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Research Paper

Study of Pharmaceutical Solid Dispersions by Microthermal Analysis

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Purpose. The main objective of the study was to determine the ability of microthermal analysis (μTA) to assess the crystallinity of the drug in two noncommercial pharmaceutical solid dispersions.
Methods. Pure substances, physical mixes, and solid dispersions were analyzed by μTA. The thermal values obtained by μTA were compared with data obtained by more conventional techniques like differential scanning calorimetry.
Results. μTA was able to detect the drug in the waxy matrix. The technique was capable of showing that relatively large amorphous drug domains (up to 70 μm) are formed during the solidification of the solid dispersion. These amorphous domains are thermodynamically unstable and can crystallize upon aging.
Conclusions. μTA was successfully applied to the physical characterization of solid dispersions. Local thermal analysis (LTA) offers a unique way to probe a selected area on the surface of the sample. It is capable of melting the drug locally without melting the lower melting point excipient. These results gave an understanding of the poor dissolution performance of these solid dispersions upon aging.

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

INTRODUCTION

Solid dispersions have been used to improve the solubility behavior of poorly soluble drugs (1–3). Making a solid dispersion essentially consists of dissolving the drug into a water-soluble excipient in the liquid state (molten or in solution) and solidifying the mix (by cooling or solvent removal). In the liquid state, the drug/excipient mixture is often one phase; however, upon solidification, the drug can exist in different solid states: a) as a solid solution (drug dissolved in crystalline excipient, α in Fig. 1B); b) as a phase separated crystalline state (eutectic mixture); or c) as a phase-separated amorphous state

Cases a and b are thermodynamically stable products, and the material of case c can evolve over storage conditions. The phase diagrams in Fig. 1 only represent the system at thermodynamic equilibrium, (cases a and b). With time, temperature, and humidity, the material of case c will evolve toward the material of case b.

One of the challenges for the characterization of solid dispersions is the assessment of the drug crystallinity, which dictates the stability and performance of the final product.

According to the phase diagram, all macrothermal analysis techniques will fail to detect the crystalline drug if the concentration is below eutectic concentration (C_E). Following path A (Fig. 1A), when the temperature reaches A1, the eutectic mixture melts with some excipient remaining solid. The drug is then a solute in a liquid solution. At A2, the remaining solid excipient melts, and the system becomes one liquid phase. Only above the eutectic concentration, the melt of the drug may be observed (path B). Figure 1B adds the complexity of having stable solid solutions (α and β) instead of pure materials.

Unfortunately, due to the low drug content frequently associated with solid dispersion, the commonly used powder X-ray diffraction (PXRD) may have difficulties detecting small percentages of crystalline drug. Moreover, distinguishing between amorphous drug (phase separation) and dissolved drug (solid solution) is not possible.

When phase separation occurs, the dissolution profile of the formulation is very sensitive to the size and crystallinity of the phase separated domains (cases b or c). It is well established that the particle size is a crucial parameter to control in conventional formulations. When the drug is phase separated in a solid dispersion formulation, it is even more important because the drug is usually poorly water soluble. The size and crystallinity of these domains will drive the dissolution kinetics once the excipient is dissolved. Sometimes, the dissolution of a freshly made solid dispersion gives satisfactory results because the drug is amorphous hence more soluble, but, after aging, the dissolution tends to decrease as the drug crystallizes and becomes less soluble.

Microthermal analysis (μTA) has recently been introduced as an investigation tool that combines microscopy and thermal analysis (4). Mounted on a three axis piezoelectric actuator, the μTA probe functions like an atomic force microscope probe in contact mode, allowing topology maps to be acquired. The resolution is much less than the atomic force

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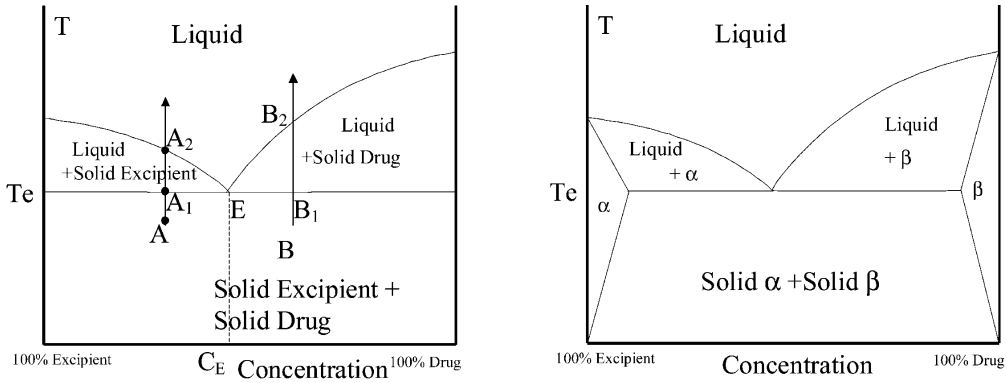
ABBREVIATIONS: LTA, local thermal analysis; MDSC, modulated differential scanning calorimetry; PEG, polyethylene glycol; PXRD, powder X-ray diffraction; TPGS, d-α tocopheryl polyethylene glycol 1000 succinate; μTA, microthermal analysis.



A) Simple Phase Diagram with Eutectic

B) Phase Diagram with Solid Solutions. α and β are the solid solution phases

Fig. 1. Possible eutectic phase diagrams of the excipient and the drug. Below eutectic concentration (path A), the sample melts at A1 with crystalline excipient remaining and becomes one liquid phase at A2. On path B, the melt of the crystalline drug can be detected.

microscope resolution because of the size of the tip (1 μm). The typical scanned surface is 100 × 100 μm. Because the dynamic range of the z actuator is about 20 μm, μTA requires relatively flat samples. When mapping the topology, the electrical power to maintain the tip at constant temperature can be monitored simultaneously as it passes on surface of the sample. This power value can be related to the thermal conductivity of the material under the probe. Once the topology and thermal conductivity images have been acquired, the user can further investigate specific areas of the images. The accuracy and low hysteresis of the piezo actuators insure a precise positioning of the μTA probe at the X-Y coordinates where local thermal analyses can be performed. In contact mode, a constant pressure is applied on the surface. Therefore, when the probe heats the sample under constant pressure, a local/micro thermomechanical analysis (μTMA) can be conducted. Because the power to heat the probe/sample can be recorded, a DSC-like signal can also be reported. These two signals constitute the local thermal analysis (LTA) feature of the μTA. One major difference with macrothermal analysis is the heating rate; in LTA, the heating rates range from 5 °C/s to 25 °C/s.

The first applications of μTA were done in the polymer field (5,6) but quickly thereafter, articles have been also published in the pharmaceutical field (5,7–10).

In this paper, micro thermal analysis is used to study pharmaceutical solid dispersions. Using the LTA feature of the μTA, one can try to melt the drug locally and quickly without melting the lower melting point excipient.

The two objectives of the study are:

- Detect whether the drug is amorphous or crystalline in the solid dispersion.
- Estimate the size of phase-separated domains.

MATERIALS AND METHODS

Materials

Drugs A and B are synthesized by GlaxoSmithKline Pharmaceuticals (King of Prussia, PA, USA). The polyethylene glycol waxes (PEG; Dow, Midland, MI & BASF, Mount Olive, NJ, USA), d-alpha tocopheryl polyethylene glycol 1000 succinate, (TPGS, Eastman, Kingsport, TN, USA), and Pluronic F68 (BASF) are used as received.

Two drug systems (A and B) are studied. The solid dispersions contain:

- A pure drug (A or B). Drug A melts at 159°C, and drug B melts at 114°C.
- A polyethylene glycol (PEG 4000 or PEG 6000) melting between 55°C and 60°C.
- A surfactant: either TPGS (MP ~40°C), or Pluronic F68 (MP ~52°C).

The compositions of the physical mixes and the solid dispersions are summarized in Table I.

The physical mixes are prepared by gently mixing together the drug and excipient powders using a mortar and pestle. The solid dispersions are prepared by melting the PEG + surfactant at 90°C and by adding the drug powder into the melt. After complete dissolution of the drug (clear liquid), the blend is allowed to solidify at room temperature.

Methods

Microthermal Analysis

The instrument is a μTA model 2990 from TA Instruments (NEW CASTLE, DE, USA). The powder samples are gently flattened using a spatula. The size of the rastered/scanned area is 100 μm × 100 μm. To map the thermal conductivity, the tip temperature is kept at 50°C and the electrical power required to maintain this temperature is plotted vs. the coordinates, X-Y, of the probe. Local thermal analysis (LTA) scans are performed from 30°C up to 250°C at 10 °C/s.

Table I. Summary of Formulation for the Different Samples

	System A	System B
Drug	15.0% (drug A)	16.8% (drug B)
PEG	76.5% (PEG 4000)	78.2% (PEG 6000)
Surfactant	8.5% (TPGS)	5.0% (Pluronic F68)

The thermal probe is typically calibrated in temperature using the melting points of at least two of the following materials: PEG 8000 (59°C), drug A (159°C), and drug B (114°C). Each sample is scanned for topology, thermal conductivity, and local thermal analysis.

RESULTS AND DISCUSSION

In the paper, the crosses and numbers on the maps represent the different locations chosen for the local thermal analysis.

Study of the Pure Products

The LTA curves (non-calibrated) of the pure products are displayed in Figs. 2, 3, and 4.

Polyethylene Glycol

The PEG powder is flattened using a spatula on the sample holder. Figure 2 gives an estimation of the good reproducibility of the LTA test for PEG 4000. The onset of the sensor position drop is associated with the penetration of the heating probe in the material when it melts. The penetration stops at about 4 μm from the surface where the V-shape geometry of the μTA probe prevents further progression into the material. This onset value is one of the values used to correct or calibrate the temperature axis.

Pure Drugs

Each of the two drug powders was gently pressed to form a relatively flat sample. Several consecutive LTAs at the same location were performed in order to detect a glass transition. These two drugs are known to form a glass after melt and cooling. Therefore, by re-scanning on the same location, the LTA of all subsequent runs after the first run will be an analysis of the amorphous drug.

For the drugs also, the sensor position curves are reproducible (Figs. 3 and 4) and give a clear indication of the softening temperatures of the material. If the material under the probe is crystalline, the softening is sharp and occurs at a temperature close to the DSC melting point (T_m), whereas when the material is amorphous, the softening is broader and appears at a much lower temperature than T_m. For calibration purposes, the onset of the penetration of the probe at the melting temperature is used in the software calibration routine. The LTA data shown for the rest of the study are temperature calibrated data.

The μTA glass transition temperature (T_g) is observed at higher temperature (about 20°C for drug A) than with the MDSC, whereas the melt temperatures measured by both techniques are comparable. The effect on T_g as a function of the cooling rate has been reported for a long time (11). The

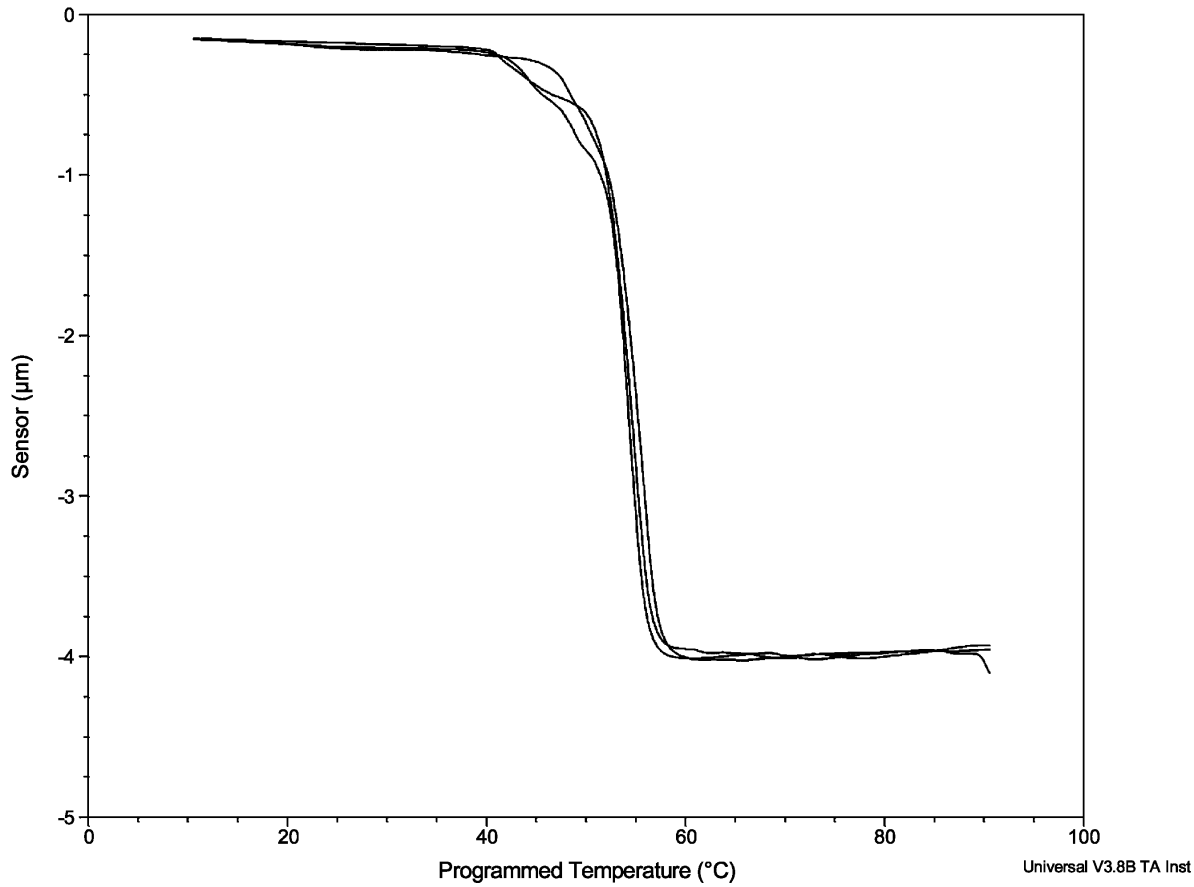


Fig. 2. Sensor position (μm) vs. temperature for three locations of PEG 4000. As the material melts, the probe sinks into the surface until the cold edges of the V-shaped probe prevent further penetration into the sample (~4 μm from the surface).

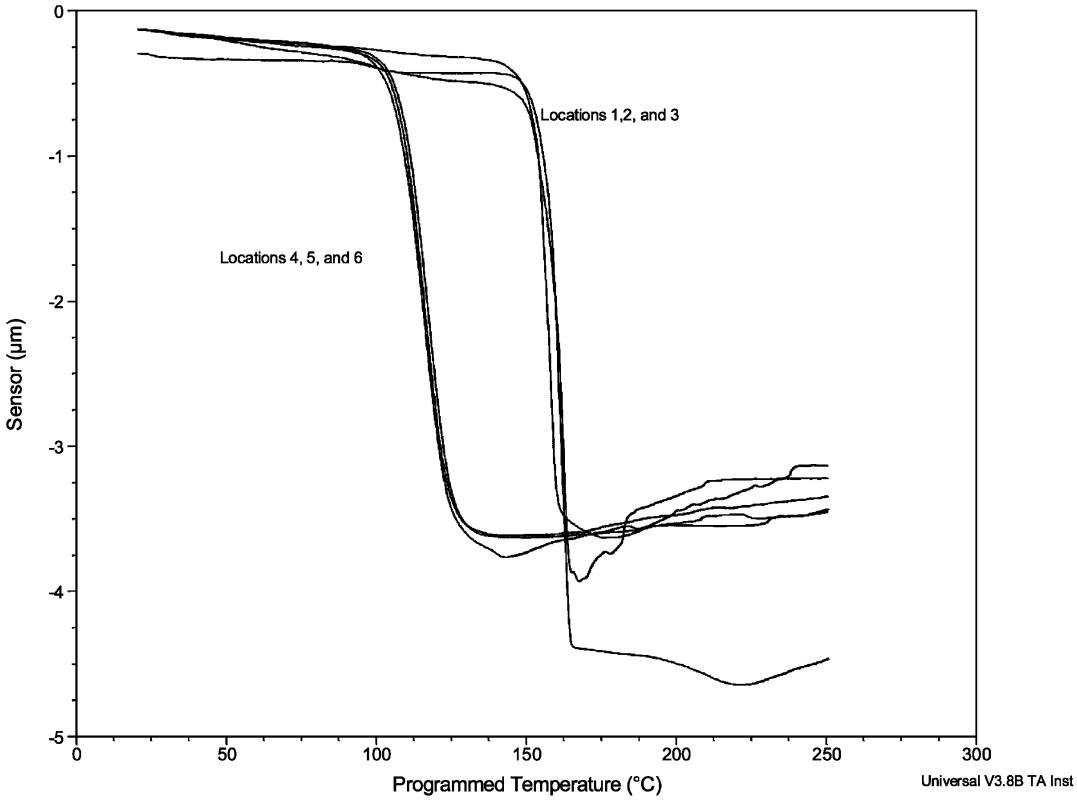


Fig. 3. Sensor position (μm) vs. temperature for the six locations in drug A sample. Locations 3 to 6 are identical. The step change at 100°C represents the penetration of the sensor as the drug softens at the glass transition. The step at 160°C corresponds to the melt.

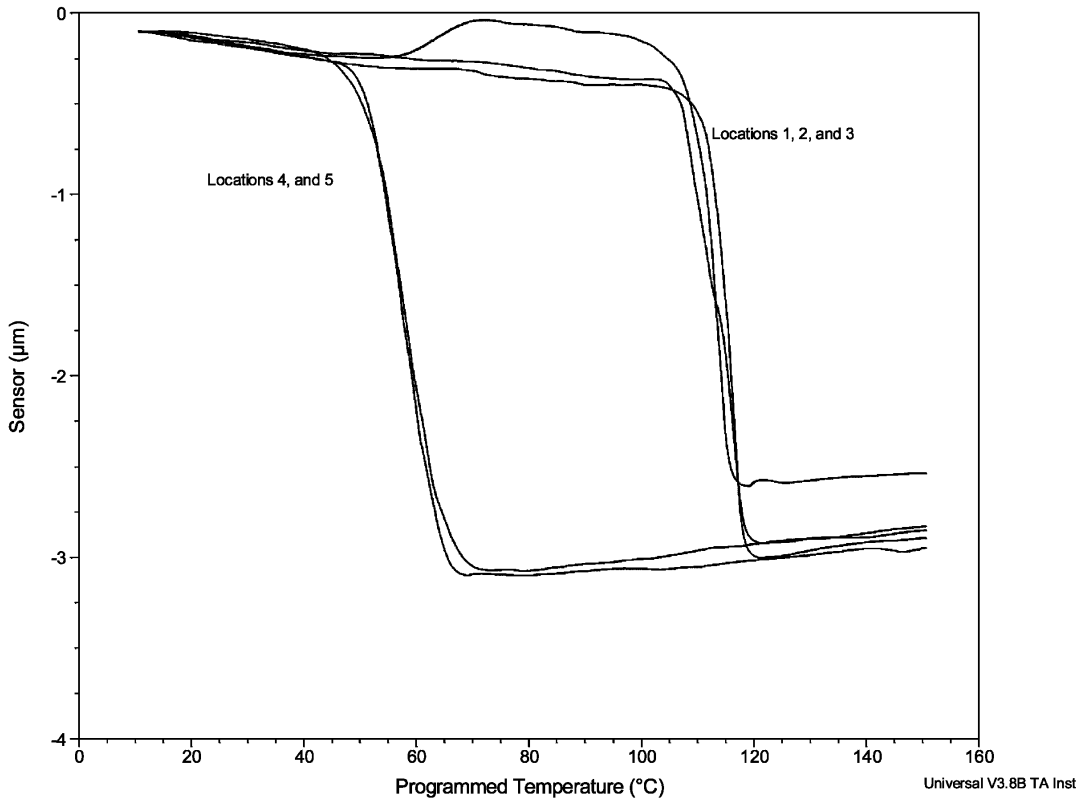


Fig. 4. Sensor position (μm) vs. temperature for the five locations in drug B sample. Locations 3 to 5 are identical. The step change at 40–50°C represents the penetration of the sensor as the drug softens at the glass transition. The step at 110°C corresponds to the melt.

μTA quenching rate is very high (25°C/s is 1500°C/min) when compared to MDSC (10 °C/min) and can certainly explain the 20°C difference. Furthermore, the T_g measured by LTA of a glass produced in-situ in the MDSC apparatus is comparable to the T_g observed by MDSC. Therefore, for this study, the potential glasses produced during the making of the solid dispersions have a glass transition at around 80°C for drug A and at around 50°C for drug B.

Study of Physical Mixes

System A

The powder of system A is gently flattened directly on the specimen holder of the μTA stage. The topology and thermal conductivity of the surface are shown in Figs. 5a and 5B. Four locations have been chosen for LTA (Fig. 5C). Location 1 illustrates one of the topological limitations of the detection in the Z direction. The piezo element used to accurately position the probe in the Z direction has a magnitude of 20 μm. In Fig. 5, obviously, location 1 is out of reach for the probe as shown by a flat LTA curve. Locations 2 and 3 have a softening offset at around 65°C and are probably made of PEG. Location 4 melts at 135°C and is probably the drug.

The melt of the drug in the physical mix occurs at a lower temperature than in the pure substance (159°C). As demonstrated by the final plastic deformation (flat surface), PEG has melted and has flowed during the sample preparation. Therefore, during the mixing process and the flattening of the sample, drug-excipient interactions can be expected. The phase diagram suggests that, locally (Fig. 1A, path B), the melting temperature of the drug can be lowered.

System B

The powder of system B is gently flattened on the specimen holder of the μTA stage. The topology and thermal conductivity of the surface are shown in Figs. 6A and 6B. Six locations have been chosen for LTA (Fig. 6C).

The colors of locations 1, 2, and 3 are similar in topology (Fig. 6A) but contrasted in thermal conductivity (Fig. 6B). This suggests that the area 1-2-3 is relatively flat but is made of different materials. The LTA confirms this hypothesis; loca-

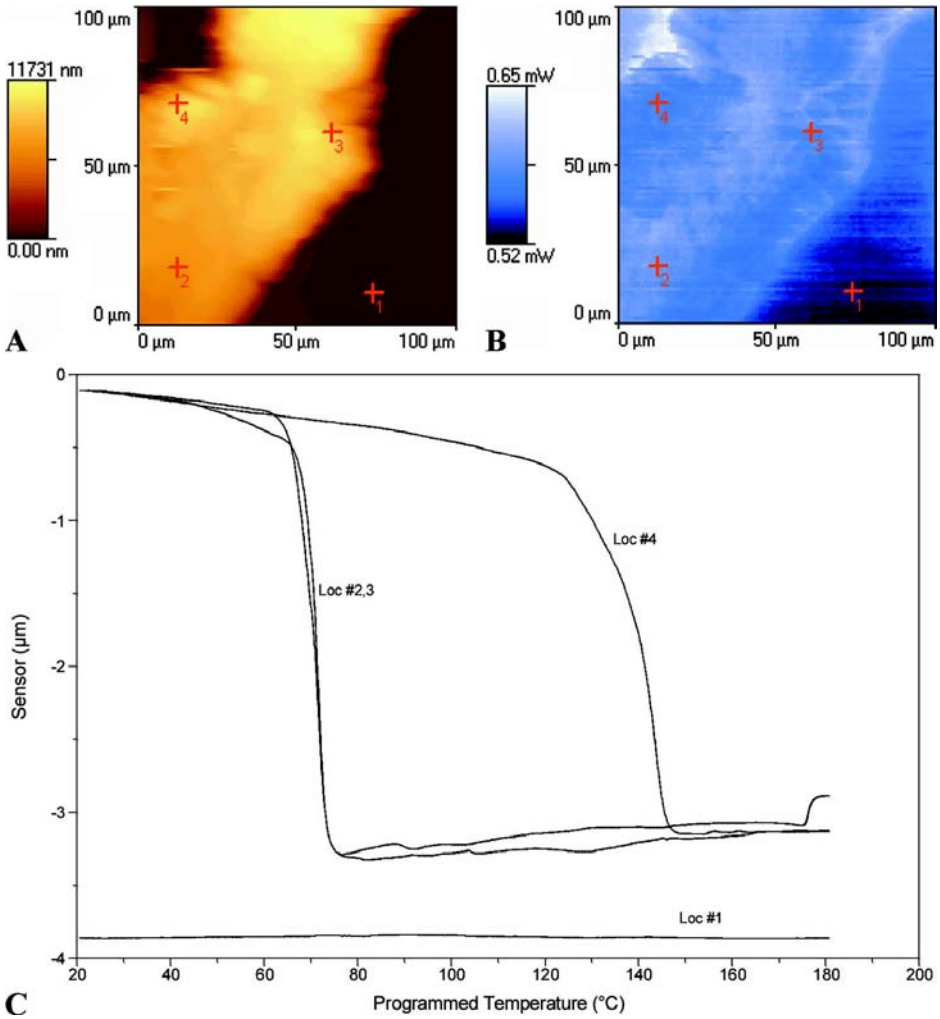


Fig. 5. (A) Topology 2D and positions for LTA (physical mix with drug A). (B) Thermal conductivity 2D and positions for LTA (physical mix with drug A). (C) Sensor position (μm) vs. temperature for the four locations in the physical mix with drug A. Locations 2 and 3 are associated with the excipient; location 4 is associated with the drug because it melts at much higher temperature (see text).

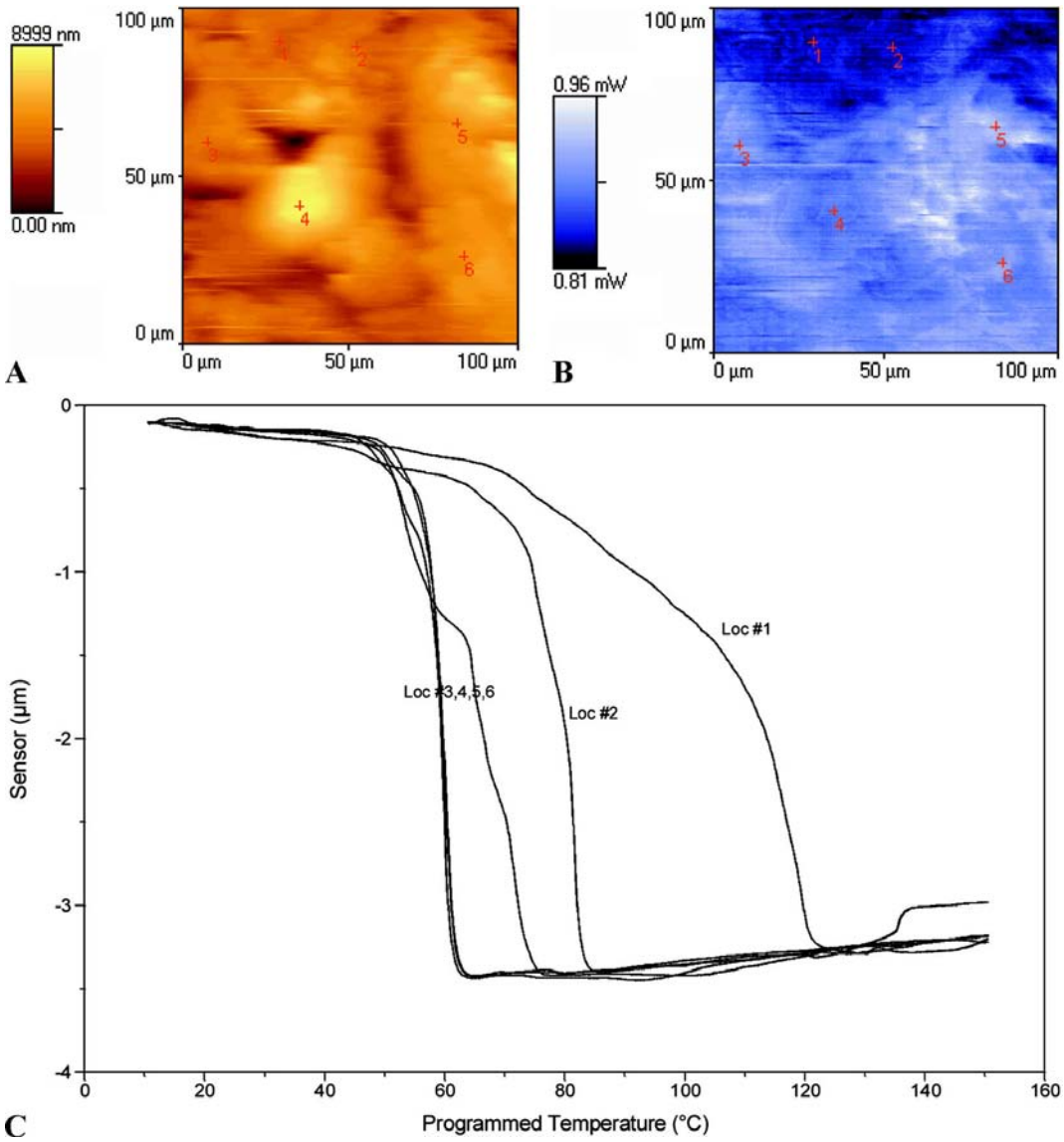


Fig. 6. (A) Topology 2D and Positions for LTA (physical mix with drug B). (B) Thermal conductivity 2D and positions for LTA (physical mix with drug B). (C) Sensor position (µm) vs. temperature for the six locations in the physical mix with drug B. Location 1 melts at 110°C and is associated with the crystalline drug B; locations 3 to 6 are associated with the excipients.

tions 1 and 2 show softening temperatures significantly higher than for locations 3, 4, 5, 6.

Location 1 melts around 110°C and can be associated with the crystalline drug. Location 2 softens at 80°C and could be associated with partially amorphous drug. Locations 3, 4, 5, and 6 melt at 60°C and are associated with PEG.

The melt of the crystalline drug (location 1) is broad probably because of heat diffusion. The heat diffuses into the sample during the LTA experiment and it can be expected that the vicinity of the drug domains reaches high temperatures. If a drug domain is surrounded by PEG, the LTA probe could melt the surrounding PEG before the drug itself, which will result in an apparent early softening of the crystalline drug.

Location 2 may give an indication that the drug is not crystalline. However, this may be explained by the precedence of the first LTA test/melting at location 1 (only 20 µm away). The LTA testing on location 1 may have created the amorphous phase detected by LTA in location 2.

Study of Solid Dispersions

System A

The topology and thermal conductivity of the surface are shown in Figs. 7A and 7B. Three locations have been chosen for LTA (Fig. 7C). Locations 1 and 3 soften at around 80°C, which corresponds to the glass transition temperature of the drug. Location 2 has a melting onset at around 55°C and is probably associated with the melting of PEG.

The study of this particular solid dispersion answers one of the questions about the crystallinity of the drug after the preparation of the solid dispersion. It seems that, during cooling, there is a phase separation as suggested by the phase

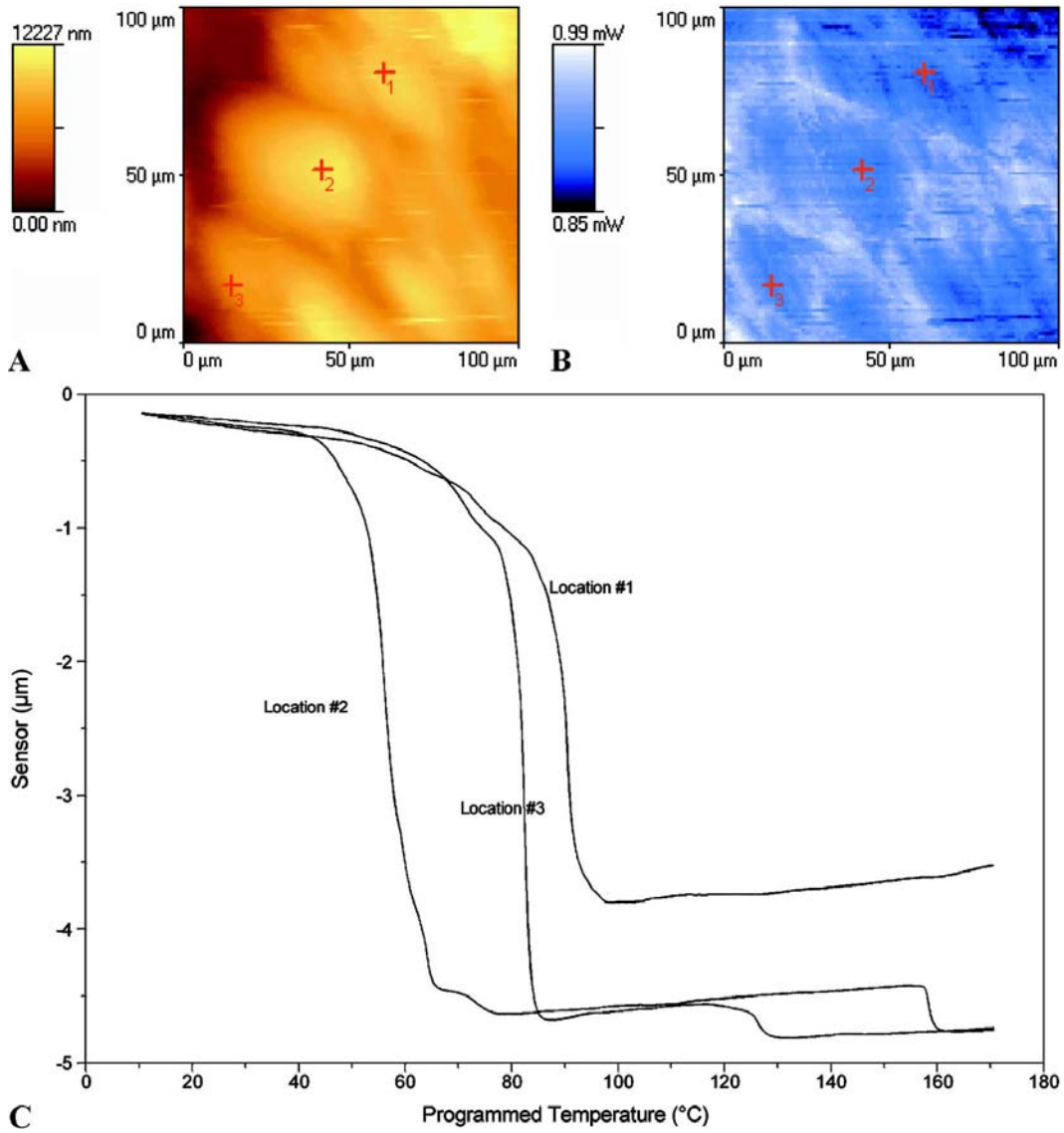


Fig. 7. (A) Topology 2D and positions for LTA (solid dispersion containing drug A). (B) Thermal conductivity 2D and positions for LTA (solid dispersion containing drug A). (C) Sensor position (μm) vs. temperature for the three locations in the solid dispersion containing drug A. Locations 1 and 3 are associated with the amorphous drug, location 2 with the excipients.

diagram. When the PEG crystallizes (at around 40°C), the drug is expelled from the PEG crystal structure and solidifies immediately as a glass. Therefore, the final product is not a solid solution, but rather a phase-separated solid material containing a PEG/surfactant crystalline matrix and some clusters of amorphous drug. From the contrast and contours of the thermal conductivity map (cf. Fig. 7B), the size of the amorphous drug domains appears to be about 40–60 μm. Likely, this amorphous drug is able to crystallize upon aging at elevated temperature and humidity. PXRD confirmed the crystallization of the amorphous drug after aging the solid dispersion at 40°C, 75% RH.

System B

The topology and thermal conductivity of the surface is shown in Figs. 8A and 8B. Four locations have been chosen for LTA (Fig. 8C). Figures 8A and 8B give an example of a topological effect on the thermal conductivity. Location 4 is located on the top of a "hill." Most of the heat provided by the probe, at this location, is dissipated in the Z direction. However, on a flat surface (locations 1, 2, or 3), the heat is dissipated in all three directions, and as a result, these locations appear to have a higher thermal conductivity than location 4. The LTA curves confirm that the 4 locations have the same properties.

After several mappings of the sample, it appears that the system has a softening temperature at around 50°C. However, it is difficult to conclude that the formulation is a solid solution or a phase separated amorphous material because the glass transition temperature of the drug is similar to the melting temperature of PEG. Even if each component is phase separated, they all soften within a narrow temperature window. For this solid dispersion system, μTA can only detect

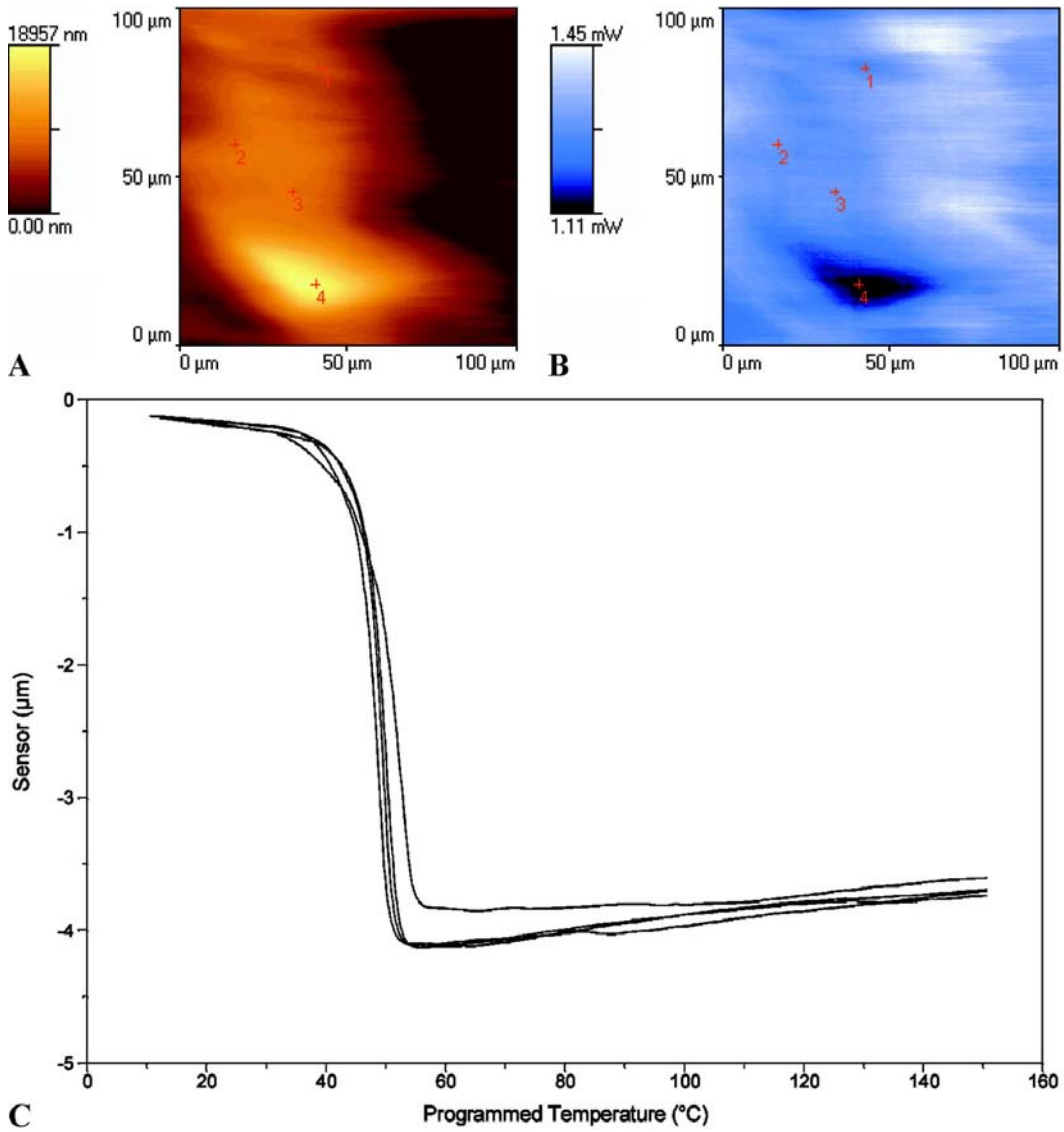


Fig. 8. (A) Topology 2D and positions for LTA (solid dispersion containing drug B). (B) Thermal conductivity 2D and positions for LTA (solid dispersion containing drug B). (C) Sensor position (µm) vs. temperature for the four locations in the solid dispersion containing drug B. All locations melt/soften at the same temperature. Amorphous phase separated drug B is impossible to detect because its T_g is similar to the melt of the excipients.

the crystalline drug and is not able to predict phase separation in freshly made solid dispersions.

Aging at 40°C /75% RH for 2 months provides information *a posteriori* on the physical structure of the drug. This aged solid dispersion formulation has a significantly slow dissolution rate. Figure 9 shows that the aged solid dispersion is very different from the freshly made solid dispersion. Location 2 in Fig. 9c clearly shows that the drug is now crystalline. Based on the contrast of the maps, the size of the crystalline drug domain, or what was once an amorphous domain, is about 50–70 µm. Crystallization of the low T_g amorphous drug domains (T_g ~40–50°C) upon aging was also confirmed by PXRD.

The physical structure of system B seems to be similar to the structure of system A. When PEG crystallizes, it creates amorphous clusters of drug. Upon aging, these amorphous domains crystallize just like for system A.

CONCLUSIONS

Solid dispersion systems were studied by microthermal analysis. The instrumentation has been found useful and reliable to study the physical structure of a drug within the solid dispersion. µTA is a sensitive tool to measure local properties where conventional macro techniques usually fail. It gives maps of both topological and thermal properties. After mapping the surface, the user can perform a local thermal analysis at any position of interest on the maps.

The study of the pure substances determined that both the crystalline and the amorphous phases of the drug can be detected.

When these two solid dispersion systems are made, phase separation occurs. The excipient crystallizes and the drug becomes a glass. Most of the drug is not trapped in the crystalline excipient but rather creates domains of several tens of

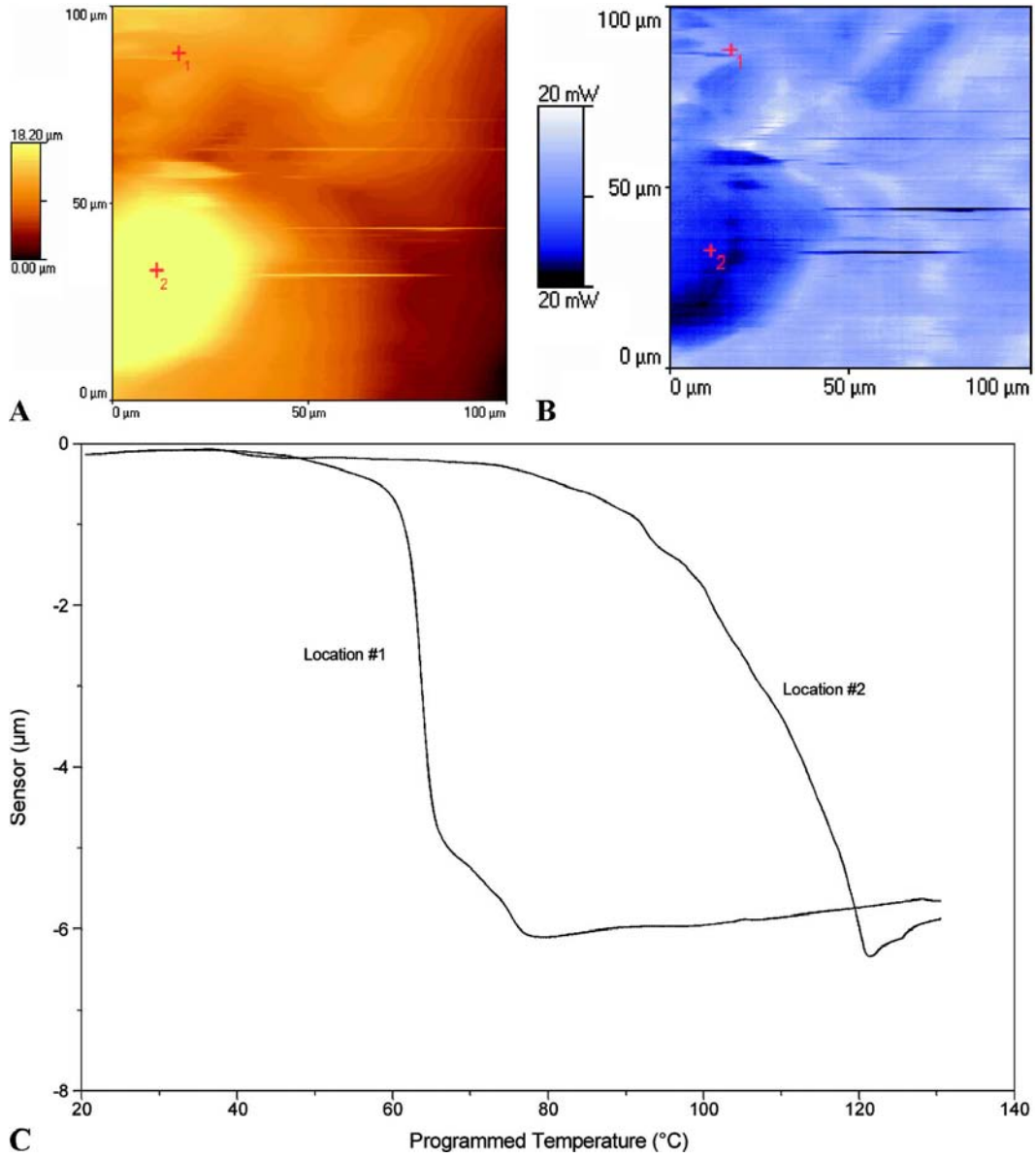


Fig. 9. (A) Topology 2D and positions for LTA (solid dispersion containing drug B aged 2 months at 40°C/75% RH). (B) Thermal conductivity 2D and positions for LTA (solid dispersion containing drug B aged 2 months at 40°C/75% RH). (C) Sensor position (μm) vs. temperature for the two locations in the solid dispersion containing drug B aged 2 months at 40°C/75% RH. Location 1 is associated with the excipients, location 2 with the crystalline drug B.

micrometers. Later, depending on the aging conditions, these amorphous domains crystallize and become less soluble. This important result can explain the poor dissolution performance of these formulations after aging.

Unfortunately, for the drug B solid dispersion, μTA could not distinguish the amorphous drug from the excipient because the transition temperatures were too similar. Only after aging could the re-crystallized drug be observed.

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