Identification of Phase Separation in Solid Dispersions of Itraconazole and Eudragit® E100 Using Microthermal Analysis

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Purpose. To evaluate the phase separation in itraconazole/Eudragit® E100 solid dispersions prepared by hot-stage extrusion.
Methods. Extrudates were prepared using a corotating twin-screw extruder at 180°C. Micro-TA was used to evaluate the phase separation, where the AFM mode is used to visualize the different phases and local thermal analysis (LTA) to characterize the different phases
Results. Itraconazole formed a homogeneous mixture with Eudragit® E100 with drug concentrations up to approximately 20%. Above this concentration, phase separation was observed. MTDSC revealed two T_gs and the mesophase of free glassy itraconazole. Performing micro-TA on the surface of these dispersions indicated an increase in sample roughness in the *z*-axis piezo signal, which could be an indication of free glassy itraconazole. However, thermal conductivity did not reveal differences between separate phases. Performing LTA, where only a small area (20×20 μm) is heated, showed two separate and mixed phases of itraconazole and Eudragit® E100. Tip penetration in itraconazole and Eudragit® E100 occurred at 332K and 383K respectively. The difference in tip penetration was explained in terms of the difference in fragility.
Conclusion. Micro-TA makes it possible to characterize separate phases of itraconazole and Eudragit® E100, thereby confirming the MTDSC results on phase separation.

KEY WORDS: itraconazole; solid dispersion; phase separation; microthermal analysis.

INTRODUCTION

The preparation of solid dispersions is a well-established technique for increasing the dissolution properties, and hence possibly the oral bioavailability, of poorly soluble drugs, particularly in class II of the biopharmaceutical classification system (1). An example of such a drug is itraconazole, a potent antifungal drug of the triazole group with very low aqueous solubility (<1 μg/ml) and a correspondingly poor dissolution profile and high permeability (P_{eff} 3.8×10^{-6} cm/s) (2). Solid dispersions have traditionally been prepared using melt-cooling or solvent evaporation techniques, each of which carries concomitant disadvantages. However, more recently there has been considerable interest in the use of melt extrusion technology (3,4), whereby the drug and carrier are heated to a softening temperature, and the material is extruded through a small orifice, after which it may be ground and incorporated into a range of dosage forms. The approach is of interest because of the comparatively low temperatures involved and the high degree of control that may be applied during the manufacturing process.

A number of explanations have been suggested for the observed increase in dissolution rate, including improved wettability, solubilization in the concentrated gel layer at the dispersion/water interface, and release of discrete particles into the dissolution medium (5); however, irrespective of the mechanism involved, it is essential to understand the nature of the distribution of the drug in a carrier in order to facilitate rational formulation of the dosage form. In this investigation we describe the novel use of microthermal analysis (μ-TA) in conjunction with differential scanning calorimetry as a means of studying the drug distribution and physical form within the dispersion matrix. This technique is a modification of conventional atomic force microscopy (AFM) in that the tip is replaced by a Wollaston wire thermistor the silver sheath of which has been etched off at the wire apex to leave the platinum core. This section of the wire will have a higher resistance than the remainder of the probe and hence may be heated in a controlled manner. The technique may be used in one of two principal applications. In the first instance, the sample may be scanned in the *xy* plane, and the temperature of the tip maintained constant, allowing spatial resolution of variations in thermal conductivity. Secondly, the method may be used in localized thermal analysis (LTA) mode in which the tip is heated, usually at 10–20 K/s, and either the heat flow from the probe or, more usually, the sensor position is measured as a function of temperature. This allows characterization of specific regions of a sample on a microscopic scale rather than averaging the response of several milligrams of material as is the case with DSC. More details of the technique and its applications in the pharmaceutical and polymer science fields may be found in a number of recent articles (6–8).

The aim of the present study was to investigate the phase separation of solid dispersions of itraconazole and Eudragit® E100, prepared by hot melt extrusion, using microthermal analysis in conjunction with modulated temperature and conventional DSC in order to evaluate the strengths and limitations of the approach as a novel means of studying solid dispersions.

MATERIALS AND METHODS

Materials

Itraconazole (<355 μm, purity more than 99%, T_g = 332.4K, T_m = 442K, MW = 705.64) and Eudragit® E100 (T_g = 315K) were kindly donated by Janssen Pharmaceutica (Beerse, Belgium) and Röhm (Germany), respectively.

Hot Stage Extrusion

Hot-stage extrusion was performed with a corotating 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 with the following temperature settings: the zones were fixed at 323.0, 352.0,

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443.0, 448.0, and 452.0K from feeder to die. 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), sieved to exclude particles >355 μm for MTDSC-analysis, and analyzed with MTA.

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

Differential Scanning Calorimetry (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 the Thermal Solutions software (TA Instruments, Leatherhead, UK). Dry helium at a flow rate of 40 ml/min was used as the purge gas through the DSC cell, and 150 ml/min 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 0.212K, the period 40 s, and the underlying heating rate 2 K/min. Samples were heated from 293K to 456K. Octadecane, benzoic acid, and indium standards were used to calibrate the DSC temperature scale; the 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.

Standard DSC measurements were carried out using a DSC-7 (Perkin Elmer, Norwalk, CT). Indium and octadecane were used to calibrate the temperature scale; enthalpic calibration was performed using indium. In order to calculate the activation energy, E_a, samples of itraconazole or Eudragit® E100 were heated at five different heating rates ranging from 0.5 to 20 K/min in conventional DSC mode, and the T_g determined from the discontinuity in the baseline.

Microthermal Analysis

The instrument used for this work was a TA Instrument μ-TA 2990 Micro Thermal Analyzer equipped with a topometrix scanning probe. The system was calibrated for temperature with nylon. The extruded samples were analyzed as such. Standard Z-piezo and conductivity images were obtained in contact mode at 400 μm/s and resolution of 300 with the probe held isothermally at 304K. Local thermal analysis data were obtained at 10 K/s from 223K to 453K.

RESULTS AND DISCUSSION

Initial visual inspection indicated that dispersions containing 15% w/w or higher of drug were opaque, in contrast to those with lower drug concentration, which were completely transparent. Similarly, powder X-ray diffraction studies indicated the absence of crystallinity in the dispersions up to 80% w/w of itraconazole (data not shown). These observations prompted investigation into the possibility of phase separation in the dispersions. Consequently, the physical properties of the milled and unmilled samples were further examined by modulated-temperature DSC (MTDSC) in order to examine the effects of dispersion preparation on the thermal behavior of the individual components; if phase separation is occurring, one would expect the thermal events of the two materials to be largely unchanged.

Figure 1 shows the reversing heat flow signal of a dispersion containing 10–20% w/w of drug. Comparison with previously published data (4) indicates that at 10% w/w a single T_g was observed indicating phase miscibility, but at drug loadings of 20% w/w of drug and higher, the dispersions show two T_gs, one of glassy itraconazole at 332.4K and one originating from the drug–polymer mixture at 319K. The T_g of Eudragit E100 (315K) can not be detected because of an overlap with the T_g of the mixing phase (319K). Phase separation is further evidenced by the endothermic signal at 363.0K corresponding to the transition from the chiral nematic mesophase to the isotropic liquid of pure glassy itraconazole (9); this transition can occur only when itraconazole is present as free glassy clusters. The exact miscibility and properties of itraconazole and Eudragit® E100 are the subject of a further communication (4); however, for the purposes of the present investigation, we may conclude that the MTDSC studies indicate that the system is at least partially phase separated at 20% w/w drug loading and above but appears to be miscible at the 10% w/w loading.

In order to visualize the phase separation and to characterize the different phases, μ-TA was performed on the polymer and drug alone. Figure 2 shows the topographic images of dispersions containing 10%, 40%, and 60% of itraconazole; the polymer alone showed no significant surface discontinuities under the equivalent scale of scrutiny. It is clear that with an increase in drug loading, an increase in surface roughness is observed, implying that the discontinuities may correspond to phase-separated drug. It was noted that the thermal conductivity followed the topography (i.e., the hot spots in conductivity corresponded to topographic features), and it was not possible to differentiate between the drug and polymer using this measurement. This effect has been previously noted (8) and is associated with changes in relief affecting the contact area between the probe and the sample, thus giving rise to changes in the amount of heat that is lost from the tip.

Localized thermal analysis (LTA) was then performed on the samples, whereby the sensor position is noted as a function of temperature. Figure 3 shows the LTAs of dispersions of Eudragit® E100 with different itraconazole concen-

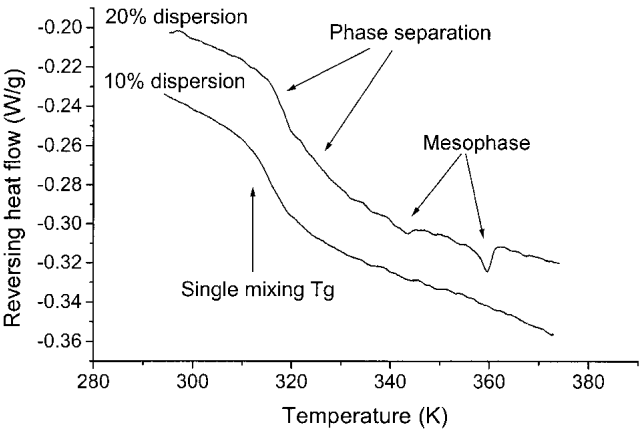

Fig. 1. Reversing heat flow of 10% and 20% dispersion in the glass transition region.

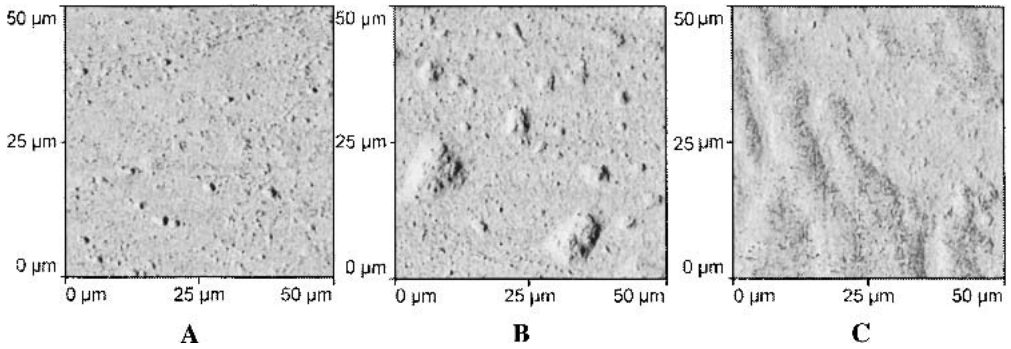

Fig. 2. Topographic images of (A) 10% dispersion, (B) 40% dispersion, and (C) 60% dispersion.

trations in comparison to pure compounds. These experiments were performed five times on different samples with reproducible results, although only one run is shown as an example in Fig. 3 for purposes of clarity. Line D represents pure glassy itraconazole and clearly shows a penetration of the tip around 333K, which coincides with the glass transition temperature of the drug (332.4K) (5), indicating that the increase in molecular mobility above T_g results in a decrease in viscosity and hence softening of the sample. This is in itself an interesting finding, as previous studies (10) have indicated that sensor indentation may occur at a considerably higher temperature than T_g, possibly because the high heating rates result in the macroscopic viscosity of the sample altering only sufficiently to allow penetration at temperatures up to 20K above the glass transition. However, line A shows the heating curve of pure Eudragit® E100, showing tip penetration to occur around 383K, although DSC studies show the T_g to occur around 318K. Clearly, therefore, the extent of discrepancy between the T_g and the softening point is sample dependent. One may intuitively suggest that this is a function of the molecular weight difference between the polymer and drug, although previous studies (10) have shown a considerable discrepancy with glassy indomethacin; hence, molecular weight alone is unlikely to explain the different profiles. A further possibility may lie in the fragility of the sample, this parameter reflecting the magnitude of deviation from Arrhenius behavior on supercooling liquids below T_g (11). A fragile system will display strong non-Arrhenius behavior above T_g and may be expected to undergo a marked change in viscosity when heated through the glass transition, whereas a strong system will show behavior approximating the Arrhenius equation and will exhibit a less marked change in molecular dynamics. In the context of the LTA observations, therefore, one may expect the itraconazole to show greater fragility than the polymer.

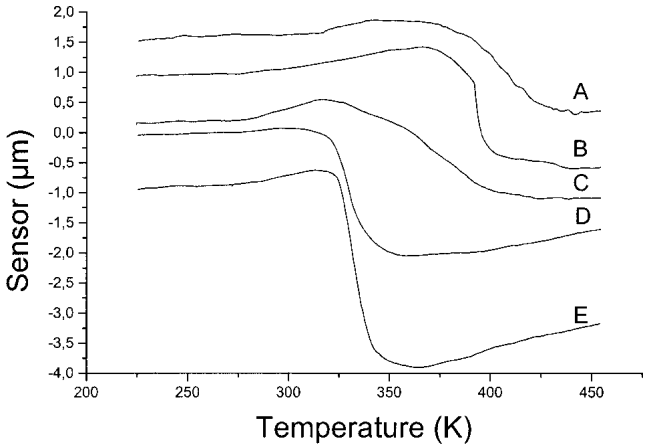

Fig. 3. Local thermal analysis (LTA) of (A) 100% Eudragit® E100, (B) 60% dispersion flat region, (C) 10% dispersion, (D) 100% glassy itraconazole, and (E) 60% dispersion rough region

The fragility may be quantified using the fragility index *m,* which may in turn be calculated via determination of the activation energy (E_a) at the glass transition temperature by measuring T_g as a function of scanning rate using the equation derived by Barton (12):

$$\ln q_+ = -\frac{E_a}{RT}$$

where q_+ is the heating rate, R the universal gas constant, and T the T_g measured at the corresponding heating rate. The activation energies for itraconazole and Eudragit® E100 were measured as 824.9 and 355.8 kJ/mol, respectively. The fragility (m) can therefore be calculated via (13):

$$m = E_a/(2{,}303\ R\ Tg)$$

with a high value indicating fragile behavior. The fragility of itraconazole and Eudragit® E100 was calculated to be 130.2 and 58.4, respectively, indicating that the drug and polymer are fragile and strong glass formers, respectively. Consequently, at the heating rates used for the MTA studies, the polymer would theoretically be expected to show a greater discrepancy in softening temperature with the DSC than would the drug, as is indeed observed in practice. We therefore suggest that fragility may be an important factor in determining the discrepancy between the measured softening and the T_g value, determined using DSC and MTDSC. Our results are supported by the observation that indomethacin, which has a reported fragility of 85 (11) and is thus a reasonably strong glass, also shows a marked difference in softening point compared to the T_g measured by DSC (10).

A further observation is that the tip appeared to rise during the heating process for the Eudragit® E100 sample (line A) but not for the drug (line D). This effect has been previously noted for HPMC/ibuprofen systems (14) and may be ascribed to a thermal expansivity of the polymer that is not seen to the same extent for the crystalline low-molecular-weight drug.

LTA studies on the solid dispersions indicated that in several cases intermediate softening responses were observed. In the case of the 10% w/w systems (line C), this may

be ascribed to the presence of a single homogeneous phase with one mixing T_g consistent with the LTA, which shows a single penetration at a temperature between that corresponding to itraconazole and Eudragit® E100. However, LTA responses of the dispersions containing 60% drug loading varied according to the chosen position on the sample. In some cases, as exemplified by line E, landing the tip on the top of a peak resulted in a sensor discontinuity that corresponded well to the drug alone. Similarly, landing the tip on flat areas often (but not always) resulted in profiles corresponding to the polymer (line B). However, in some cases intermediate profiles were observed. This has been previously reported (10) and may be interpreted on the basis of the scale of scrutiny of the LTA measurement, which, using the currently available apparatus, corresponds to an area of approximately 20×20 μm. If more than one structure is present within the region under study, the LTA profile may appear as an intermediate softening between the values of the individual components. This is an important limitation of the technique and must be considered in using the approach to study drug dispersions in matrices.

Overall, therefore, the study has demonstrated that in characterizing glassy materials by MTA, it is helpful to consider the fragility of that material when interpreting the data. In addition, the technique may be used to assess the thermal properties of individual components within mixes, but it is essential to consider the scale of scrutiny of the measurement with reference to the size of the regions under study.

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