersions.

In a first set of experiments MTDSC measurements are performed in open pans because they allow water to evaporate during heating. Immediately after manufacture, it can be assumed that the amount of water will be lower in the extruded material than in the nonprocessed polymer because extrusion is performed in the range of 100°C to 185°C. However, additional water will be taken up by the polymer during storage and normal handling of the material. An MTDSC study in open pans will therefore give us a picture of the extrudates after processing. MTDSC enables the determination of the Tg separately from the accompanying relaxation. Heat capacity phenomena, such as glass transition, are able to follow the fast temperature modulation and will be resolved in the reversing heat flow, whereas kinetically hindered phenomena, such as enthalpic relaxation, which are time and temperature dependent, appear in the nonreversing heat flow (10–12).

Figure 2 shows the reversing heat flow signal of the solid dispersions with the presence of one single Tg, which shifts to lower values with increasing itraconazole concentration. This single Tg, between those of itraconazole and of the polymer, indicates that itraconazole shows miscibility with HPMC E5. The MTDSC curves reveal that up to 60% of the drug is miscible with the polymer; this is much higher than the binary system with Eudragit E100 that we reported on in a previous paper; in which itraconazole was reported to be miscible with Eudragit E100 up to a drug loading of approximately 20% (6). When the drug concentration in the HPMC solid dispersions is increased to 80%, another endothermic signal at approximately 87°C was observed in addition to the Tg. This event indicates the transition of the chiral nematic mesophase to isotropic liquid, characteristic of pure glassy itraconazole (9).

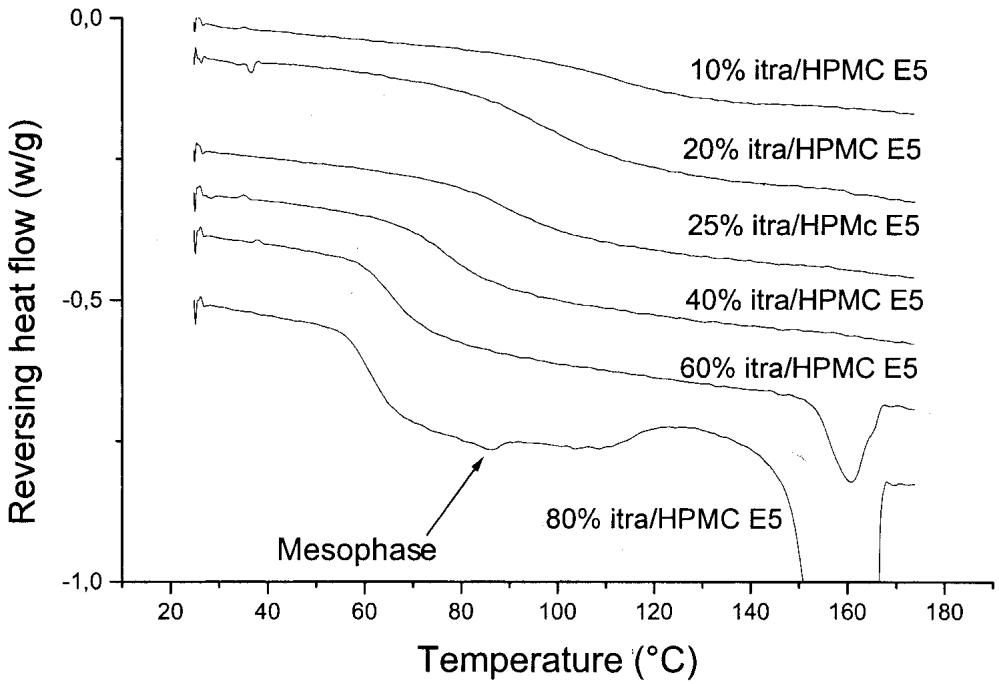

Fig. 2. The reversing heat flow of solid dispersions with different itraconazole concentrations measured in open pans.

Cycles of heating and subsequent cooling of this dispersion showed the reversibility of this transition. This observation indicates that at 80% drug loading we are no longer dealing with a homogeneous system because free clusters of glassy itraconazole are present. The melting endotherms in the 60% or 80% dispersions result from melting of a crystalline fraction that is formed during heating in the MTDSC. Indeed, at room temperature, all samples were amorphous as evidenced by x-ray powder diffraction (data not shown).

The experimental values of the glass transition temperature can be compared with the calculated values to evaluate the mixing behavior. A common relationship is that proposed by Gordon-Taylor/Kelly-Bueche (13,14):

$$Tg_x = \frac{Tg_1 w_1 + Tg_2 K w_2}{w_1 + K w_2}$$

in which Tg_1 and Tg_2 are the glass transition temperatures of itraconazole and HPMC, respectively, w_1 and w_2 are the weight fractions of itraconazole and HPMC in the dispersions, respectively, and K is a constant that can be calculated using the Simha-Boyer rule (15):

$$K \cong \frac{\rho_1 Tg_1}{\rho_2 Tg_2}$$

where ρ is the density of the amorphous solids. The densities are 1.326 and 1.270 for HPMC E5 and glassy itraconazole, respectively, and K was calculated to be 0.81.

Although the Gordon-Taylor relationship was originally derived for compatible polymer blends, it has been used successfully for small organic molecules as well (16,17). When volume additivity holds, and when the magnitudes of the heteromolecular interactions are of the same magnitudes as those of the homomolecular interactions, values should coincide. Figure 3 shows the comparison of experimental and theoretical mixing Tg's of itraconazole and HPMC E5. Qualitatively similar behavior was observed for HPMC 603 and 615. It is clear that the experimental and theoretical Tg's deviate significantly. The fact that the observed Tg is significantly lower than the theoretical one suggests that the free volume in the homogeneous phase is larger than that in the ideal mixture; hence, the system must be cooled to a lower temperature to vitrify. This also points to the weakness of the heteromolecular interactions and is discussed below. Other phenomena may also contribute to the observed behavior. First, water is a well-known plasticizer and could theoretically be absorbed by the hydrophilic polymer. However, this can not explain the observed deviation because the experiments were performed in open pans, which allows evaporation of water during the measurement. Moreover, subsequent heating/cooling cycles from room temperature to 140°C always showed the same value of Tg, confirming that the dispersion was truly binary. Second, the theoretical Tg assumes ideal miscibility of the binary system over the entire concentration range. However, if one of the components separates from the homogeneous phase, it follows that the relative concentration in the homogeneous phase will no longer correspond to the theoretical concentration. Because we observed a separate itraconazole phase only at 80% and above, we attempted to investigate the possibility of the existence of a separate HPMC (rich) phase. Because of resolution problems including overlap of the Tg of pure HPMC with the melting of recrystallized itraconazole [recrystallization takes place as a consequence of applied heat because at room temperature all solid dispersions were amorphous, as evidenced by x-ray powder diffraction (data not shown)] and restriction to sample mass, a Tg for the pure HPMC phase could not be detected. (see below: discussion of setaram DSC). Nevertheless, broad Tg regions (as observed in Fig. 2) suggest that the drug and polymer are still mixing during heating in the MTDSC apparatus. The solid dispersions are measured while they are in a nonequilibrium state because the heating rate has a different time scale than the mixing process. This explains the broadness of the Tg region, but what is the driving force for mixing in this case? This must be the evaporating water that creates available sites on the polymer for interaction with itracona-

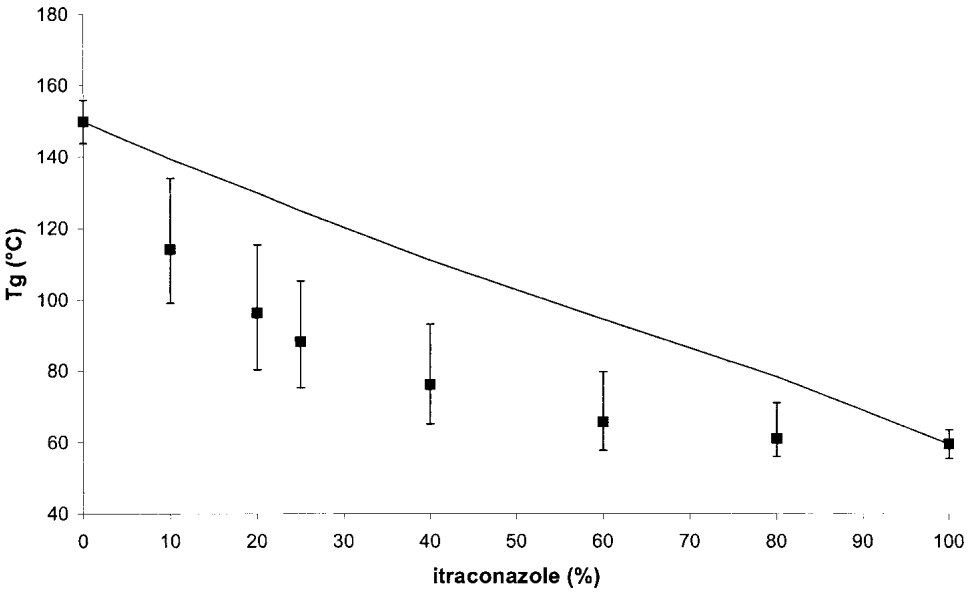

Fig. 3. Comparison of experimental (■) and theoretical values (full line) of Tg calculated with the Gordon-Taylor equation. The bars indicate the width of the Tg region.

zole during the first heating. However, as a result of the time scale of the MTDSC experiments, mixing is kinetically hindered. This also explains why consecutive heating/cooling cycles showed the same broadness of the Tg region.

Based on the above observations, we hypothesize the following set of consecutive events. During preparation the drug is mixed with a part or the total amount of the polymer but starts to demix during storage by taking up water. Heating in an open pan permits the water to evaporate, and the drug and the polymer are able to mix again with a broad transition as a consequence. Mixing is hindered for kinetic reasons because there is not enough time to mix itraconazole with all HPMC in the time course of the MTDSC experiment, leading to an HPMC-rich phase. The resultant lower percentage of HPMC mixed with itraconazole explains the deviation between theoretical and actual Tg values. In addition, one can question the significance of plotting the midpoint of the glass transition in dispersions of this type, although this is done very often in literature. We therefore also plotted the complete glass transition region in Fig. 3. In this respect it would have been interesting to investigate the influence of prolonging the residence time of the solid dispersions in the extruder on the mixing behavior. Unfortunately, this is not possible because of decomposition of the polymer.

In order to further study the influence of water on the mixing behavior and to strengthen the abovementioned hypothesis, a further set of MTDSC experiments was performed in hermetically closed pans. This revealed a totally different picture compared to that obtained in open pans. Figure 4 shows the total and reversing heat flow of solid dispersions with different ratios of itraconazole and HPMC E5. A mixing Tg is again observed, but the most striking effect was that the midpoints of the mixing Tg's were observed at lower values than those obtained in open pans, and the dispersions with 10 and 20% drug loading had an even broader glass transition. The drug is still mixed with (part of) the HPMC because the nematic mesophase is not present until the drug concentration reaches 80%. It is clear that the presence of water has a major influence on the sample properties. First, water acts as a plasticizer on the sample, leading to a drop in Tg. This, however, can only partially explain the lower values because weight loss after drying of these dispersions was never higher than 1.6%. Second, water may cause a further phase separation, as it is a possible competitor with itraconazole to interact with HPMC. If water is absorbed onto HPMC, a large fraction of the hydroxyl groups, and thus the ability of itraconazole to interact with the polymer by hydrogen bonding, may be blocked.

Vibrational spectroscopy has been shown to be a reliable tool to localize the site and the nature of drug–polymer interactions. HT-DRIFT was performed on solid dispersions with 40% drug loading as well as on the pure components, and the results are shown in Fig. 5. The spectra of the pure polymer (Fig. 5B) show hydrogen bonds between 3,000 and 3,500 cm^{-1}. Increasing the temperature from 42°C to 185°C clearly shows a reduction in hydrogen bonding; the maximum of the difference spectrum is localized at 3,300 cm^{-1}. The disappearance of hydrogen bonds at higher temperature is also evidenced by reflection changes independent of mass and by the greater intensity of C-O stretching and OH deformation in the area around 1,000 cm^{-1}. The spectrum of pure glassy itraconazole does not seem to be influenced substantially by a change in temperature (Fig. 5A). The spectrum of the solid dispersion (Fig. 5C) corresponds in most regions to the algebraic sum of the spectra of the pure compounds. An important exception is that the maximum of the hydrogen-bonding interaction is now shifted from 3,300 cm^{-1} in the pure polymer to 3,250 cm^{-1} in the solid dispersion. This shift may reflect formation of a new type of hydrogen bond: those between the drug and the polymer.

So far we have identified different events that contribute to the observed deviation from ideal mixing behavior. First,

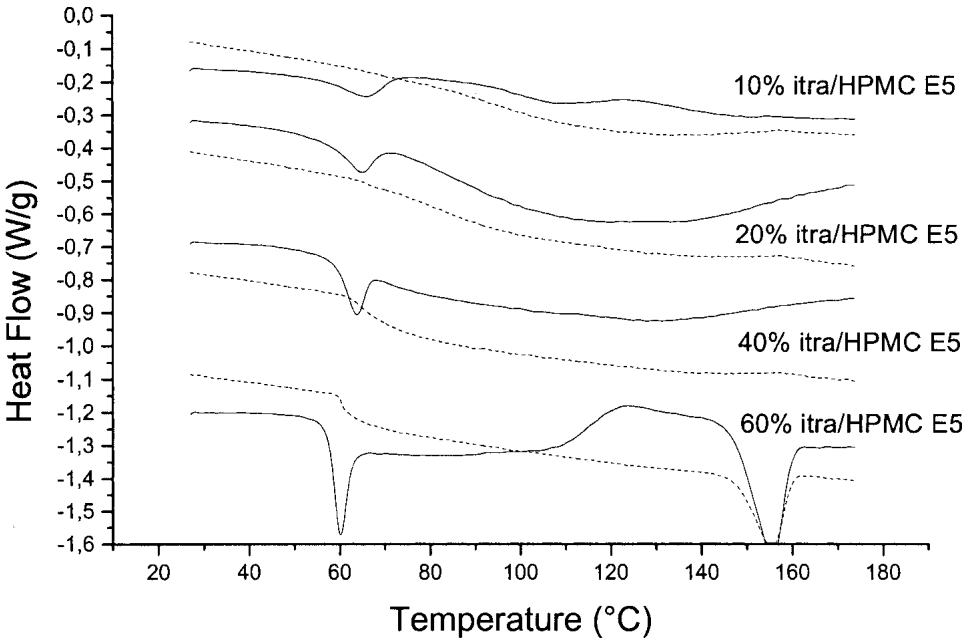

Fig. 4. Total (full line) and reversing (dotted line) heat flow of solid dispersions with different itraconazole concentrations measured in hermetically closed pans.

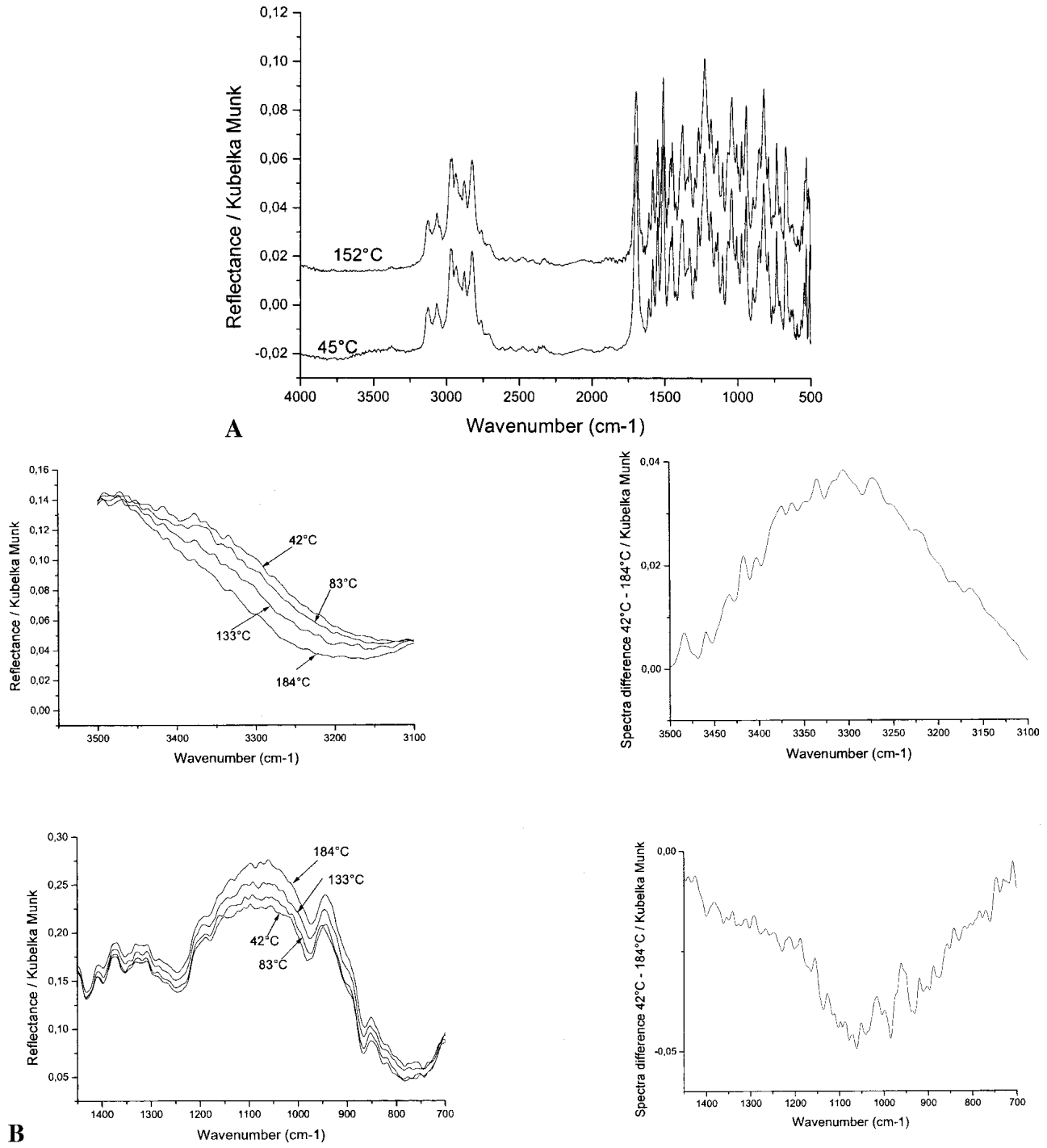

Fig. 5. HT-DRIFT spectra: A, pure itraconazole; B, pure HPMC; C, solid dispersion with 40% itraconazole.

the presence of water is important because it will compete with itraconazole for interaction with HPMC. Second, there is an interaction between itraconazole and HPMC. Because of steric effects resulting from the complex itraconazole chemical structure, the interaction between itraconazole and HPMC via hydrogen bonding may be rather loose. Therefore, the interaction is expected to lead to a system with increased free volume of the homogeneous phase. A third event, which could partly result from above phenomena, would be the formation of an HPMC-rich phase. However, the Tg of pure HPMC in Fig. 4 cannot be clearly distinguished because of resolution problems. Solid dispersions were subsequently analyzed with a setaram DSC 111; in this case sample masses up to 100 mg can be used. Figure 6 is a representative DSC curve of a solid dispersion containing 40% of itraconazole. Two transitions are observed; the first is located at approximately 60 to 70°C and corresponds to the itraconazole-rich phase. The second transition at approximately 140°C corresponds to a glass transition. Given its position, it most likely corresponds to an HPMC-rich phase.

The broad Tg region at low drug concentration in closed sample pans indicates that there are different phases rich in

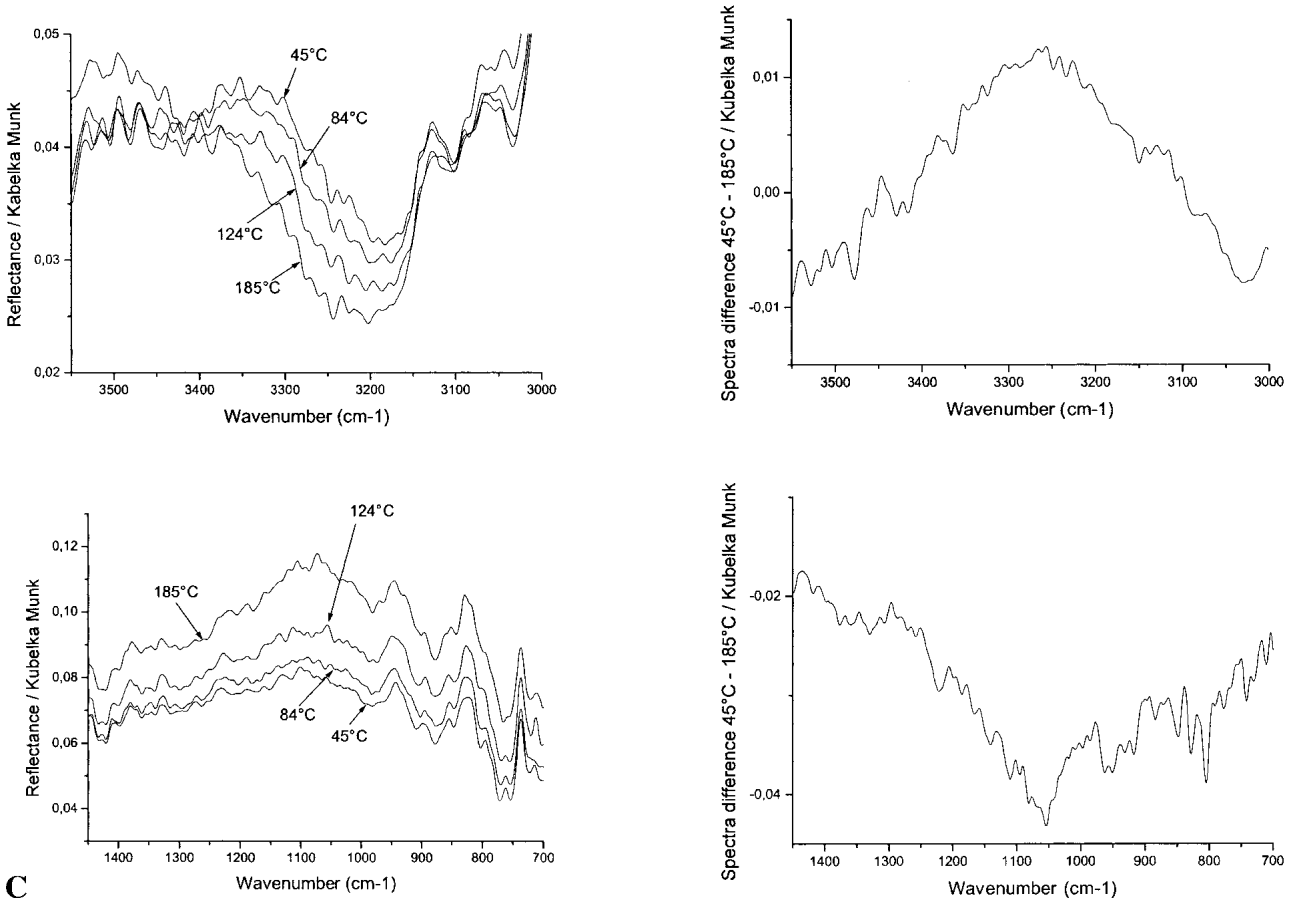

Fig. 5c.

itraconazole that are mixing during heating of the sample as a result of the slight loss of water from HPMC. The latter is similar to the process taking place in open pans. Water is eliminated during heating, and itraconazole can interact with the free hydroxyl positions on HPMC, thereby forming a mixed phase. This mixing during heating can be seen as the broad transition. Probably mainly because of kinetically controlled events (although steric hindrance will be involved as well to some extent), not all HPMC can sufficiently interact with itraconazole, leaving a residual HPMC-rich phase.

This phase separation can not be improved by changing the extrusion parameters in order to obtain sufficient mixing. This is discussed in a previous paper (14).

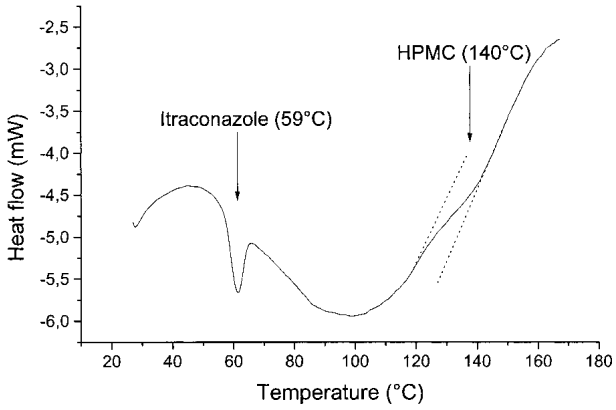

Fig. 6. Heat flow of solid dispersion with 40% drug loading measured in setaram DSC 111.

CONCLUSIONS

Although the dissolution rate of itraconazole significantly increased when it was formulated as a solid dispersion with HPMC using hot-stage extrusion, the present report revealed that these systems are not homogeneous. A different picture was obtained depending on the way MTDSC analysis was performed, i.e., using open or closed sample pans. Water can evaporate in open pans, which allows itraconazole to interact with HPMC, leading to a partially mixed phase. The experimental Tg's significantly deviate from the theoretical ones calculated by the Gordon-Taylor equation, mainly because of the presence of an HPMC-rich phase and the formation of a loose structure with an increase in free volume. Analysis in hermetically closed pans revealed a further phase separation as water remains on the sample and impedes the interaction between drug and polymer. The presence of hydrogen bonding in the dispersions was confirmed by HT-DRIFT. The paper therefore also aims to contribute to the calorimetric analysis of solid dispersions using hydrophilic polymers in the presence or absence of water. The former case is representative of solid dispersions during normal handling, and the latter represents the system immediately after processing. With this report, we would also like to emphasize the pitfalls of drawing conclusions from experiments solely performed in open or closed pans. Most studies use only one

type of sample pan, possibly leading to wrong conclusions concerning the miscibility of the samples. Also more attention should be drawn to the broadness of the Tg region as observed during DSC analysis because this can be an indication of mixing during heating or the presence of different drug/polymer phases.

ACKNOWLEDGMENTS

The authors acknowledge the financial support from Johnson and Johnson Pharmaceutical Research and Development (Beerse, Belgium) and FWO-Vlaanderen.

REFERENCES

1. J. A. Barone, J. G. Koh, R. H. Bierman, J. J. Colaizzi, K. A. Swanson, M. C. Gaffar, B. L. Moskovitz, W. Mechlinski, and V. Van De Velde. Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers, *Antimicrob. Agents Chemother.* **37**:778–784 (1993).
2. S. M. Grant and S. P. Clissold. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. *Drugs* **37**:310–344 (1989).
3. G. L. Amidon, H. Lennernäs, V. P. Shah, and J. R. Crison. Theoretical basis for a biopharmaceutical drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailibility. *Pharm. Res.* **12**:413–420 (1995).
4. D. Q. M. Craig. The mechanism of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.* **231**:131–144 (2002).
5. C. Leuner and J. Dressman. Improving drug solubility for oral delivery using solid dispersion. *Eur. J. Pharm. Biopharm.* **50**:47–60 (2000).
6. K. Six, C. Leuner, J. Dressman, G. Verreck, J. Peeters, N. Blaton, P. Augustijns, R. Kinget, and G. Van den Mooter. Thermal properties of hot-stage extrudates of itraconazole and Eudragit E100: Phase separation and polymorphism. *J. Therm. Anal. Cal.* **68**:591–601 (2002).
7. G. Verreck, K. Six, G. Van den Mooter, L. Baert, J. Peeters, and M. E. Brewster. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion, part 1. *Int. J. Pharm.* **251**:165–174 (2003).
8. K. Six, G. Verreck, J. Peeters, P. Augustijns, R. Kinget, and G. Van den Mooter. Characterization of glassy itraconazole: a comparative study of its molecular mobilty below Tg with that of structural analogues using MTDSC. *Int. J. Pharm.* **213**:163–173 (2001).
9. K. Six, G. Verreck, J. Peeters, K. Binnemans, H. Berghmans, P. Augustijns, R. Kinget, and G. Van den Mooter. Investigation of thermal properties of glassy itraconazole: identification of a monotropic mesophase. *Thermochim. Acta* **376**:175–181 (2001).
10. T. A. Instruments. *Modulated DSC Compendium 1997.* TA-Instruments, New Castle, Delaware.
11. M. Reading, D. Elliot, and V. Hill. MDSC, a new approach to the calorimetric investigation of physical and chemical transitions. *J. Thermal Anal.* **40**:949–955 (1993).
12. M. Reading, A. Luget, and R. Wilson. Modulated differential scanning calorimetry. *Thermochim. Acta* **238**:295–307 (1994).
13. S. Gordon and J. S. Taylor. Ideal copolymers and the second-order transitions of synthetic rubbers. I Non-crystalline copolymers. *J. Appl. Chem.* **2**:493–500 (1952).
14. F. N. Kelley and F. Bueche. Viscosity and glass temperature relations for polymer-diluent systems. *J. Pol. Sci.* **50**:549–556 (1961).
15. R. Simha and R. F. Boyer. General relation involving the glass transition temperature and coefficient of expansion of polymers. *J. Chem. Phys.* **37**:1003–1007 (1962).
16. T. Matsumoto and G. Zografi. Physical properties of solid molecular dispersions of indomethacine with PVP and PVPVA in relation to indomethacine crystallization. *Pharm. Res.* **16**:1722–1728 (1999).
17. G. Van den Mooter, M. Wuyts, N. Blaton, R. Busson, P. Grobet, P. Augustijns, and R. Kinget. Physical stabilization of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur. J. Pharm. Sci.* **12**:261–269 (2001).