Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 303 (2005) 54–61
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Solid state characteristics of ternary solid dispersions composed of PVP VA64, Myrj 52 and itraconazole

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, B-3000 Leuven, Belgium

Received 3 January 2005; received in revised form 15 June 2005; accepted 1 July 2005
Available online 18 August 2005

Abstract

The purpose of the present study was to characterize the solid state properties of ternary solid dispersions made up of PVP VA64, Myrj 52 and itraconazole. The solid dispersions were prepared by dissolving the materials in methylene chloride, followed by evaporation under reduced pressure of the solvent at 55 °C in a rotovapor. Binary and ternary solid dispersions were characterized by standard and modulated temperature differential scanning calorimetry and X-ray powder diffraction. Although PVP VA64 and itraconazole were found to be completely miscible in the solid state, addition of a small amount of Myrj 52 to the drug–polymer system leads to separation of itraconazole thus demonstrating that Myrj 52 expels the drug from the polymer phase.

Keywords: PVP VA 64; Myrj 52; Itraconazole; MTDSC; X-ray powder diffraction; Solid dispersions

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 is recognized as a strategy that can increase the solubility and dissolution rate of drugs (Chiou and Riegelman, 1971). Although the use of solid dispersions has been reported frequently in the pharmaceutical literature, still few marketed products rely on the solid dispersion strategy. The main reason for this discrepancy is the possible physical instability of these structures that can be metastable (Serajuddin, 1999; Leuner and Dressman, 2000). Phase separation, crystal growth or conversion from the amorphous (metastable) to the crystalline state during storage, inevitably results in decreased solubility and dissolution rate. However, the presence of a carrier (polymer) is often adequate to prevent recrystallization (Motsumoto and Zografi, 1999; Van den Mooter et al., 2001).

* 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 © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.07.002

The interest to use surface-active and self-emulsifying carriers for the solid dispersion of poorly water-soluble drugs increased in recent years (Serajuddin, 1999; Serajuddin et al., 1990; Morris et al., 1992). Gelucire 44/14, Vitamine E TPGS NF and polysorbate 80 are examples of such carriers. Furthermore, it was reported that a solid dispersion in a mixture of polyethylene glycol and polysorbate 80 could improve the dissolution rate and enhance the bioavailability of LAB687, a poorly water-soluble drug (Dannenfelser et al., 2004). The bioavailability of this kind of solid dispersion showed a 10-fold increase compared to the dry blend of micronized drug with microcrystalline cellulose. In addition the solid dispersion system was physically and chemically stable for at least 16 months at 25 °C/60% RH.

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 order to improve the stability and dissolution properties of itraconazole, new combinations consisting of itraconazole, a hydrophilic polymer and a surfactant are currently being investigated by our research group. The selection of the polymers and the surfactants is based on the fact that one must dissolve the drug in the solid state, leading to a stable system without phase separation, while the other one must increase the solubility and dissolution rate of the drug.

In the present study PVP VA64 is selected as the polymer because it was able to molecularly disperse itraconazole in the solid state after hot-stage extrusion (Six et al., 2004). Polyoxyethylene (40) monostearate (Myrj 52) was the selected surfactant because of its solubilising action on several drugs (Yu-li, 2003; Serajuddin, 1999). The compatibility between the carrier and drug seems to be a stabilizing factor for the solid dispersion. However, little is reported on ternary systems. The purpose of the present study was therefore to investigate the solid state properties of ternary solid dispersions made up of itraconazole, PVP VA64 and Myrj 52 to contribute to our understanding how materials behave in a ternary system. This study was part of a preformulation study to develop an oral formulation of itraconazole.

2. Materials and methods

2.1. Materials

PVP VA64 was obtained from BASF (Ludwigshafen, Germany), itraconazole was generously donated by Janssen Pharmaceutica N.V. (Beerse, Belgium), and Myrj52 was obtained from Uniqema (Everberg, Belgium).

2.2. Preparation of solid dispersions

Binary or ternary solid dispersions were prepared by dissolving different amounts of polymer, surfactant and itraconazole in methylene chloride, followed by evaporation under reduced pressure of the solvent at 55 °C in a rotovapor (Buchi, Switzerland). In this study, four systems were prepared: PVP VA64-itraconazole, Myrj52-itraconazole, PVP VA64-Myrj52 and PVP VA64-Myrj52-itraconazole. Ternary solid dispersions were made up of 1 g of PVPVA64 and Myrj 52 (900:100 or 800:200) to which either 50, 100, 200 or 300 mg of the drug was added. The solid dispersions were subsequently stored in a vacuum oven over P_2O_5 until constant weight after which they were milled by mortar and pestle and analyzed.

In order to investigate the compatibility between Myrj 52 and PVP VA64, additional dispersions made up of PVP VA64-PEG 1500 and PVP VA64–stearic acid, which are the possible impurities of Myrj 52, were prepared as well.

2.3. DSC methods

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. MTDSC measurements were carried out using a 2920 Modulated DSC (TA-Instruments, Brussels, Belgium), equipped with a refrigerated cooling system (RCS). The samples were analyzed using aluminum open pans and each sample was scanned twice from 25 to 200 °C. The amplitude used was 0.212 K, the period 40 s and the underlying heating rate 2 °C/min. Octadecane, benzoic acid and indium standards were used to calibrate the DSC temperature scale; enthalpic response was calibrated with

indium. Heat capacity was calibrated with sapphire. Validation of temperature, enthalpy and heat capacity measurement was performed using the same standard materials.

2.4. X-ray powder diffraction (XRD)

X-ray powder diffraction was performed with a Philips PW Diffractometer (Philips, Eindhoven, The Netherlands) (beam 173 mm). Monochromatic Cu $K\alpha_1$ radiation ($\lambda = 1.5406$ Å) was obtained with a Ni filtration and a system of diverging and scattering slides of 1°, 0.2 mm and 1°, respectively. The diffraction pattern was measured with a voltage of 40 kV and a current of 32 mA in the region of $4° < 2\theta < 60°$ in a step scan mode of 0.02° every second.

3. Results and discussion

As part of the design an oral dosage form based on a ternary solid dispersion of itraconazole – PVPVA 64 – Myrj 52, the phase behavior of the drug in the system was investigated. Preliminary experiments had shown aqueous solubility improvement of itraconazole in the presence of either PVPVA64 or Myrj 52. Fig. 1 shows the reversing heat flow curves of ternary systems in which the ratio of polymer towards surfactant is 9:1. The value of the T_g varies only slightly from 74.1 °C in the case of 4.8% of itraconazole to 71.4 °C in the case of 23% of itraconazole. The same observations were made for the ternary systems with a polymer to surfactant ratio of 4:1 and variable amounts of itraconazole. At the same time an endothermic peak in the total heat flow signals was observed (data not shown). XRD confirmed that this peak corresponded to a separate crystalline drug phase (Fig. 2). These observations were rather surprising since previous investigations showed a significant and concentration dependent change of the T_g in binary systems made up of PVPVA64 and itraconazole; complete miscibility was observed in the concentration range between 0 and 100% drug (Six et al., 2004). In order to explain the behavior of the ternary system, different binary dispersions were prepared and analyzed.

The DSC curves of solid dispersions, made up of PVP VA 64 and itraconazole using rotary solvent evaporation, show only one single T_g and no melting

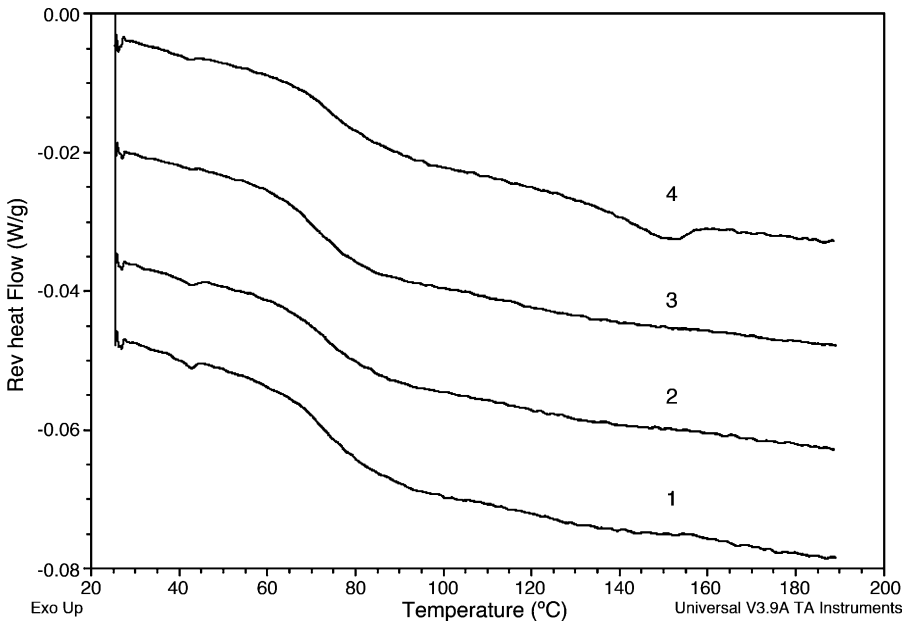

Fig. 1. Reversing heat flow curves of ternary solid dispersions. (1) PVP VA64 (85.7%); Myrj52 (9.5%); itraconazole (4.8%); (2) PVP VA64 (81.8%); Myrj52 (9.1%); itraconazole (9.1%); (3) PVP VA64 (75.0%); Myrj52 (8.3%); itraconazole (16.7%); (4) PVP VA64 (69.2%); Myrj52 (7.7%); itraconazole (23.1%).

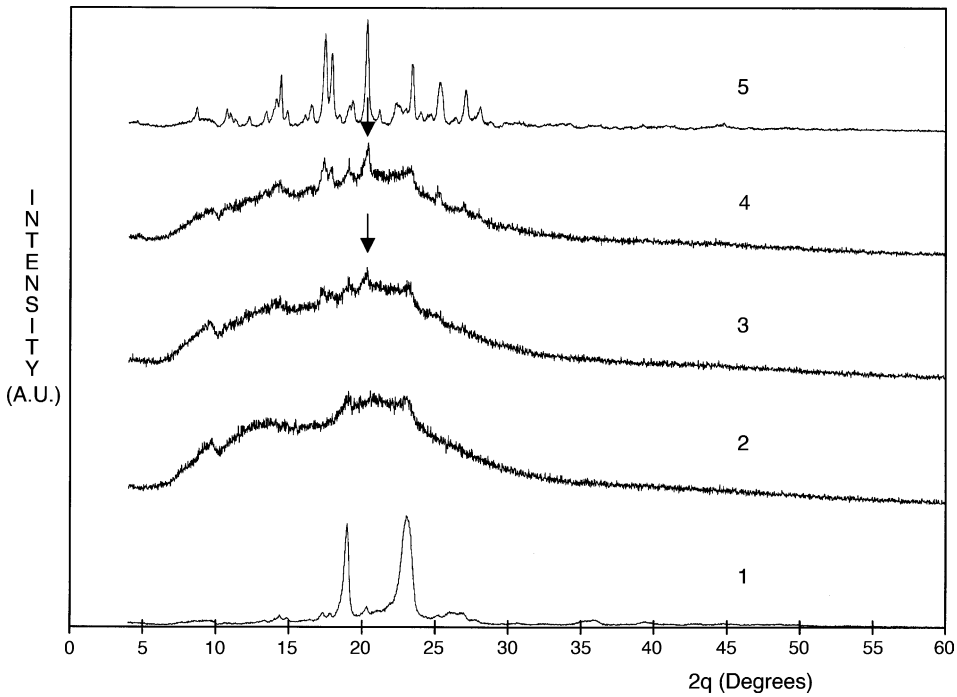

Fig. 2. X-ray powder diffraction curves of ternary solid dispersions. (1) pure Myrj 52; (2) PVP VA64 (76.2%); Myrj52 (19.0%); itraconazole (4.8%); (3) PVP VA64 (66.7%); Myrj52 (16.6%); itraconazole (16.7%); (4) PVP VA64 (61.5%); Myrj52 (15.4%); itraconazole (23.1%); (5) pure itraconazole.

peak or transition due to the presence of itraconazole mesophase could be observed (Six et al., 2001) (Fig. 3). As a matter of fact no difference could be observed between these systems and the ones prepared by hot-stage extrusion (Six et al., 2004). This proves that also in this binary system, itraconazole is molecularly dispersed in the polymer matrix. T_g values were found to increase with the amount of PVP VA64 in the solid dispersions and lie between that of glassy itraconazole and PVP VA64. Fig. 4 shows experimental T_g values and theoretical T_g values predicted by the Gordon–Taylor equation for binary mixtures (Gordon and Taylor, 1952). The correspondence between experimental and theoretical values points to volume additivity of PVP VA64 and itraconazole, suggesting equality in magnitude between homo and heteromolecular interactions. This conclusion agrees with the results of solid dispersions of PVP VA64 and itraconazole prepared by hot-stage extrusion (Six et al., 2004).

The miscibility of polymer and surfactant may also influence the behavior of the drug in ternary solid dispersions, because the surfactant may influence to a certain extent the mixing of the polymer and the drug (Serajuddin et al., 1990; Morris et al., 1992). In order to study the mixing behavior between PVPVA64 and Myrj 52, the samples were heated in the DSC from 25 to 200 °C, then cooled down and reheated. From the difference of the two heating DSC curves, not only information can be obtained about the miscibility of the two compounds after the preparation procedure using the rotovapor but it will also give additional information about heat induced mixing. Fig. 5 shows the difference of the T_g's in the two heating procedures. Both the T_g's of first heating and second heating of the Myrj 52 and PVP VA64 mixtures, decreased up to approximately 20–30% Myrj 52. Above 85% PVP VA64, the T_g in the second heating is higher than that of the first heating, mainly due to the presence of residual solvent during the first heating. A wide endothermic peak around 40 °C in the total heat flow signal of the first heating run confirms this (data not shown). Below 85% PVP VA64, T_g in the second heating is lower than in the first

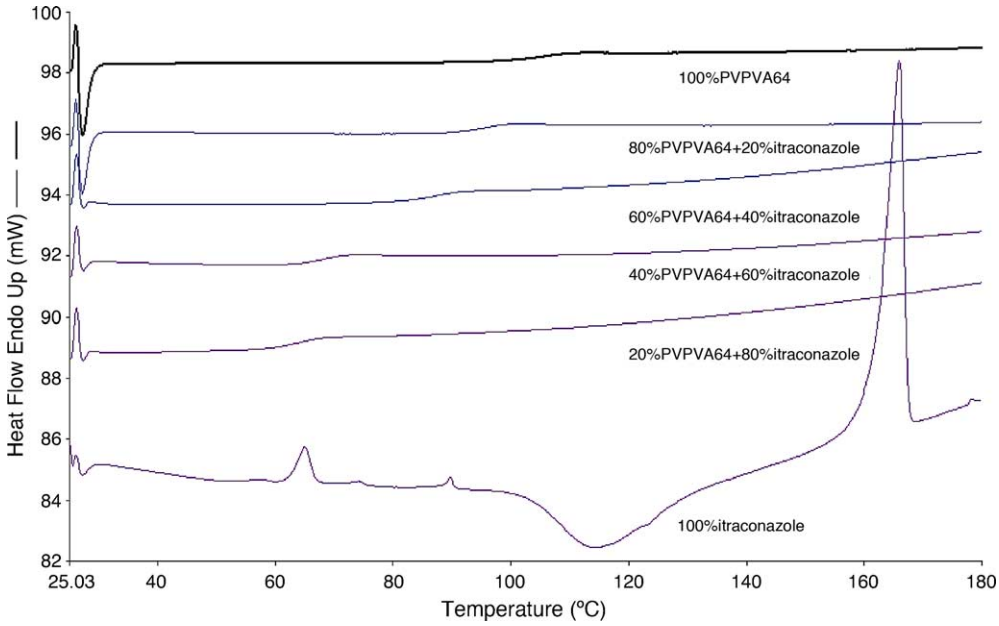

Fig. 3. DSC curves (power compensation DSC) of glassy itraconazole, the solid dispersions composed of different ratios of PVP VA64 and itraconazole, and 100% PVP VA64, respectively.

heating, pointing to further mixing of both compounds during heating and indicating that the manufacturing method used is not adequate to fully mix both compounds.

It can be seen in Fig. 6, that the DSC curves with 10% or a higher percent of Myrj 52 also show a small endotherm (see "Note 1" at the end of this section) approximately at the position of the melting point of Myrj 52. This seems to be in contradiction with the conclusion of miscibility up to approximately 20% Myrj52. However, the shape of this endotherm is different from the melting endotherm of pure Myrj 52. This signal may point to an impurity present in Myrj 52 that is not miscible with PVP VA64 and hence does

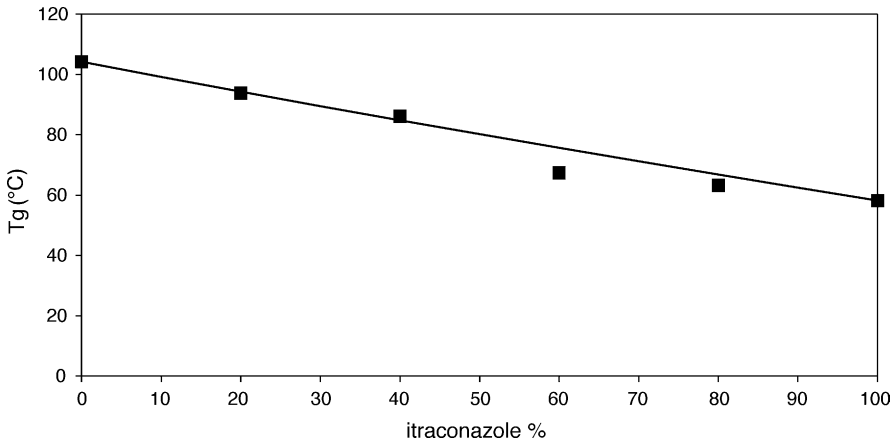

Fig. 4. Variation of T_g as a function of percent (w/w) of itraconazole in the solid dispersion with PVP VA64. The line represents theoretical values calculated with the Gordon–Taylor equation for the binary compatible mixtures; the solid cubes represent the experimental values.

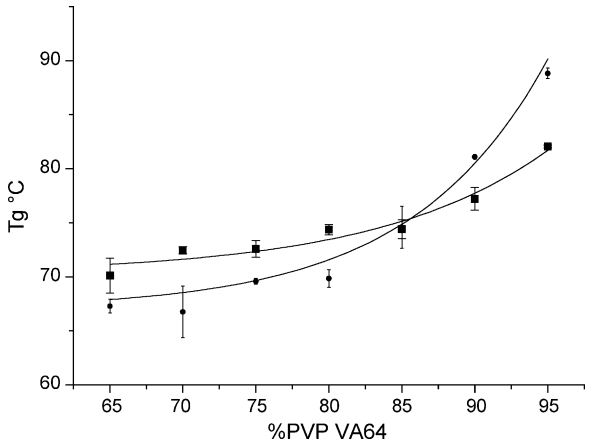

Fig. 5. T_g's of the first heating and second heating of PVP VA64 and Myrj 52 mixtures ((■) first heating, (●) second heating).

not contribute to lowering of the T_g of the polymer. When the Myrj 52 concentration is increased to 20%, we observed that the shape of this endotherm is similar to that of pure Myrj 52. Due to the synthetic procedure of Myrj 52 possible impurities of Myrj 52 are PEG 1500 and stearic acid. Mixtures of PEG 1500 or stearic acid and PVP VA64 were therefore prepared and analyzed. Similarly shaped endotherms (*see* "Note 1" at the end of this section) can be observed in the mixtures of stearic acid and PVP VA64 (Fig. 7) while no similar signals could be detected in the case of PEG 1500. Therefore, the small endothermic peak most likely corresponds to the presence of pure stearic acid in Myrj 52. XRD spectroscopy confirmed the DSC data and hence the presence of a separated Myrj 52 phase at 20% or higher percent of Myrj 52 (Fig. 8).

DSC analysis always showed two melting transitions in the binary systems made up of Myrj52 and itraconazole indicating that both compounds form a separate phase. The position of the melting peak of Myrj 52 remains largely unchanged, while that of itraconazole shifts depending on the concentration. This results in a phase diagram of the "eutectic" type (Fig. 9), indicating that no solid solution was obtained in this system. The heat of fusion of itraconazole and Myrj 52 in the solid dispersion was not significantly different from those of physical mixtures with the same composition.

The observations made with the binary systems help in explaining those of the ternary systems. They clearly indicate that the presence of Myrj 52 in the ternary solid dispersions is responsible for the marginal Tg shift with increasing drug concentration and the presence of a crystalline itraconazole phase. The values of the glass transition are indeed only marginally lower than those of the binary systems Myrj 52–PVPVA 64. The contribution of the drug to the T_g shift can thus be neglected. Although we showed that itraconazole forms a compatible system with PVPVA 64, the present results suggest

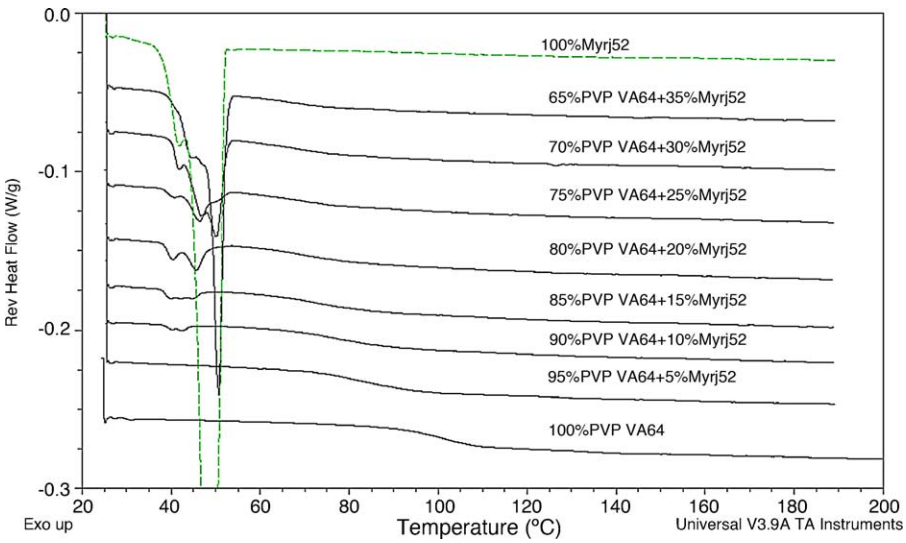

Fig. 6. Reversing heat flow curves of PVP VA64 and Myrj52 mixtures.

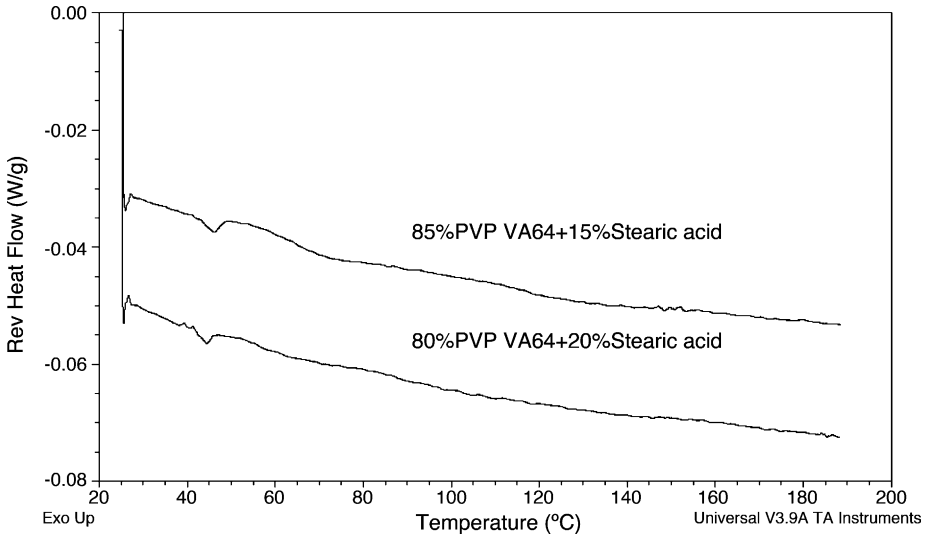

Fig. 7. Reversing heat flow curves of PVP VA64 and stearic acid mixtures.

that the drug is expelled from the polymer phase in the presence of Myrj 52.

Note 1. Melting phenomena should be studied in the total heat flow curves if one is using MTDSC for quantitative purposes. In this case we had to rely on the reversing heat flow signal due to a broad peak of solvent evaporation overlapping with that of melting in the total heat flow. The signal in the reversing heat flow was highly reproducible and was therefore used, but only qualitatively.

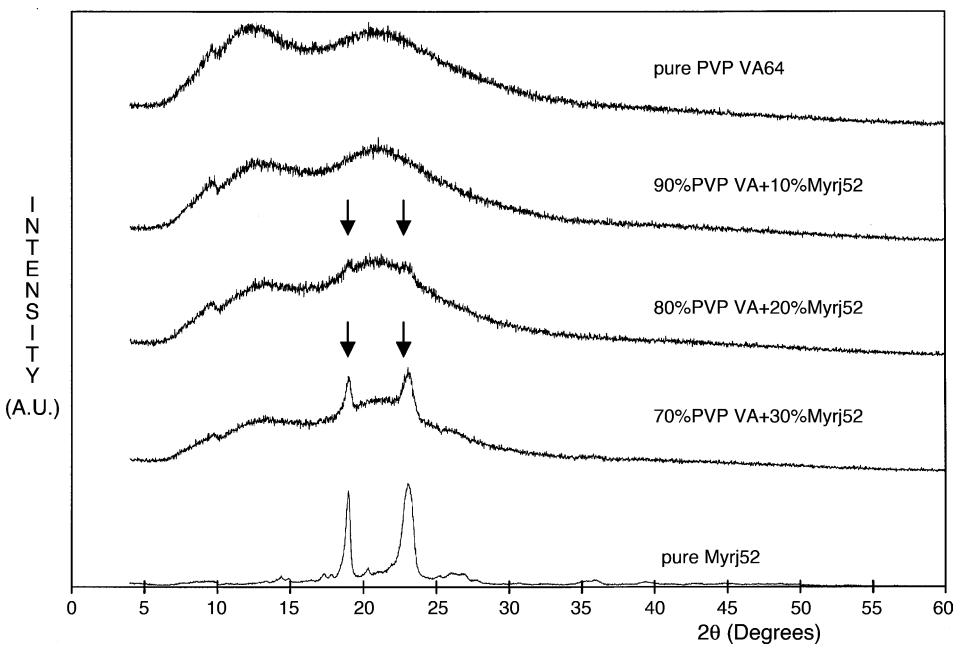

Fig. 8. X-ray powder diffraction curves of PVPVA64 and Myrj52 solid dispersions.

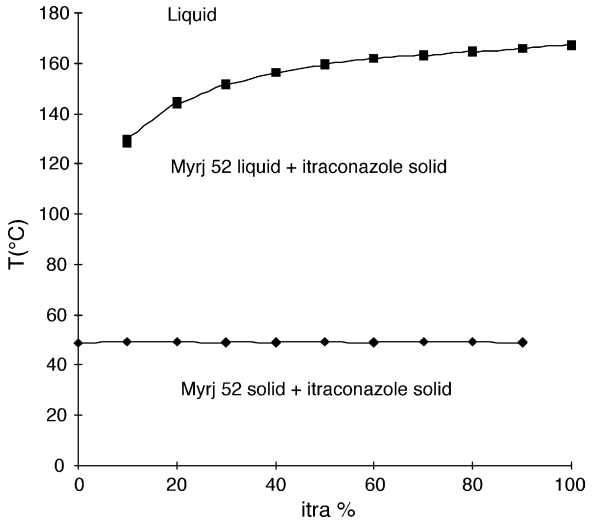

Fig. 9. Phase diagram of Myrj 52 and itraconazole solid dispersions.

4. Conclusion

Ternary solid dispersions made up of itraconazole, Myrj 52 and PVPVA 64 are not forming a complete molecular dispersion since a separate drug phase can be observed. Although we demonstrated that the preparation method used leads to a molecular dispersion of itraconazole in PVPVA 64, our study shows that Myrj 52 expels the drug from the polymer phase.

Overall, this paper points to the importance of performing compatibility studies in the light of the formulation of stable (ternary) solid dispersions.

References

Chiou, W.L., Riegelman, S., 1971. Parmaceutical applications of solid dispersion systems. J. Pharm. Sci. 60, 1281–1302.

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

Gordon, M., Taylor, J.S., 1952. Ideal copoplymers and the second-order transitions of synthetic rubbers. I. Non-crystalline copolymers. J. Appl. Chem. 2, 493–501.

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.

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

Morris, K.R., Knipp, G.T., Serajuddin, A.T.M., 1992. Structural properties of poly(ethylene glycol)–polysorbate 80 mixture, a solid dispersion vehicle. J. Pharm. Sci. 81, 1185–1188.

Motsumoto, T., Zografi, G., 1999. Physical properties of solid molecular dispersions of indomethacine with PVP and PVP VA in relation to indomethacine crystallization. Pharm. Res. 16, 1722–1728.

Report by Technology Catalysts International, 2002. Delivery of poorly soluble drugs. Technology and Business Review.

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

Serajuddin, A.T.M., Sheen, P.C., Augustine, M.A., 1990. Improved dissolution of a poorly water-soluble drug from solid dispersions in poly(ethylene glycol): polysorbae 80 mixtures. J. Pharm. Sci. 79, 463–464.

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

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

Yu-li, L., 2003. Relationships between the hydrophilic–lipophilic balance values of pharmaceutical excipients and their multidrug resistance modulating effect in Caco-2 cells and rat intestines. J. Control. Rel. 90, 37–48.