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THERMAL PROPERTIES OF HOT-STAGE EXTRUDATES OF ITRACONAZOLE AND EUDRAGIT E100
Phase separation and polymorphism

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Abstract

Solid dispersions of itraconazole and eudragit E100 were prepared by hot-stage extrusion. Analysis of the physical structure revealed the existence of different phases, depending on the manufacturing condition. Extrudates prepared at 453 K existed as a molecular dispersion of itraconazole in eudragit E100 when the drug concentration did not exceed ca. 13% mass/mass. At higher concentrations, a second phase consisting of pure glassy itraconazole emerged. In other dispersions prepared at 413 K, the second phase consisted of pure crystalline itraconazole. The difference can be attributed to the relation of the process-temperature to the melting point. Heating of both dispersions induced cold crystallization. Extrudates prepared at 453 K showed comparable behavior before and after milling, with the exception that unmilled dispersions with a drug load of ≥60% mass/mass recrystallized upon heating into a polymorphic modification of itraconazole (T_m=431 K). Upon further heating the polymorph recrystallized to the stable crystalline form (T_m=441 K).

Keywords: hot-stage extrusion, itraconazole, phase separation, solid dispersions

Introduction

Itraconazole is a potent antifungal drug of the triazole class with activity against histoplasmosis, blastomycosis and onychomycosis. The pharmacological mechanism is the same as that of its structural analogues ketoconazole and miconazole, which interfere with the synthesis of ergosterol of the fungal membrane by inhibition of 14 α-demethylase, a CYP 450 iso-enzyme [1]. Because of its very low aqueous solubility (S<1 μg mL^{-1}) and poor dissolution rate, itraconazole shows a large

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inter-individual difference in bioavailability after oral administration [2]. It is classified as a class II compound in the Biopharmaceutical Classification System [3].

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 a carrier, in some cases on the molecular level, together with the enhanced wettability and microenvironment created by the carrier can result in an increase in both solubility and dissolution rate. In solid dispersions, the physical state of the drug is often changed from the crystalline to the amorphous state. Although 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. However, the presence of the polymer is often adequate to prevent recrystallization. Recently, it was stated by Motsumoto and Zografi [4] that stabilization of amorphous indomethacin in PVP and PVPVA64 dispersions was mainly the consequence of drug-polymer interactions, while Van den Mooter *et al.* [5] clearly showed that the antiplasticizing effect of those polymers in dispersions with ketoconazole was the only stabilizing factor. A proper choice of polymer will increase the glass transition temperature of the binary system in a way that the molecular mobility becomes extremely low at room temperature.

In a previous paper we reported that glassy itraconazole showed good shelf life stability if stored at 40 K or more below its T_g (T_g=332.4 K) due to the extremely small molecular mobility [6]. In contrast to its structural analogues miconazole and ketoconazole, liquid itraconazole undergoes an isotropic liquid to chiral nematic mesophase transition at 363.0, followed by a second transition at 347.5 K which is caused by rotational restriction of the molecules. Finally, this structure is frozen into a glass at 332.4 K [7].

In order to overcome the solubility limited oral absorption of itraconazole several formulation strategies are currently being developed, including use of eudragit E100 as a carrier. The aim of the present study was to investigate the physical properties of solid dispersions of itraconazole and eudragit E100, prepared by hot-stage extrusion. More specifically, the influence of the processing temperature and milling of the extrudates was studied. The extrusion process has many advantages compared to frequently used methods such as coevaporation; the absence of organic solvents which makes the method more practical, economical and environmental friendly. The extrusion process is controlled by parameters such as feeding rate, screw rate, temperature setting and cooling rate, all of which can have a significant influence on the physical state and hence pharmaceutical performance of the solid dispersions.

Experimental

Materials and methods

Materials

Itraconazole (<355 μm) (purity more than 99%) and eudragit E100 (Röhm, Germany) were kindly donated by Janssen Pharmaceutica (Beerse, Belgium) and Röhm (Germany) respectively.

Hot-stage extrusion

Hot-stage extrusion was performed with a co-rotating twin screw extruder MP19 PH 25:1 (APV, UK). The screw-configuration consisted of two mixing zones and three transport zones over the whole barrel length; the screw rate was 300 rpm. Experiments were performed at two temperature settings. In the first, the zones were fixed at 323.0, 352.0, 443.0, 448.0, and 452.0 K from feeder to die, while in the second temperatures of 322.0, 376.0, 404.0, 406.0, and 413.0 K were employed. The extrudates were collected after cooling at ambient temperature on a conveyer belt. Samples were milled for 1 min with a laboratory-cutting mill (Kika, Germany) and sieved to exclude particles >355 μm.

All samples were stored in a desiccator at room temperature and analyzed within 3 weeks in order to avoid thermodynamic instability.

Modulated temperature DSC (MTDSC)

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 the Thermal Solutions software (TA Instruments, Leatherhead, UK). Dry helium at a flow rate of 40 mL min^{-1} was used as the purge gas through the DSC cell and 150 mL min^{-1} of nitrogen was used through the RCS unit. TA Instruments (Leatherhead, UK) aluminum open pans were used for all calorimetric studies; the mass of each empty sample pan was matched to the mass of the empty reference pan within ±0.1 mg.

The amplitude used was 0.212 K, the period 40 s and the underlying heat rate 2 K min^{-1} [8].

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 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 reference value was less than 0.5 K for temperature measurement, less than 0.1 for enthalpy measurement and less than 0.7% for measurement of the heat capacity at 329.8 K.

Hot-stage microscopy

Hot-stage microscopy was performed with an Olympus BX60 polarizing optical microscope equipped with a LINKAM THMS600 hot stage and a LINKAM TMS93 programmable temperature-controller. Samples were heated at 2 K min^{-1} from room temperature to 373.0 K.

Powder X-ray diffraction

Powder X-ray diffraction was performed with a Philips PW Diffractometer (beam 173 mm). Monochromatic CuK_{α_1} radiation (λ=1.5406 Å) was obtained with a Ni fil-

tration and a system of diverging, receiving and scattering slides of 1°, 0.2 mm and 1° respectively. The diffraction pattern was measured with a voltage of 45 kV and a current of 20 mA in the region of $4° < 2\theta < 65°$ in a step scan mode of 0.2° every second.

Preparation of glassy itraconazole

Glassy itraconazole was prepared by melting crystalline itraconazole on an oil bath of 453 K and cooling of in ice water until room temperature. Glassy itraconazole was milled and sieved (<355 μm) and the physico-chemical properties were examined with MTDSC. Glassy itraconazole is stored in a desiccator at room temperature and dissolution is performed within 1 week.

Preparation of physical mixtures

Physical mixtures were prepared by mixing itraconazole and eudragit E100 in a mortar for 5 min and sieved (355 μm).

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 sine pepsin (USP 24) is used as dissolution medium at a temperature of 310.0 K and a paddle speed of 100 rpm. Powdered extrudates and physical mixtures (always containing 200 mg itraconazole) or pure glassy itraconazole was added to the dissolution medium all with a particle size smaller than 355 μm. 5 mL samples were taken and immediately replaced with fresh dissolution medium at 5, 10, 15, 30, 45, 60, 120, 180, 240 min, filtered with a Teflon filter of 0.45 μm (Schleicher & Schüll Rezist® 30/0.45 PTFE) whereby the first 2 mL were discarded, diluted with mobile phase (below) 1 to 10 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 sulphate 0.01 N (55:45; *v/v*) was used as mobile phase at a flow rate of 1.0 mL min^{-1}; 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

An increase in dissolution rate and solubility has been reported for several amorphous drugs [9]. From Fig. 1 it is clear that glassy itraconazole has a higher dissolution rate in aqueous medium compared to its crystalline modification.

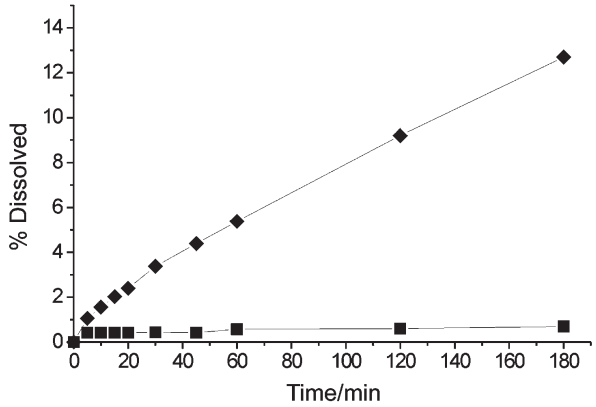

Fig. 1 Comparison of the dissolution of crystalline and glassy itraconazole in simulated gastric fluid; ◆ – glassy itraconazole, ■ – crystalline itraconazole

The pharmaceutical performance of the dispersions is evaluated by measuring their dissolution properties in simulated gastric fluid. In this acidic medium the solubility of itraconazole is favored, since it is a weak base with pK_a value of 3.4.

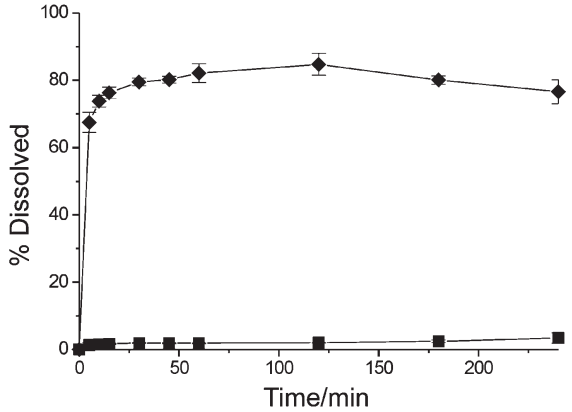

Fig. 2 Dissolution profiles of a 20% mass/mass solid dispersion and a physical mixture in simulated gastric fluid; ◆ – solid dispersion ■ – physical mixture

Figure 2 shows the dissolution of a dispersion containing 20% mass/mass of itraconazole prepared at 453.0 K and milled. Eighty percent of itraconazole was released within 30 min from this dispersion, a tremendous increase compared to the physical mixture. In the dispersion itraconazole is partially dissolved in the polymer (see below), while in the physical mixture it is present in the crystalline form. The results in Figs 1 and 2 indicate that not only the physicochemical state of the drug that is important in improving the dissolution properties, but also the carrier. The high dissolution rate of itraconazole from the dispersion results in part from the microenvironment and wettability created by eudragit E100.

In order to stabilize the high-energy form of itraconazole, we prepared several binary solid (molecular) dispersions by hot-stage extrusion using a co-rotating twin screw extruder. The extrudates were milled for a very short period of time to avoid heating of the samples, which could cause recrystallization of the glassy drug and flow of the polymer, which in time could lead to major changes in the properties of the solid dispersions. The thermodynamic properties of the milled and unmilled samples were examined by modulated temperature DSC (MTDSC). This technique provides the possibility of determining the T_g 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 while kinetically hindered phenomena, such as enthalpic relaxation, which are time and temperature dependent, appear in the non-reversing heat flow [10–12].

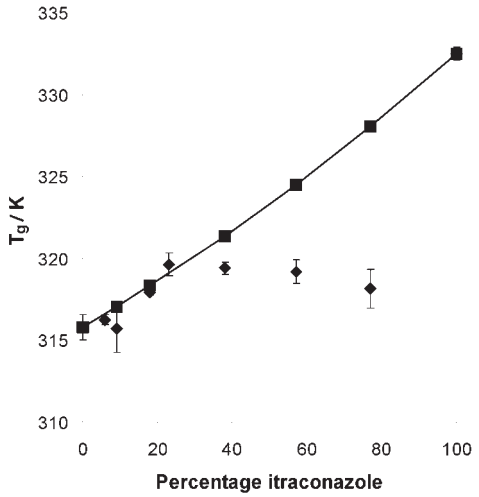

Fig. 3 Experimental (◆) and theoretical (■) values of T_g calculated by the Gordon–Taylor/Kelley–Bueche equation of itraconazole–eudragit E100 dispersions prepared at 453 K, followed by milling

Figure 3 shows the experimental and theoretical values of T_g of extrudates prepared at 453.0 K, followed by milling for 1 min using a laboratory scale mill. The theoretical values were calculated using the Gordon–Taylor/Kelly–Bueche equation [13, 14]:

$$T_{g_x} = \frac{T_{g_1} w_1 + T_{g_2} K w_2}{w_1 + K w_2}$$

in which T_{g_1} and T_{g_2} are the glass transition temperature of eudragit E100 (315.9 K) and itraconazole (332.4 K), respectively, w_1 and w_2 are the mass fractions of eudragit E100 and itraconazole in the dispersions, respectively, and K is a constant which was calculated using the Simha–Boyer rule [15]:

$$K \cong \frac{\rho_1 T_{g_1}}{\rho_2 T_{g_2}}$$

where ρ is the density of the amorphous solids.

The densities are 1.09 and 1.27 for Eudragit E100 and glassy itraconazole, respectively and K is calculated to be 0.82.

Although the Gordon–Taylor relationship was originally derived for compatible polymer blends, it has been used successfully for small organic molecules as well. Uptil approximately 20% mass/mass of itraconazole, the experimental values coincide with the theoretical ones but from that point on, the T_g remains more or less constant and deviates significantly from the theoretical values (Fig. 3). Given the structures of itraconazole and Eudragit E100, it is unlikely that this deviation is caused by drug-polymer interactions. Moreover, dispersions containing 15% mass/mass or higher of drug were opaque, in contrast to those with lower drug concentration which were completely transparent. This observation prompted us to investigate the possibility of phase separation in the dispersions. Powder X-ray diffraction experiments at room temperature indicated the absence of crystallinity in the dispersions up to 80% mass/mass of itraconazole (data not shown). Figure 4 shows the reversing heat flow signal of a dispersion containing 10 and 20% mass/mass of drug. At 10% mass/mass one single T_g was observed indicating phase miscibility, but from 20% mass/mass of drug on, the dispersions clearly show two T_g's, one of glassy itraconazole at 332.4 K and one originating from the drug–polymer mixture. The endothermic signal at 363.0 K corresponds to the transition from the chiral nematic mesophase to the isotropic liquid of pure glassy itraconazole [7]. Hot-stage microscopy confirmed the presence of liquid crystals in these dispersions, which appeared as a 'blurred Schlieren' texture. Further heating of the dispersions containing 20% mass/mass or more of itraconazole led to cold crystallisation into pure itraconazole (*m. p.* 441.2 K). Compared to pure glassy itraconazole, formulation of molecular dispersions with eudragit E100 protects the drug from recrystallization.

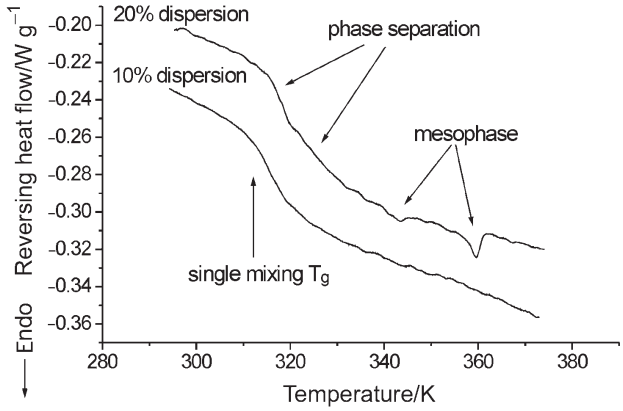

Fig. 4 Reversing heat flow of a 10 and 20% mass/mass solid dispersion prepared at 453 K, followed by milling

In order to further explore the phase separation, extrudates were also prepared at 413.0 K which is 28.0 K below the melting point of itraconazole. The same trends were observed as with dispersions prepared at 453.0 K, i.e. transparent dispersions up to approximately 15% mass/mass of drug. Up to 15% the physical properties of both preparation modes are complete identical in MTDSC and X-ray diffraction experiments (data not shown), above 15% opacity was observed. However, in contrast to the extrudates prepared at 453.0 K, powder X-ray diffraction experiments showed diffraction lines typical for crystalline itraconazole at ≥20% mass/mass of drug (Fig. 5). These dispersions also recrystallized upon heating (Fig. 6). Calculation of the initial crystallinity of the drug in these dispersions was based on the enthalpy of

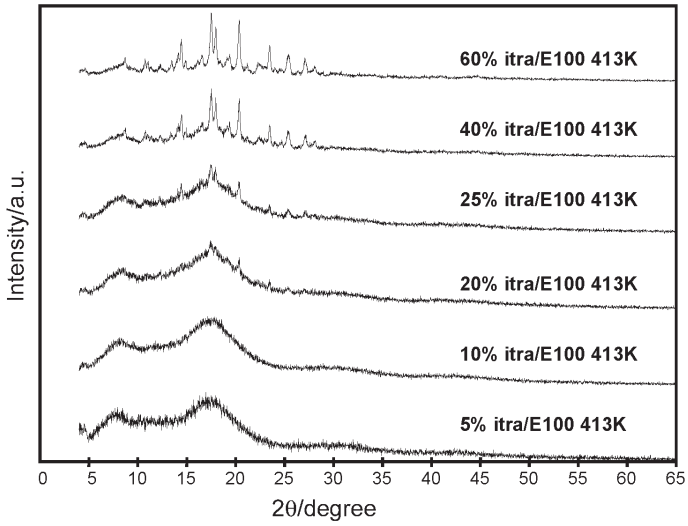

Fig. 5 Powder X-ray diffraction pattern of the dispersions extruded at 413 K

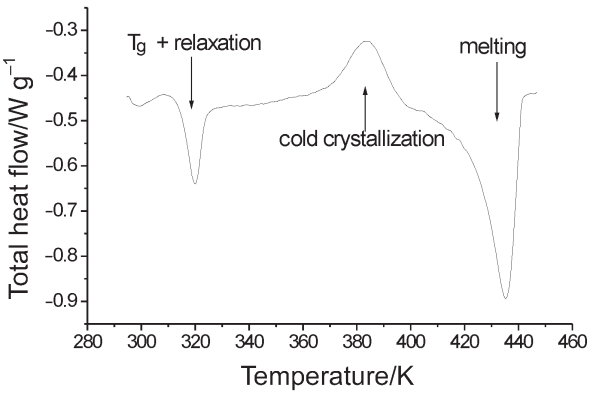

Fig. 6 Total heat flow of 25% dispersion prepared at 413 K and milled showing cold crystallization upon heating

fusion and recrystallization as described in detail elsewhere by Van den Mooter *et al.* [5]. Subtraction of the initial crystallinity from the total amount of drug gives a good estimate of the amount of itraconazole dissolved in the polymer at room temperature. The data are summarized in Table 1 and show that approximately 13% mass/mass of itraconazole is dissolved in eudragit E100.

Table 1 Calculated values of the amount of crystalline and dissolved itraconazole in the solid dispersions prepared at 413 K and milled

Percentage itraconazole in the dispersions mass/mass%	Enthalpy of fusion/ J g^{-1} (n=3)	Calculated initial crystallinity of itraconazole mass/mass%	Calculated amount itraconazole dissolved mass/mass%
5.0	0.0	0.0	5.0
10.0	0.0	0.0	10.0
20.0	5.5	6.5	13.5
25.0	9.7	11.4	13.6
40.0	23.0	27.0	13.0
60.0	39.7	46.8	13.2

In order to understand the influence of milling on the physical structure, extrudates were prepared at 453.0 K and immediately analyzed by DSC without milling. The results obtained were comparable with those of the milled samples, with phase separation occurring above drug concentrations of about 13–14% mass/mass, and recrystallization of drug upon heating in samples containing approximately 25% mass/mass of itraconazole. However, above 60% mass/mass of drug, the unmilled extrudates recrystallized upon heating into a polymorphic modification (431.3 K), which further recrystallized into the stable modification (Fig. 7). This second recrystallization is not seen in Fig. 7 due to

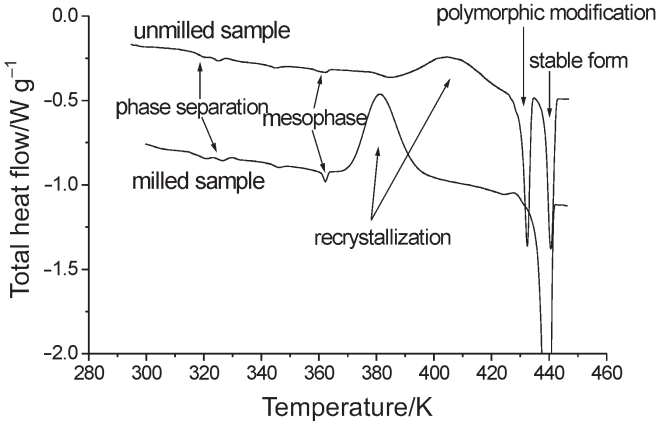

Fig. 7 DSC curve of a milled and unmilled dispersion extruded at 453 K containing 80% mass/mass of itraconazole

overlapping with the melting peak of the less stable form. By using optimized modulation parameters the melt can be resolved totally in the reversing heat flow, which enables a total separation of crystallization and melting (data not shown). When the samples are milled the formation of a less stable polymorph does not occur. It appears that the polymer molecules in the unmilled samples act as a barrier to the formation of the most stable form and together with the kinetic effect of recrystallization, the polymorph at 431.3 K is favored upon heating.

Conclusions

The results obtained in this study demonstrate the influence of processing on the physical structure of binary solid dispersions. Itraconazole was found to form a one-phase system consisting of a molecular dispersion (solid solution) of the drug in eudragit E100 at concentrations below about 13% mass/mass, irrespective of the mode of preparation.

Extrusion at 453.0 K of blends containing a drug load of more than 13% mass/mass produced a two-phase system consisting of a molecular dispersion of itraconazole in eudragit E100 and a phase consisting of pure itraconazole showing its characteristic liquid crystalline structure (chiral nematic mesophase), frozen into the glassy state. A two-phase system was also observed in milled extrudates processed at 413.0 K having a drug load of more than 13% mass/mass. However, in this case the second phase consists of pure crystalline itraconazole. As well as the processing temperature, milling was found to have a significant influence on the physical structure of the binary solid dispersions. Indeed, unmilled dispersions extruded at 453.0 K with a drug load of 60% mass/mass or more showed cold crystallization into a polymorphic modification of itraconazole, which recrystallized into the stable crystalline modification upon further heating.

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