Thermal Probe Methods for Nano-Scale Characterisation of Solid Dispersions Prepared by Hot Melt Extrusion

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Introduction

Understanding the form and distribution of components within a solid dispersion is of great interest in the pharmaceutical industry. Conventional analytical methods such as differential scanning (DSC) can only provide information on the bulk scale. Thermal atomic force microscopy (AFM) probes can provide spatially resolved thermal analysis on the nano-scale.

Materials and Methods

Thermal AFM probes can produce similar topographical images as conventional probes but also have the ability to provide nano-scale thermal analysis by heating the tip of the probe. The probe can be positioned at a desired location on a sample surface and a scanning voltage profile applied. As the material beneath the tip heats, it expands, pushing the probe upwards. A thermal event such as melting or a glass transition is detected as penetration of the probe into the surface. This type of measurement is known as local thermal analysis (LTA). The probe is calibrated for temperature by measuring three polymeric standard with well known melting temperatures (Fig. 1).

An extension of this method is known as transition temperature microscopy (TTM) whereby a series of these thermal measurements is carried out across a selected area. At each location a transition temperature is detected and assigned a colour code, subsequently generating map based on transition temperatures. These methods were employed to analyse hot melt extrudates containing cyclosporine A (CsA) and Eudragit® EPO prepared at temperatures below (110°C) and above (150°C) the solid-to-liquid transition temperature of the drug.

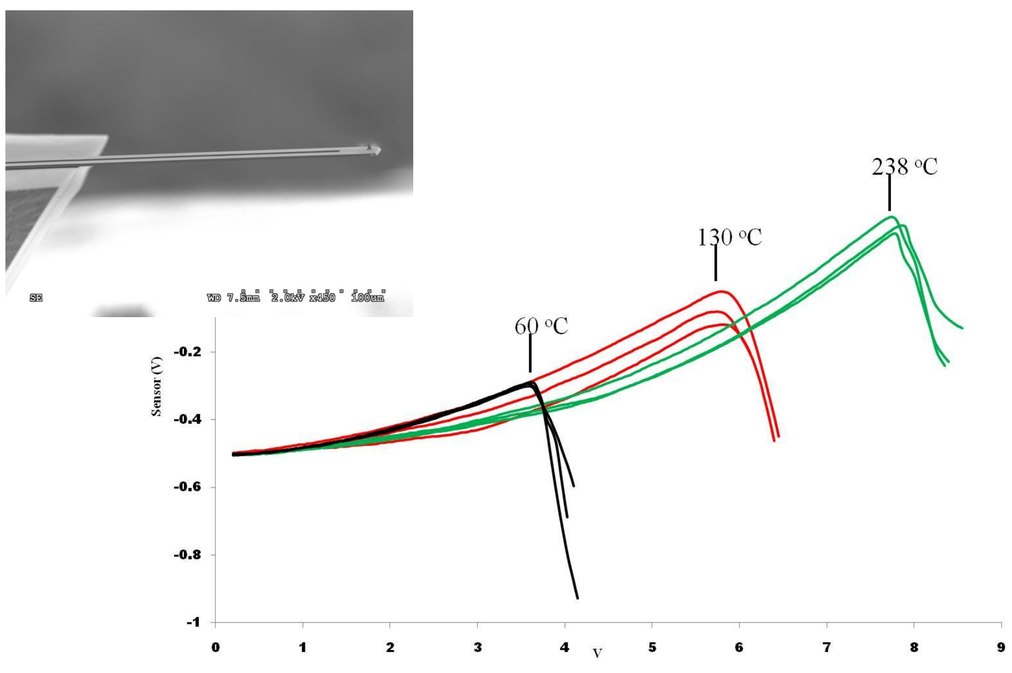

Figure 1. Local thermal analysis scans on three polymeric standards and a SEM micrograph (inset) of the probe used to carry out the measurements.

Results and Discussion

An example of a typical LTA measurement is shown in Figure 2. A topography image was generated on a sample prepared at 150°C and location selected for interrogation. The majority of measurements showed a transition temperature of ~85°C indicating the production of a solid solution. There were some measurements with a transition temperature of ~125°C, which is equal to the glass transition temperature of CsA, thus showing that not all drug was incorporated into the solid dispersion. This detection of 2 phases was not observed with DSC.

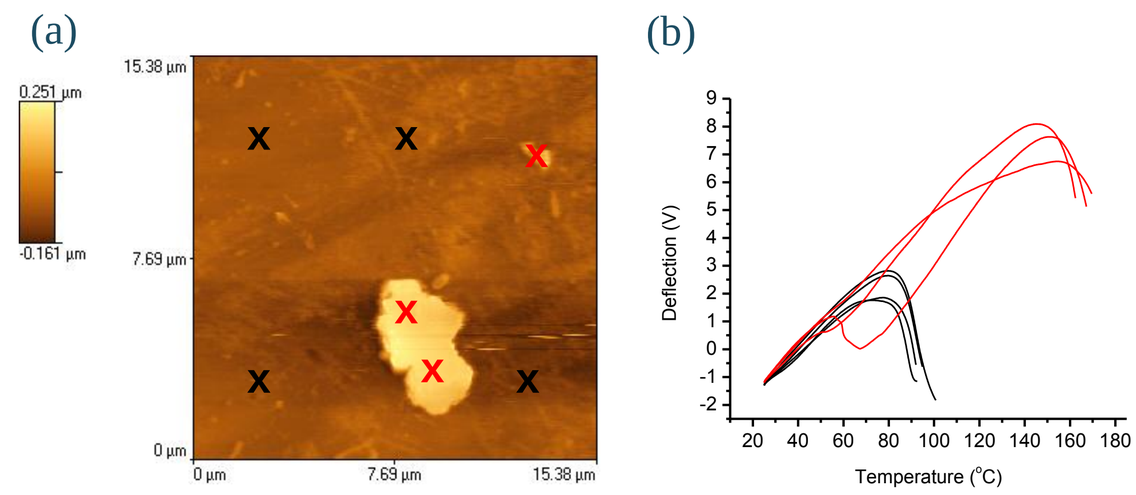

Figure 2. Topography image (a) and representative LTA scans (b) at locations marked with an x.

Figure 3 shows examples of TTM maps of samples produced at 150°C (3a) and 110°C (3b). Figure 3a shows a largely uniform map with one red pixel indicating non-dispersed drug, each pixel represents and area of size 1x1 µm. For the sample produced at the lower temperature, the sample shows 3 phases which could be assigned as polymer (blue), solid solution (green) and drug (red). This shows that at temperatures where the drug is solid, a solid solution was not produced.

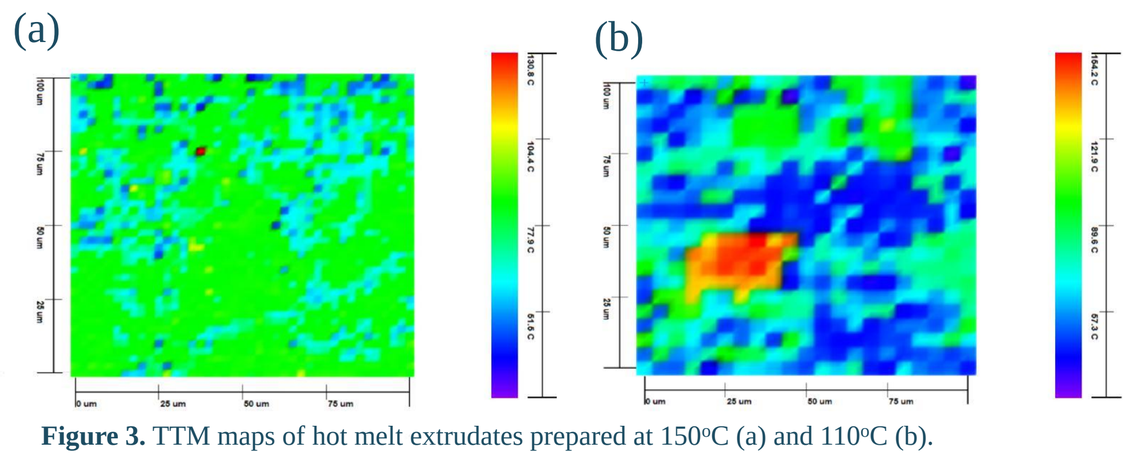

Figure 3. TTM maps of hot melt extrudates prepared at 150°C (a) and 110°C (b).

Conclusions

Thermal probe methods were employed to provide the visual realisation of the form and distribution of components within a solid dispersion.

Acknowledgements

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