Characterization of the Thermal Properties of Powder Particles Using Microthermal Analysis

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Received 30 October 2002; accepted December 4, 2002

Purpose. Microthermal analysis is a recently introduced thermoanalytical technique whereby discrete regions of complex samples may be scrutinized at micron or submicron resolution. In this investigation, the novel use of the technique to study individual powder particles is described.

Methods. A TA Instruments microthermal analyzer was used in local thermal analysis mode using a heating rate of 10°C/s. Powder samples of crystalline ibuprofen, spray-dried salbutamol sulphate, spray-dried and crystalline trehalose, and two polymorphic forms of indometacin were studied using differential scanning calorimetry as a supportive technique as appropriate.

Results. The ibuprofen showed a probe position discontinuity corresponding to the melting point of the material. Spray-dried salbutamol sulphate showed a discontinuity corresponding to decomposition but not to the glass transition, whereas both crystalline and amorphous trehalose showed a single discontinuity corresponding to physical collapse of the material. Studies using the α and γ forms of indometacin showed that the technique was able to distinguish between the two polymorphic forms.

Conclusion. The study suggests that micro-TA may be used to assess interparticulate composition and homogeneity.

KEY WORDS: calorimetry; ibuprofen; microthermal analysis; polymorph; powder; salbutamol sulphate; trehalose.

INTRODUCTION

There is a persistent need within the pharmaceutical field to characterize the physical and structural properties of powder batches, particularly in terms of issues such as polymorphic form and degree of crystallinity. A number of techniques are available for this purpose, including differential scanning calorimetry (DSC), microcalorimetry, X-ray diffraction, and Fourier transform infrared/Raman spectroscopy. However all these methods rely on assessing a mass of powder (usually in the range of 5–20 mg) and accepting the response as being a representative average of the properties of the individual powder particles. Although this is reasonable for homogeneous systems, the assumption becomes more tenuous when multicomponent (with reference to chemical or physical composition) powders are studied. For example, if a mix of polymorphs is found to be present in a sample (which may well occur if there is kinetic hindrance to conversion to the more stable form) or if a powder is considered to be partially amorphous, then it is not currently clear whether this indicates that all particles contain mixes of the two physical forms or whether individual particles may occur in one or other form.

In this investigation, we outlined proof-of-concept studies whereby we assess the utility of micro-thermal analysis (micro-TA) as a means of characterizing powder samples. This technique combines the thermal analysis principles of DSC with the high spatial resolution of scanning probe microscopy (1–3), albeit with lower resolution than the standard technique resulting from the size of the probe used. In essence, a thermal probe composed of a Wollaston wire (a length of fine platinum/rhodium alloy wire 3–5 μm in diameter coated by a sheath of silver approximately 75 μm thick) is prepared by bending the wire into a V-shape and etching away the silver sheath to form a pointed tip with a diameter in the region of 1 μm. The probe is attached to a conventional scanning probe microscope interfaced to a Wheatstone bridge circuit. The removal of the silver sheath results in a higher resistance at the tip than in the remainder of the wire; hence, on applying a voltage the tip may be heated in a controlled manner. A mirror attached to the back of the probe allows the position of the tip to be controlled and monitored in the same manner as for conventional scanning probe microscopy. The apparatus may be used in several modes; the temperature distribution of the sample may be assessed as a function of position simply by using the probe as a thermocouple, whereas the thermal conductivity may be (semiquantitatively) assessed by holding the probe at a constant temperature with reference to a remote probe and measuring the voltage required to maintain that temperature. The most widely applied use of the apparatus, at least for pharmaceutical systems, has been to apply the technique using localized thermal analysis (LTA) whereby the probe is heated rapidly to minimize thermal diffusion through the sample and the response of the region in immediate proximity to the tip measured as a function of temperature. This in turn may be performed in two modes. In the simplest case, the probe position may be measured as a function of temperature; hence, if a thermal event results in an alteration to the physical integrity of the surface this may be measured via the probe indentation. This approach is therefore essentially a combination of thermomechanical analysis and microindentation, whereby the penetration distance (P) by a probe of radius R under a force F is related to the shear modulus G by (4)

$$P^3R = F^2(3/16G)^2 \quad (1)$$

Hence, the change in modulus associated with either the glass transition or the melting of the sample will be detected by an abrupt change in penetration distance. Alternatively, the heat flow to the tip may be measured as a function of temperature with reference to the remote sensor, thereby allowing the instrument to be used as a scanning calorimeter.

The technique has attracted considerable interest in the polymer science (5–7) and, more recently, the pharmaceutical fields (8–10). The purpose of the current investigation was to explore the potential of using the technique to study powder samples, particularly in terms of using LTA experiments to perform scanning thermal analysis on discrete powder particles. The development of such an approach involves a series of technical and interpretive challenges that are critically as-

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0724-8741/03/0300-0500/0 © 2003 Plenum Publishing Corporation

sessed here; these include the need to fix the particles in a manner whereby movement is prevented without influencing the LTA response, the considerations pertaining to the high scanning rates involved, the accuracy and precision of the measurements in relation to the differences between components, and the interpretation of the data for complex thermal events.

MATERIALS AND METHODS

Samples of Nylon 6 (Goodfellows, Cambs, UK), ibuprofen (Sigma, mean particle size approximately 50 μm), salbutamol sulphate (Fisons Pharmaceuticals, Leics, UK, mean particle size approximately 10 μm), α,α-trehalose dihydrate (Pfanstiehl IL, mean particle size approximately 50 μm), and indomethacin (Sigma, Dorset, UK, mean particle size approximately 10 μm) were treated as follows. Nylon 66 and ibuprofen particles were used as received, whereas salbutamol sulphate and α,α-trehalose dihydrate was used as received and spray-dried using a Buchi spray drying apparatus, yielding particles with an approximate size of 10–20 μm. Indometacin was used as received (γ form) and prepared in the α form using the method of Andronis and Zografi (11).

The instrument used throughout was a TA Instruments (New Castle, DE) 2990 μTA, scanning at 10°C/s. The instrument was calibrated for temperature and displacement (in the X, Y, and Z axis) according to the manufacturers recommendations using Nylon 6 for the high-temperature calibrant; the recorded room temperature "kick-in point" was used as the other known temperature in the calibration procedure. Particles were attached to a microscope slide using one of two methods. For the α,α-trehalose dihydrate (in both crystalline and spray-dried forms), indometacin (α and γ forms) and the spray-dried salbutamol sulphate double-sided adhesive tape was used, whereas for the ibuprofen samples, a commercially available epoxy resin (Araldite Rapid, Bostik, Leics, UK) was used. Adherence of the powder sample was achieved, in the case of the samples fixed by double-sided adhesive tape, by fixing the tape to a clean glass slide. The powder sample was then lightly dusted over the exposed adhesive surface of the tape, with the resulting surface being compressed mildly with the back of a spatula before dragging a razor blade across the exposed surface. The slide was then shaken to remove loose powder and subjected to a jet of compressed air to remove weakly adhered particles. To affix the ibuprofen powder epoxy resin was prepared by mixing the resin component and the hardening agent of a commercially available preparation and leaving the resin to partially set. Once the resin had hardened sufficiently to support the weight of powder particles while still being adhesive enough to hold them securely in position, the ibuprofen powder was dusted over the adhesive surface. In this method compressed air alone was used as a means to remove loosely adhered particles, with no compression or other flattening of the sample surface.

DSC studies were conducted using a TA Instruments 2920 MTDSC operating in standard mode. The instrument was calibrated for each heating rate used with three temperature standards (n-decane, indium, tin), and a baseline performed with two empty pans of matched mass. The cell constant was calculated from the same calibration run as the indium temperature standard.

RESULTS

Nylon 6 and Ibuprofen Samples

Because the methodology for assessing the thermal properties of individual particles is novel, a study was conducted on a crystalline sample with a comparatively large particle size to ascertain the basic experimental and interpretive parameters associated with the measurement. Before that, however, it was considered necessary to establish the typical reproducibility that may be expected for a well-defined flat sample so as to ascertain the precision effects of measuring a particle as opposed to a continuous surface. To this effect, samples of Nylon 6 were measured five times, both before and after the other experimental observations, with a range of typical LTA responses shown in Fig. 1. The plots show sensor position as a function of temperature, with a raising of the probe corresponding to thermal expansion followed by a sharp discontinuity seen as the material immediately underneath the thermal probe melts. If one takes the extrapolated onset value as being the melting point, as shown in Fig. 1, the melting point is measured as 204 ± 2°C. It was interesting to note that a shoulder was seen on the indentation profile; this has been seen previously for crystalline indometacin (12) and may be related to the microcrystalline structure of the material resulting in the penetration involving a series of steps rather than a continuous process. It should also be noted that it was not possible in the present case to calculate rheological parameters using, for example, Eq. (1) as the spring constant of the probe was high in relation to the surface modulus.

Ibuprofen was selected as a typical crystalline drug powder, having a melting point of 77–78°C. Preliminary studies involving immobilization of this material using double-sided tape indicated difficulties associated with reproducibility. Given the relatively large mean particle diameter of the sample used (in the region of 50 μm) in comparison with the relatively small area of the particle in contact with the surface of the adhesive tape, it was suggested that the difficulty may be associated with sample movement caused by the contact of the probe with the particle surface. Consequently, an epoxy resin was used, which resulted in greatly improved reproducibility and did not exhibit significant softening during the heating process, almost certainly due to the high localization of heat on the particles caused by the rapid scanning rate.

Figure 2a shows the sensor position for the ibuprofen as a function of temperature. It was noted that the sensor position showed very good reproducibility with an extrapolated onset of 85 ± 1°C; this value is some 5°C higher than the accepted DSC value and almost certainly reflects the use of the extrapolated as opposed to absolute onset value. The heat flow response (not shown) was considerably more variable because of the heat dissemination pathways being sufficiently varied so as to render reproducibility poor. This effect will be exacerbated for particulate systems because of the complex topography of the samples. It was also noted that reproducibility of the sensor position measurements was maximized when the probe was landed at the vertical apex of the particle.

Previous studies using flat surfaces (12) demonstrated that scanning the sample after heating allowed the operator to estimate the scale of scrutiny of the thermal analysis by examining the crater left after melting or softening, with LTA studies on indometacin interrogating regions of circa 20 × 20

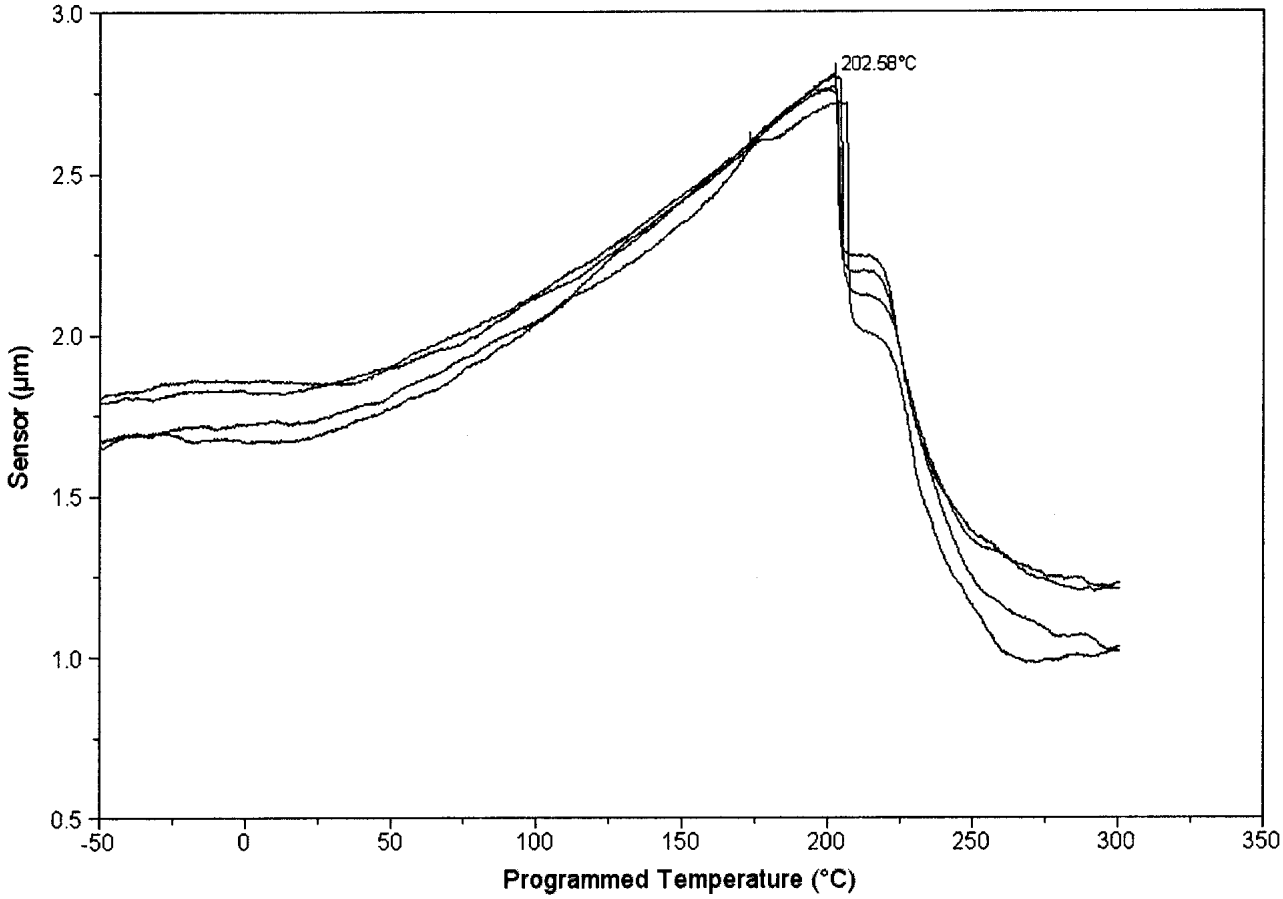

Fig. 1. Localized thermal analysis responses of Nylon 6, showing indentation of the probe corresponding to melting of the sample.

μm (12). This was found to be more difficult to perform for powder samples because of the rough topography of the powder particles (i.e., z-piezo limitation). However, in some instances it was possible to image the previously melted ibuprofen, as shown in Fig. 2b, demonstrating that the region of interrogation appears to be similar to that found for indometacin. However, this figure must be considered in the context of surfaces that are themselves larger in area than this value; for particles with a diameter less than 20 μm the scale of scrutiny will be equivalent to the size of the particle itself.

Spray-Dried Salbutamol Sulphate

As an example of an amorphous particulate material, spray-dried salbutamol sulphate, was then studied. This system undergoes a glass transition, a recrystallization exotherm, and a melt decomposition, as indicated in Fig. 3a. Consequently, there are three thermal events that may possibly be detected using the micro-TA technique. The samples were fixed to the microscope slide using double-sided adhesive tape, allowing the sample surface to be scanned as indicated in Fig. 3b. LTA studies were then performed, again using sensor position as the principle means of measurement due to the poor reproducibility seen for heat flow measurements. A sharp discontinuity was seen in the region of 170–180°C that corresponded well to the melt/decomposition temperature seen using DSC (Fig. 3c). It is interesting to note that a very similar response was noted when crystalline salbutamol sulphate was studied (data not shown); because this material shows only the melt-decomposition response (confirmed using thermogravimetric analysis), the similarity between the behavior of the two samples can be considered to be confirmation that the amorphous material is indeed undergoing this response rather than, for example, a late-onset softening. The study therefore indicates that in the present case, the glass transition, or more specifically associated softening, is not detected, nor is the recrystallization observed using DSC.

Amorphous and Crystalline α,α-Trehalose

Although many systems of pharmaceutical relevance show relatively straightforward thermal behavior, many materials exhibit complex responses that may be dependent on factors, such as particle size, heating rate, and initial physical state; hence, the ability of micro-TA to characterize one such system was explored. α,α-trehalose is a naturally occurring disaccharide that has been extensively studied as a freeze-drying excipient because of its ability to protect proteins on freezing and lyophilization. However, several studies have indicated that the material may undergo a series of thermal events on heating depending on the experimental conditions used and initial state of the trehalose. More specifically, crystalline trehalose dihydrate (the as received material) may either dehydrate to the anhydrous form or convert to the amorphous form depending on factors such as particle size and scanning rate, whereas amorphous trehalose may crystallize into the dihydrate, a mixed dihydrate/anhydrous form (the γ form), the anhydrous form, or may remain amorphous up to

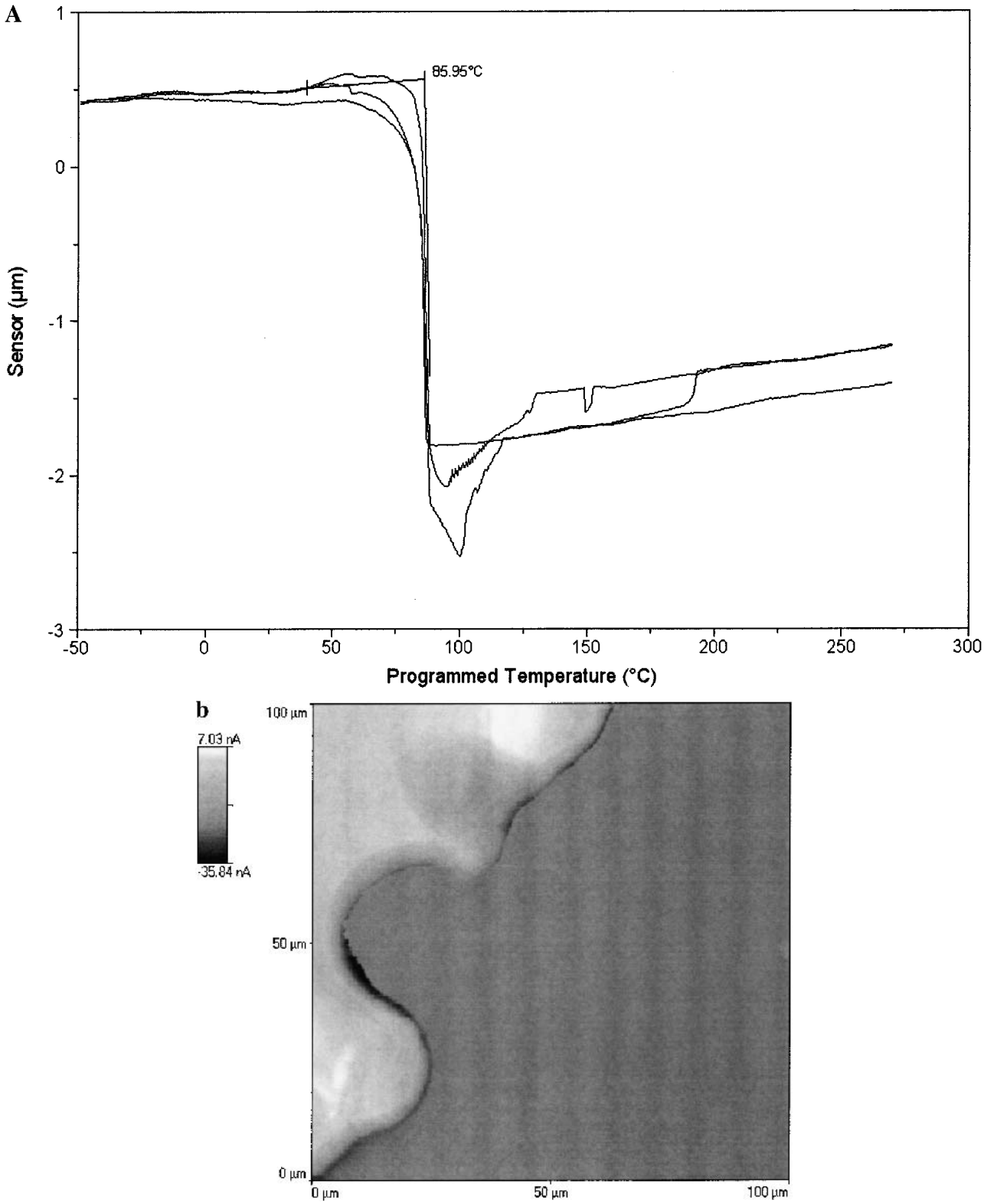

Fig. 2. (A) Localized thermal analysis response of ibuprofen particles, showing sensor position and heat flow as a function of temperature. (b) Topographic image of ibuprofen particle after melting.

decomposition, again depending on the experimental conditions (13–15). A comparison of the amorphous spray-dried material and the crystalline dihydrate therefore provides an opportunity to examine the performance of the micro-TA approach for a complex but reasonably well characterized material.

The spray-dried trehalose and the crystalline dihydrate were both fixed using double-sided adhesive tape. The re-

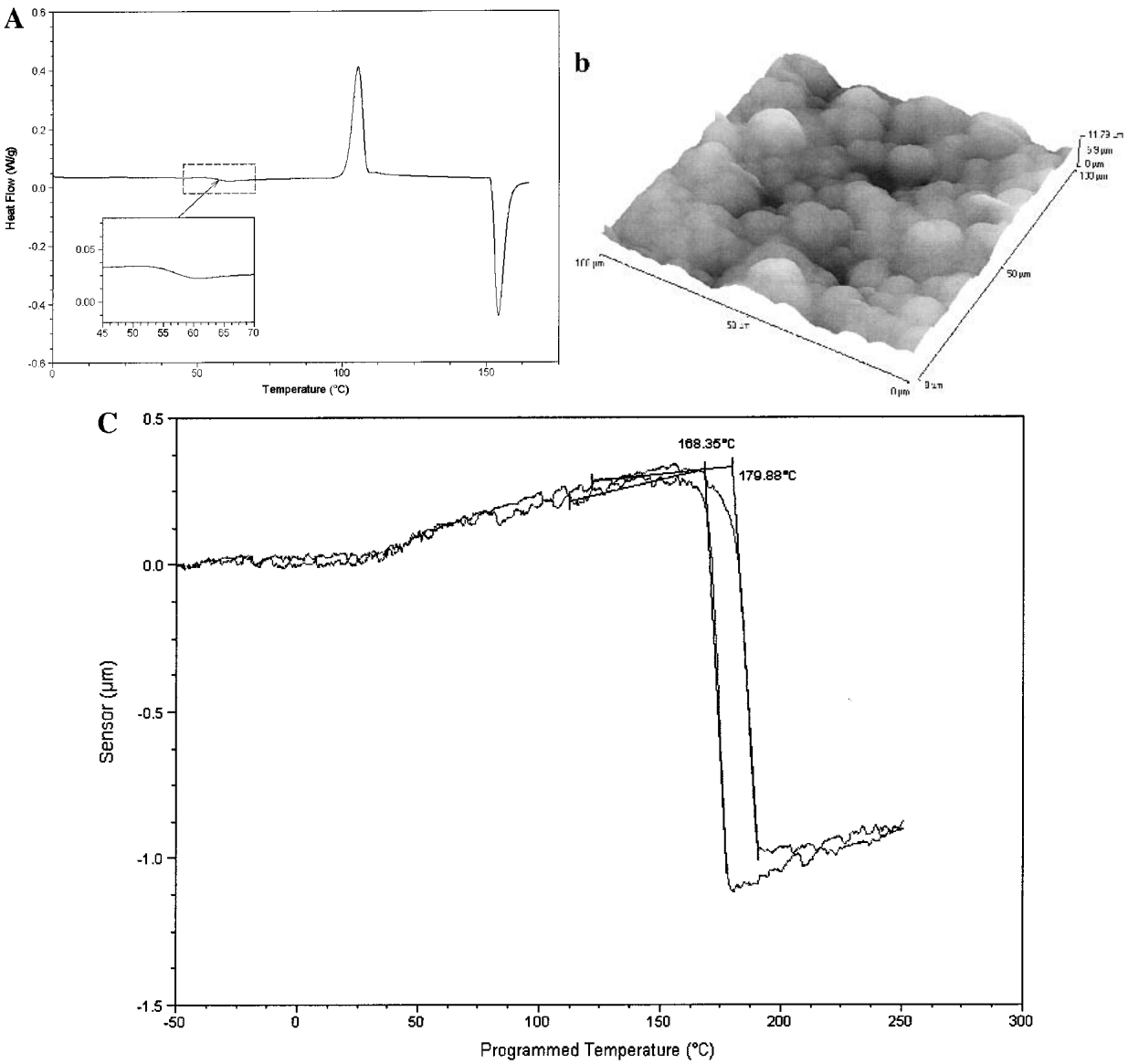

Fig. 3. (A) Differential scanning calorimetry response of spray-dried salbutamol sulphate (10°C/min) showing the glass transition (inset), recrystallization, and melt/decomposition. (b) Topographic image of fixed spray-dried salbutamol sulphate particles. (C) Localized thermal analysis responses of spray-dried salbutamol sulphate particles.

sponses of the amorphous and crystalline material are shown in Fig. 4a. Perhaps surprisingly, both showed very similar responses, with a single sharp reproducible discontinuity noted at 141°C for the spray-dried material. The crystalline material showed poorer reproducibility but exhibited transitions in the same temperature range of 150 ± 10°C. However, it was considered possible that the apparent discrepancy lay in the difference in heating rate between the DSC and micro-TA studies, with the latter using heating rates that were greater by almost two orders of magnitude. To this effect the DSC studies were repeated using a heating rate of 40°C/minute, the most rapid rate that could be used with confidence (Figure 4b). Based on previous investigations [13–15] it is reasonable to suggest that at this rate the amorphous material is recrystallizing into an intermediate partially hydrated form (the T_γ form [16]) that then dehydrates to the anhydrous conformation, while the crystalline material dehydrates directly to the anhydrate. Comparison with the micro-TA profile clearly indicates that the two sets of data (DSC and micro-TA) are not equivalent, almost certainly due to the higher scanning rates used for the microscopy technique. The presence of a single, well defined transition and the absence of any further melting responses for the amorphous sample would strongly indicate that at these heating rates the material in immediate proximity to the tip does not have time to undergo nucleation-growth and simply remains amorphous, whereupon collapse occurs. Similarly, we suggest that the equivalent region for the dihydrate undergoes dehydration to the amorphous form (as has been noted for small particle size fractions in earlier DSC studies [13]) and again collapses on further heating. This section of the study has therefore demonstrated the necessity to consider the high scanning rates used when interpreting micro-TA data.

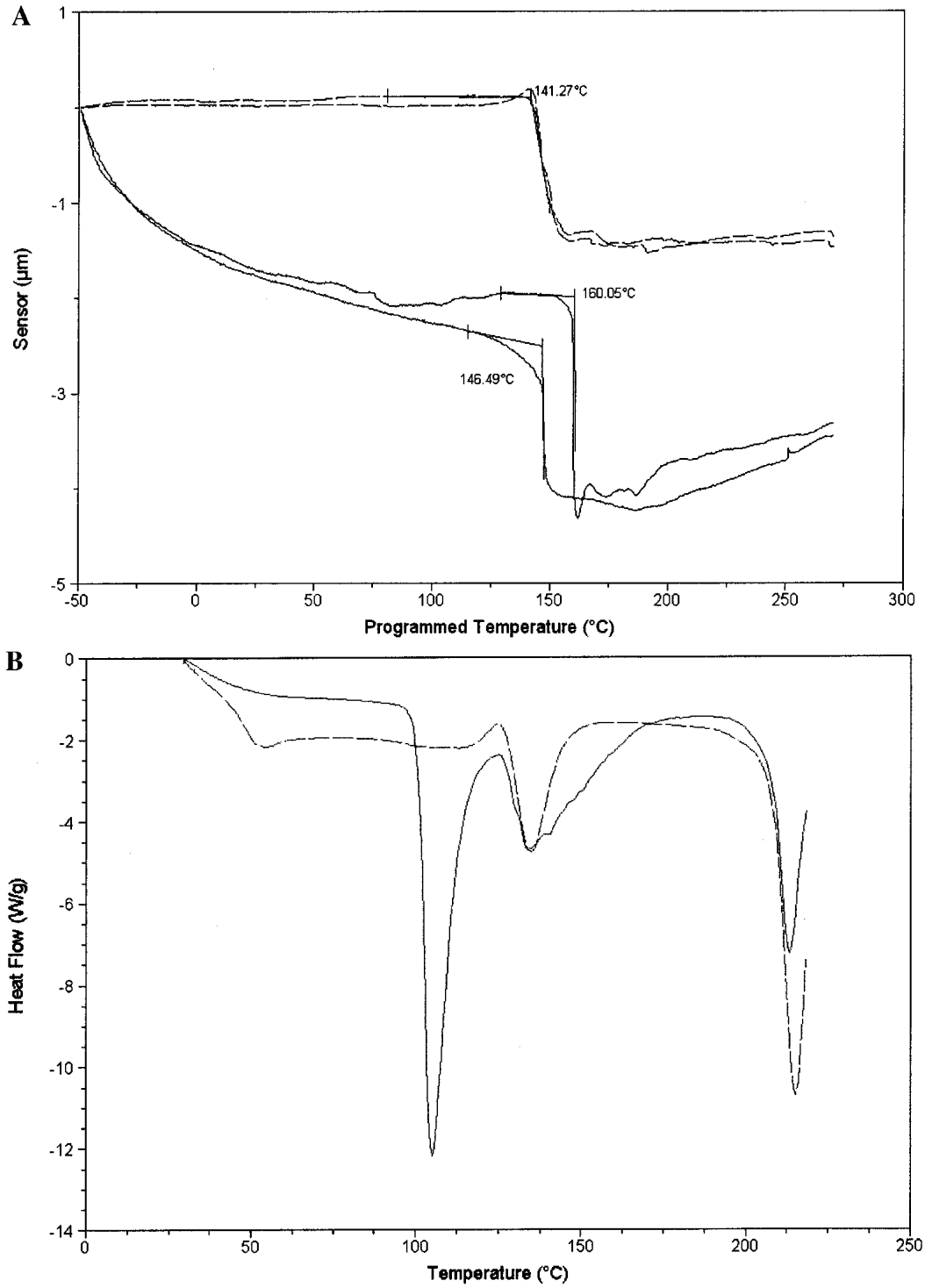

Fig. 4. (A) Localized thermal analysis response of spray-dried amorphous trehalose (dashed line) and crystalline trehalose dihydrate (solid line). (B) Differential scanning calorimetry response of spray-dried amorphous trehalose (dashed line) and crystalline trehalose dihydrate (solid line) at 40°C/min.

Characterization of Indometacin Polymorphs

A clear potential application of the approach is to distinguish between polymorphs within powder samples. It was noted that, because of the similarity of melting points in terms of the precision of the technique, appropriate sample fixing was essential. In this case double-sided adhesive tape was used; preliminary studies indicated an interaction between the indometacin and the commercial adhesive in that the former appeared to partially dissolve in the semi-hardened matrix.

The DSC responses for the two systems are shown in Fig. 5a, with the onset melting of the γ form seen at 160°C for sample as received and the melt/recrystallization of the α form seen at 153°C; this compares favorably with the literature values of 161°C and 155°C (11). Figure 5b shows the corresponding LTA responses for the two systems. The mean

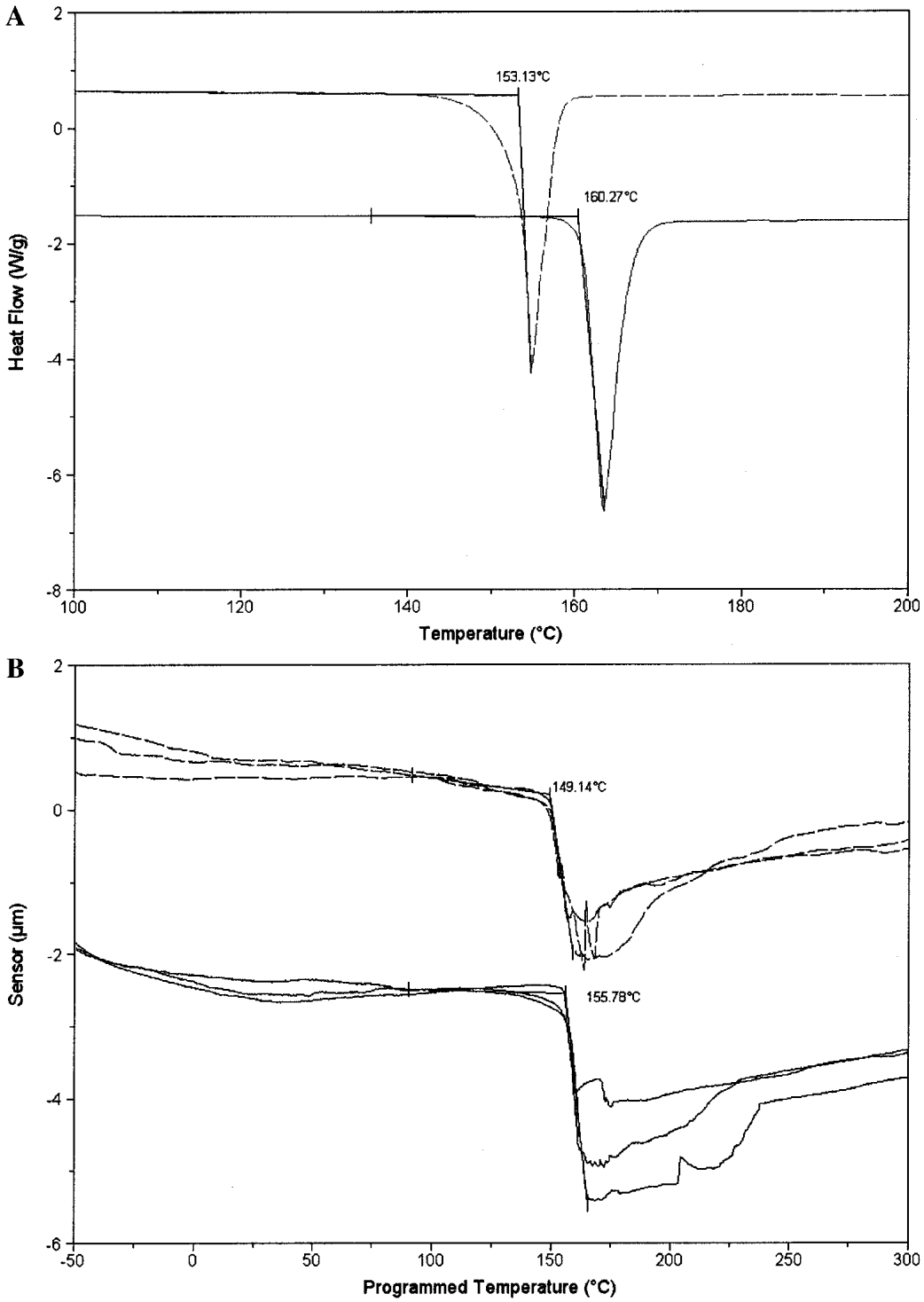

Fig. 5. (A) Differential scanning calorimetry responses of α (dashed line) and γ (solid line) indometacin. (B) Localized thermal analysis responses for α (dashed line) and γ (solid line) indometacin.

onset values were noted to be 155 ± 1°C and 149° ± 1°C, these being in reasonable agreement with the DSC data.

DISCUSSION

The study has provided proof-of-concept with regard to the use of micro-TA as a means of characterizing individual powder particles, highlighting both the strengths and limitations of the approach. In terms of strengths, micro-TA appears to provide a novel means of providing thermoanalytical data on specific regions of a sample in isolation from the remainder of the material, in this case an individual particle. In this respect it differs fundamentally from, for example, hot-stage microscopy whereby the sample in its entirety is heated, leading to difficulties when multicomponent systems are studied because of one material influencing the thermal behavior of another. However, the micro-TA technique is itself only semiquantitative at present, with DSC being the technique of choice for highly accurate thermal measure-

ments. This may be largely ascribed to the nature of the heating process for the former, whereby an unspecified volume of sample is scrutinized by a furnace that is extremely small in comparison to the sample (i.e., the reverse of the situation using DSC), thereby necessitating the use of high heating rates to minimize thermal diffusivity effects that would simply lead to (very) slow heating of the entire sample. The approach makes spatially specific heat flow measurement theoretically possible, resulting in the technique being used as a microscopic version of DSC. However, our experience thus far is that this approach is limited by issues with poor control of the heat flow pathway (exacerbated for irregularly shaped samples), rendering sensor position rather than heat flow the most reliable method of detecting thermal transitions in many cases. A further consideration, highlighted by the present study, is the necessity to fix mobile materials to prevent movement of the sensor due to gross sample shifting.

These general issues aside, the study has highlighted several features of the thermal characterization of individual particles. The measurement of simple melting processes appears to work well (provided the fixing is adequate), allowing discrimination between different materials or indeed different polymorphs. However, care is required in terms of the choice of transition temperature. Because melting is a first-order thermodynamic response, the transition will theoretically takes place over an infinitely narrow temperature range. In practice, many samples will show some degree of premelting due to the presence of surface defects (17), whereas the "lead" into the main transition may represent some degree of sample movement. Consequently, the values obtained are in reasonable but not exact agreement with DSC values and are probably best used for comparative purposes.

A related issue is the influence of the high heating rates used for micro-TA studies. This is a pertinent consideration in two respects. First, if one is dealing with a material that undergoes a series of transitions on heating when studied using DSC (salbutamol sulphate and trehalose being two such examples), then the kinetics of the process may be such that the micro-TA response reflects only those transitions that occur within the timescale of the experiment and which involve a marked change in sample modulus. Therefore, responses such as recrystallization may not be observed because of the experimental time being insufficient to allow nucleation and growth prior to the decomposition temperature being reached. A further implication for this is that the apparent glass transition values may be markedly different from those observed using DSC. Six et al. (18) have suggested that the difference between the values measured using DSC and micro-TA may be related to the fragility of the sample, with less fragile systems showing a greater discrepancy between the micro-TA and DSC values for Tg.

Overall, therefore, the technique does appear to present unique capability in terms of characterizing individual powder particles. However, it is essential to consider the type of transition that the material is likely to undergo and to include the high scanning speeds used for micro-TA when interpreting the behavior of samples with complex thermal profiles.

CONCLUSIONS

The study has outlined the potential use of micro-TA as a novel means of characterizing the thermal properties of individual powder particles. If particle fixing has been performed adequately, the method does allow identification and characterization based on melting behavior with reasonably good precision. The approach may also be used for samples showing more complex thermal behavior but in this case it is necessary to perform the data interpretation with care, particularly bearing in mind the possible effects of the high scanning speed used. Nevertheless, the method does appear to have considerable potential as a unique means by which the thermal properties of individual powder particles may be characterized.

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