Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 272 (2004) 181–187
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Note

Study of the phase behavior of polyethylene glycol 6000–itraconazole solid dispersions using DSC

Xin Wang, Armand Michoel, Guy Van den Mooter*

Laboratorium voor Farmacotechnologie en Biofarmacie, Faculteit Farmaceutische Wetenschappen, K.U. Leuven, Campus Gasthuisberg O+N, Herestraat 49, Leuven 3000, Belgium

Received 29 January 2003; received in revised form 24 November 2003; accepted 27 November 2003

Abstract

The aim of the present study was to investigate the phase behavior of solid dispersions made up of PEG 6000 and itraconazole using DSC. Solid dispersions were prepared by solvent evaporation. DSC analysis of pure PEG 6000 showed three endothermic events, representing the melting transitions of the three different crystal modifications. It was shown that itraconazole decreased the formation of the polymer modifications with melting transitions at 56 and 59 °C but promoted the formation of the modification with a melting transition at 63 °C. All dispersions investigated showed the presence of crystalline itraconazole indicating that the drug is not molecularly dispersed in the polymer matrix. However, the presence of an endothermic peak in DSC curves of all solid dispersions at approximately 85–90 °C showed that at least a second phase of pure itraconazole is present also: glassy itraconazole. The protective effect of the polymer is clear at low concentration of drug since no recrystallisation exotherm can be detected. However, at drug concentrations at or above 80%, a recrystallization exotherm at approximately 117 °C can be detected. At least three different phases can be distinguished at room temperature: a polymer phase, crystalline itraconazole and glassy itraconazole. The findings of the present study thus demonstrate the coexistence of multiple drug phases in a solid dispersion.

Keywords: Polyethylene glycol 6000; Itraconazole; Differential scanning calorimetry (DSC); Phase separation

It is generally recognized that low solubility and/or dissolution rate in the gastro-intestinal tract, compromise oral bioavailability. Formulation of solid dispersions is a possible pharmaceutical strategy to increase solubility and dissolution rate.

Although the use of solid dispersions has been reported frequently in the pharmaceutical literature, very few marketed products rely on the solid dispersion strategy. The main reason for this discrepancy is the physical instability of these structures that can be metastable from a thermodynamical point of view. Phase separation, crystal growth or conversion from the amorphous (metastable) to the crystalline state during storage, inevitably results in decreased solubility and dissolution rate. There are many systems described in literature dealing with solid dispersions using PEG 6000 as carrier. The majority is described as binary phase systems, made up of the polymer and the drug. It is however a fact that a number of systems that are reported as binary systems are not truly binary. Indeed, in some cases the solid dispersion systems are poorly studied and coexisting drug phases are therefore not noticed.

* Corresponding author. Tel.: +32-16-34-5830; fax: +32-16-34-5996.
E-mail address: guy.vandenmooter@pharm.kuleuven.ac.be (G. Van den Mooter).

0378-5173/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2003.11.026

The aim of the present paper is to report the phase behavior of solid dispersions made up of PEG 6000 and the model drug itraconazole as an example of a system with coexisting drug phases. In addition we aim to stimulate thorough phase analysis in order to upgrade our understanding of solid dispersions.

Itraconazole is a potent antifungal drug of the triazole group. Because of its very low aqueous solubility and poor dissolution rate, itraconazole shows a large inter-individual difference in bioavailability after oral administration (Grant and Clissold, 1989). Currently, several formulations are being developed to overcome the dissolution rate limiting oral absorption of itraconazole. In these formulations, the physical state of the drug is changed from the crystalline to the glassy state. The presence of the glassy state also leads to improved dissolution properties because of the absence of a crystalline lattice. The glassy form of itraconazole shows a particular thermal behavior. Besides the glass transition at approximately 60 °C, glassy itraconazole showed two endothermic transitions at 74 and 90 °C, respectively (Fig. 1).

The purpose of the present study was to investigate the phase behavior of binary solid dispersions of itraconazole and PEG 6000. Previous studies of our research group showed that this drug forms a one phase system with PVP-VA64, but a two phase system with Eudragit E100 and with HPMC 2910 (Six et al., 2002, 2003a,b; Verreck et al., 2003; Six et al., 2004 in press).

In this study, solid dispersions of itraconazole and PEG 6000 were prepared by dissolving different ratios of drug and polymer in methylene chloride, followed by solvent evaporation under reduced pressure at room temperature in a rotovapor. The solid dispersions were subsequently stored in a vacuum oven over P_2O_5 until constant weight after which they were milled and an-

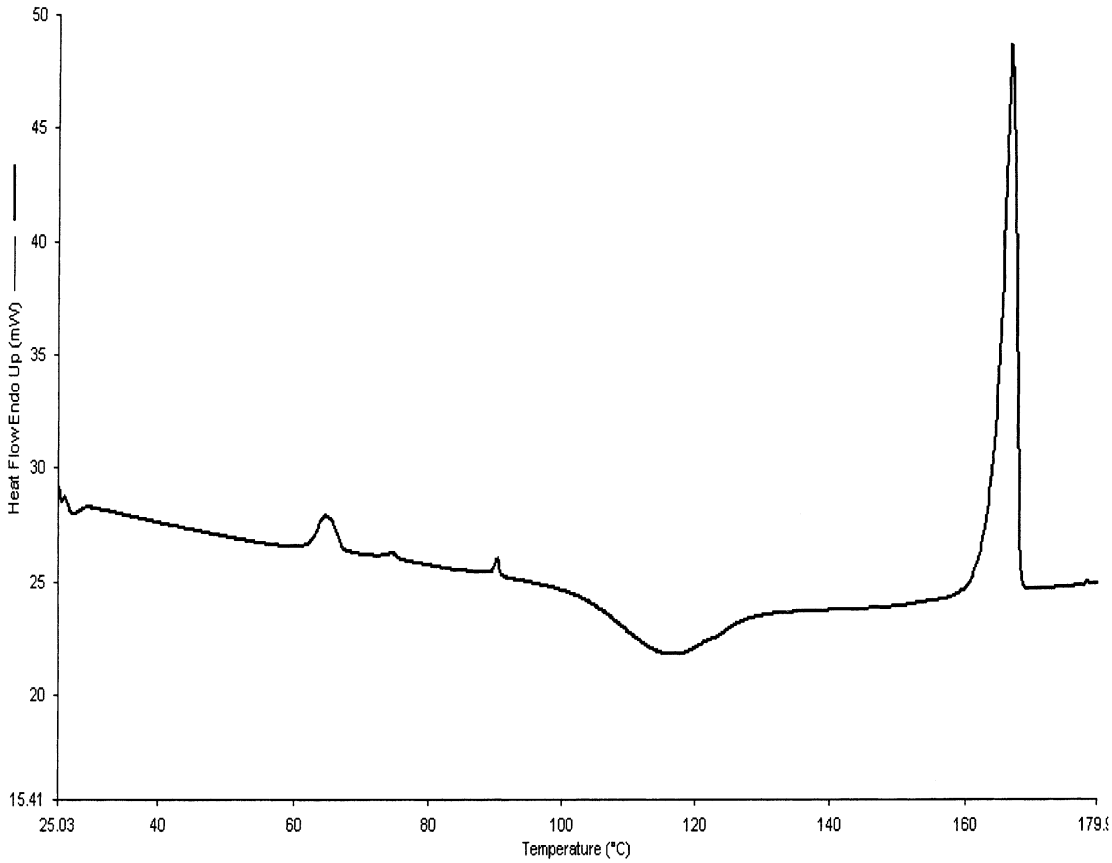

Fig. 1. DSC curve of glassy itraconazole.

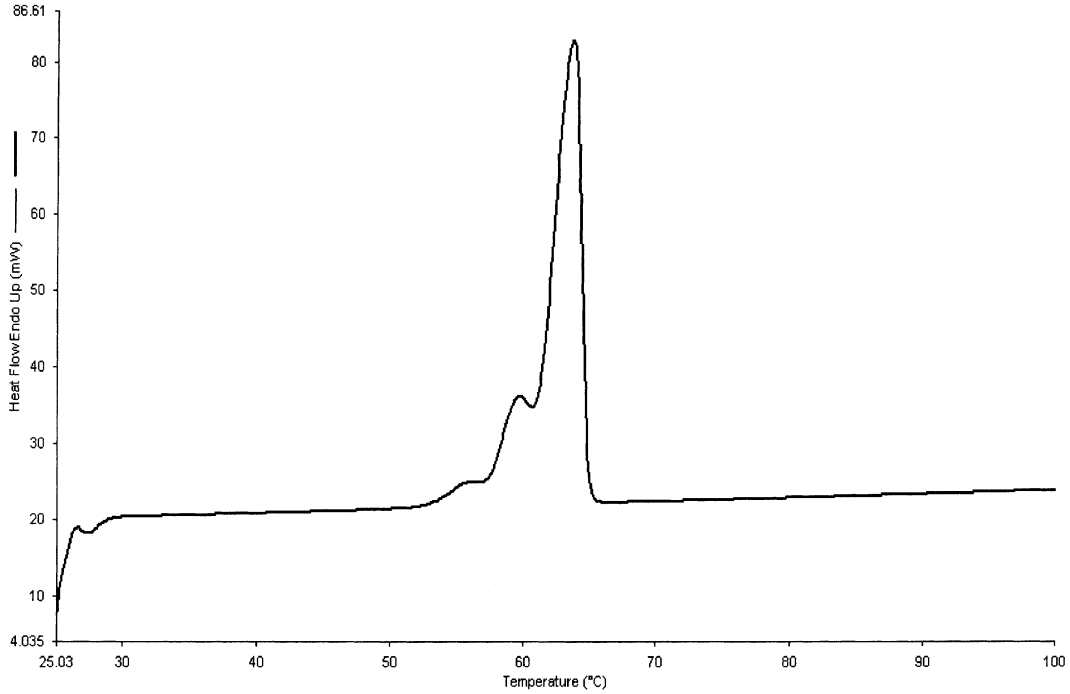

Fig. 2. DSC curve of pure PEG 6000.

Table 1
Thermal characteristics of PEG 6000 in different dispersions with itraconazole

Itraconazole (%, w/w)	T3 (°C)	T2 (°C)	T1 (°C)	% T3	% T2	% T1
0	63.37	59.53	57.03	75.79	19.34	4.86
	63.70	59.70	57.03	76.78	19.16	4.06
5	64.33	63.7	Shoulder	52.34	47.66	Shoulder
	64.87	63.7	Shoulder	51.99	48.01	Shoulder
10	64.17	63.03	Shoulder	51.61	48.39	Shoulder
	64.17	62.70	Shoulder	51.67	48.33	Shoulder
20	63.20	59.37	Shoulder	67.16	32.84	Shoulder
	62.90	59.65	Shoulder	68.65	31.35	Shoulder
30	62.70	59.87	–	98.72	1.28	–
	64.00	59.87	–	97.63	2.37	–
40	64.53	–	–	100	–	–
	62.69	–	–	100	–	–
50	60.17	–	–	100	–	–
	61.50	–	–	100	–	–
60	63.84	–	–	100	–	–
	63.42	–	–	100	–	–
80	58.03	–	–	100	–	–
	57.97	–	–	100	–	–

T1, T2 and T3 represent peak temperatures.

alyzed with DSC. DSC experiments were carried out using a DSC-7 equipped with a liquid nitrogen subambient accessory (Perkin-Elmer, Norwalk, CT, USA). The samples were analyzed using aluminium open pans and scanned at 10 °C/min from 25 to 200 °C.

PEG 6000 crystallizes forming lamellae with chains either fully extended or folded once or twice (Verheyen et al., 2001). Pure PEG 6000 showed three endothermic events at 56 °C (T1), 59 °C (T2) and 63 °C (T3) (Fig. 2). These represent the melting transition of the three different crystal folding modifications of this semi-crystalline polymer. As it is shown in Table 1, when the percentage of itraconazole was increased up to 20%, the T1 peak can still be found, but it diminished into a shoulder of the T2 peak. In the DSC curve of the solid dispersion with 30% itraconazole, the T1 peak disappeared and the T2 peak diminished into the shoulder of the high melting form T3 peak. When the percentage of itraconazole was higher than 40%, the T1 and T2 peak disappeared with only one remaining melting peak of PEG 6000 in the DSC curve. This strongly suggests that the presence of itraconazole influenced the folding behavior of the polymer. Itraconazole decreased the formation of the T1 and T2 modification but promoted the formation of a high melting form T3 (Figs. 3 and 4), the thermodynamically most stable form in the three different crystal modifications.

All dispersions investigated showed the presence of crystalline itraconazole indicating that the drug is not molecularly dispersed in the polymer matrix. However, the presence of an endothermic peak in DSC curves of all solid dispersions at approximately 85–90 °C showed that at least a second phase of pure itraconazole is present also: glassy itraconazole. The peak at 85–90 °C is due to the transition of the chiral nematic mesophase to the isotropic liquid phase, typical for glassy itraconazole (Six et al., 2001). It was shown in a previous paper that indeed glassy itracona-

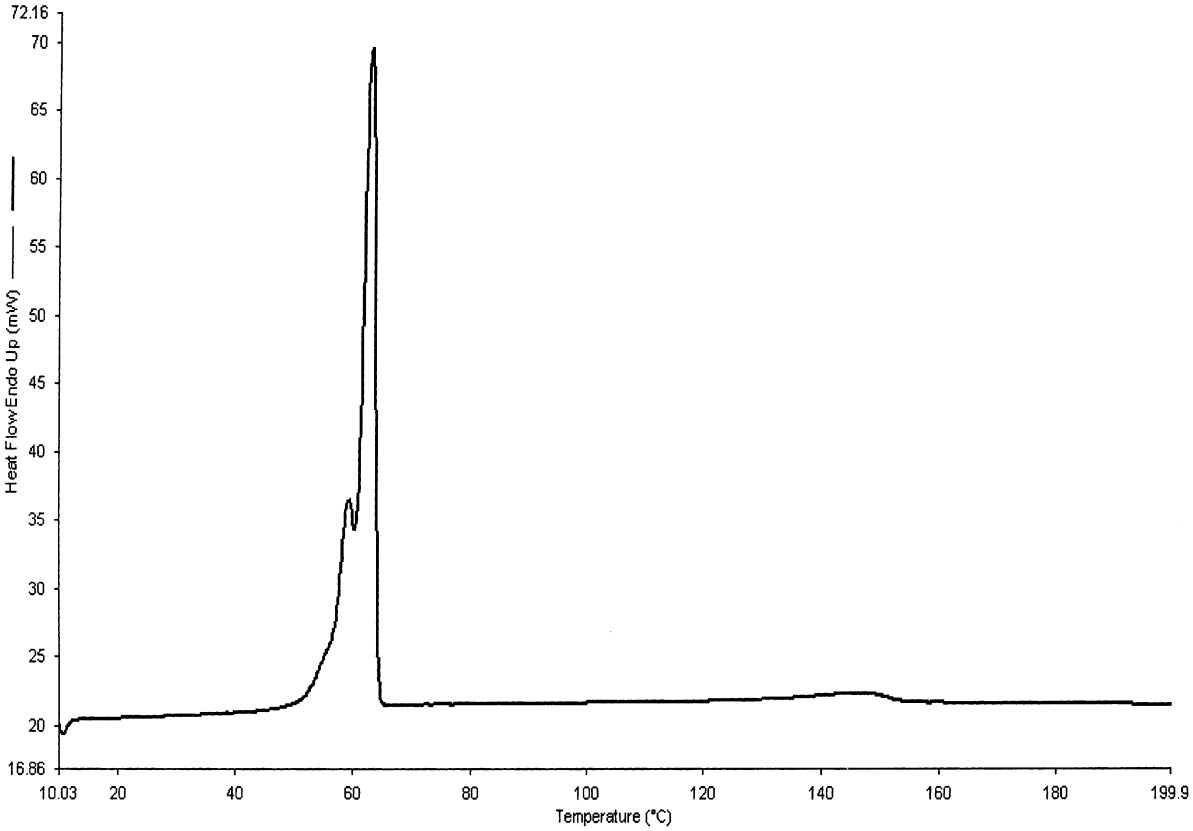

Fig. 3. DSC curve of a solid dispersion with 20% itraconazole.

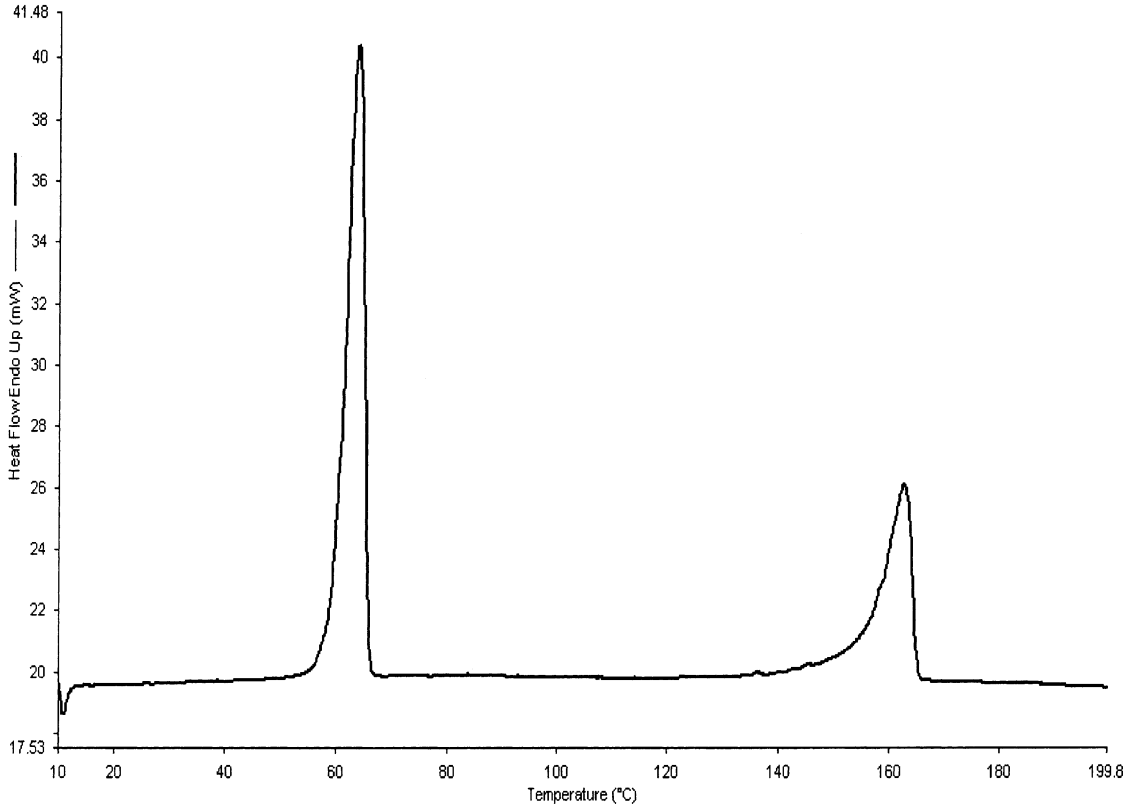

Fig. 4. DSC curve of a solid dispersion with 60% itraconazole.

zole is not amorphous, but structured due to its liquid crystalline properties. The protective effect of the polymer is clear at low concentration of drug since no recrystallisation exotherm can be detected indicating that the glassy fraction remains in its metastable state. However, at drug concentrations at or above 80%, a recrystallization exotherm at approximately 117 °C can be detected. The recrystallization peak further illustrates that the glassy phase of itraconazole was not completely protected by the polymer. Therefore, when heating the glassy state of itraconazole, part of it will recrystallize.

It is noticeable that the melting peak of PEG 6000 in the dispersion of 80% itraconazole is not around 63 °C as we expected, but is 58 °C. This has two possibilities, one possibility is the melting depression of the high melting form of PEG 6000 due to the high concentration of itraconazole; the other possibility is the promotion of the T2 form of PEG 6000 when the ratio of itraconazole is higher than a certain percentage. Further study on this phenomenon is ongoing (Fig. 5, Table 2).

From the results it can be concluded that itraconazole promotes the high melting form of PEG 6000 in solid dispersions prepared by solvent evaporation. Contrary to solid dispersions of this drug with polymers such as PVP-VA64, Eudragit E100 or HPMC, at least three different phases can be distinguished at room temperature in these solid dispersions: a polymer phase, crystalline itraconazole and glassy itraconazole. Therefore, it seems to be that PEG 6000 is of limited value for the formulation of solid dispersions containing itraconazole. Indeed, the optimal situation is when the drug is molecularly dispersed in a carrier forming a one phase system in a way that recrystallisation or drug clustering can be prevented. In the PEG 6000–itraconazole system, the presence of the crystalline phase acts as a trigger for recrystallisation of the existing free glassy itraconazole phase.

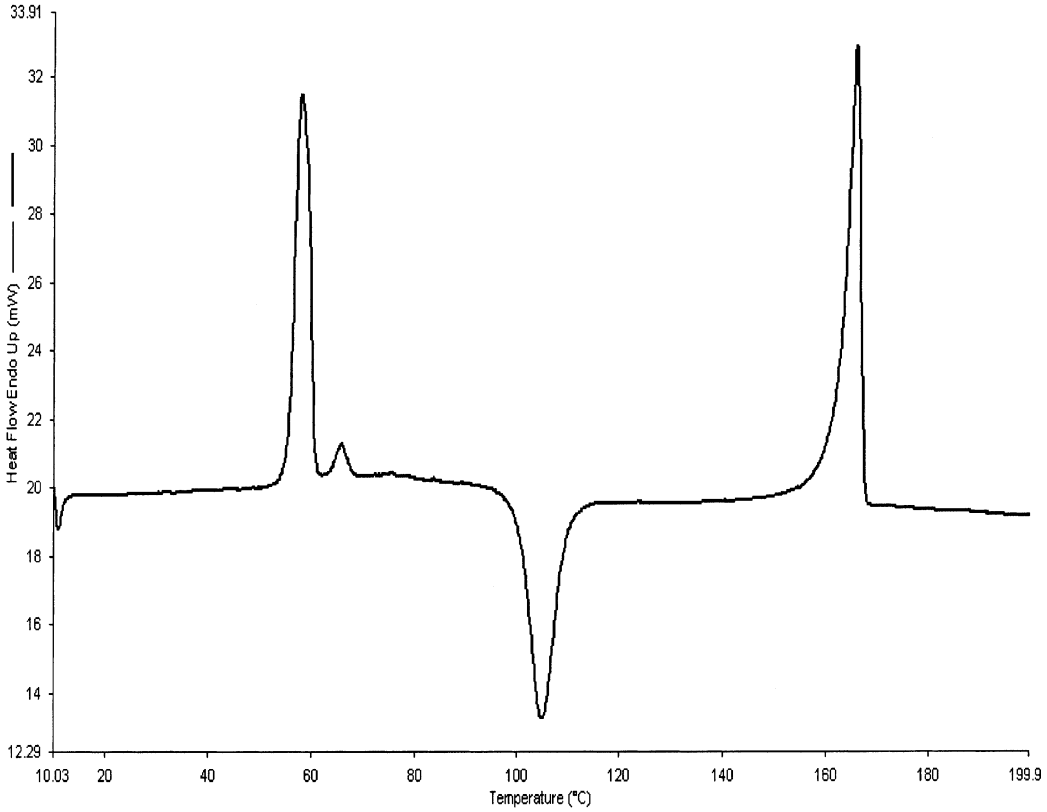

Fig. 5. DSC curve of a solid dispersion with 80% itraconazole.

Table 2
Thermal characteristics of itraconazole in different dispersions with PEG 6000

Itraconazole (%, w/w)	Glass transition (°C)	Glassy itraconazole peaks (°C)	Recrystallisation temperature (°C)	Melting peak (°C)
5	–	–	–	119.20
	–	–	–	118.67
10	–	–	–	129.83
	–	–	–	130.33
20	–	75–90	–	145.87
	–	75–90	–	145.87
30	–	–	–	153.67
	–	–	–	153.54
40	–	75–90	–	159.20
50	–	75–90	–	162.67
	–	75–90	–	162.23
60	–	75–90	–	163.77
80	60.7	75–90	105.03	166.03
	60.4	75–90	105.6	166.20
100	60.7	75–90	115.7	167.03
	60.2	75–90	116.0	167.25

With this paper, we showed an example of a ternary system and want to make other researchers in the field aware of the fact that in some cases multiple drug phases can and do coexist.

References

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.

Six, K., Verreck, G., Peeters, J., Augustijns, P., Kinget, R., Van den Mooter, G., 2001. Investigation of thermal properties of glassy itraconazole: identification of a monotropic mesophase. Int. J. Pharm. 213, 163–173.

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 E100: phase separation and polymorphism. J. Therm. Anal. Calor. 68, 591–601.

Six, K., Murphy, J., Weuts, I., Craig, D., Verreck, G., Peeters, J., Brewster, M., Van den Mooter, G., 2003a. Identification of phase separation in solid dispersions of itraconazole and Eudragit E100 using micro-thermal analysis. Pharm. Res. 20, 135–138.

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., Van den Mooter, G., 2003b. Characterization of solid dispersions of itraconazole and hydroxypropylmethyl-cellulose 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., in press.

Verheyen, S., Augustijns, P., Kinget, R., Van den Mooter, G., 2001. Melting behavior of pure polyethylene glycol 6000 and polyethylene glycol 6000 in solid dispersions containing diazepam or temazepam: a DSC study. Thermochim. Acta 380, 153–164.

Verreck, G., Van den Mooter, G., Baert, L., Peeters, J., Brewster, M., 2003. Characterisation of solid dispersions of itraconazole and hydroxypropyl methyl cellulose prepared by melt extrusion. Part I. Int. J. Pharm. 251, 165–174.