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Rapid communication

Nanoscale thermal analysis of pharmaceutical solid dispersions

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ABSTRACT

Formation of a solid solution of a drug in a water-soluble polymer is one of the primary techniques used to improve the dissolution rate and thus bioavailability of a poorly water-soluble drug. Understanding and detecting the state of the drug inside such a polymer matrix is critically important since issues such as drug stability, safety and efficacy can be greatly affected. In this study, two model formulations were prepared containing low and high levels of drug content. The heterogeneity of the formulations has been investigated using a novel nanothermal analysis technique. This technique has demonstrated a promising capability for imaging and quantitatively characterising the nanoscale properties of solid dispersion formulations.

1. Introduction

Among the numerous methods of enhancing drug dissolution for poorly water-soluble drugs, preparation of a 'solid solution' of the drug in a water-soluble polymer is one of the most widely researched methods (Craig, 2002). An issue in the pharmaceutical product development of such technology is assuring the stability of the dissolved phase such that crystallisation of the nano/microdomains of the active does not occur, for which even a small fraction can significantly alter the bioavailability, stability and efficacy. This is a particularly pertinent issue for high drug loaded formulations (Okonogi and Puttipipatkhachorn, 2006). For lower loadings, identification of this solid-state transition can become challenging using bulk scale techniques such as XRD and DSC due to their sensitivity limits. Here we explore a new technology 'nanothermal analysis' (nano-TA), which in conjunction with other techniques provides a powerful analytical strategy for characterising nano- and micro-scale heterogeneity in the solid-state properties of drug–polymer formulations.

Nanothermal analysis is an emerging localized thermal analysis technique which combines the high resolution imaging capabilities of atomic force microscopy (AFM) with the ability to characterize the thermal properties of materials (Harding et al., 2007; Nelson and King, 2007; Ye et al., 2007; Dai et al., 2008). It offers significantly enhanced spatial resolution compared with its predecessor, scanning thermal microscopy (SThM) (Pollock and Hammiche, 2001; Sanders et al., 2000; Bond et al., 2002). The typical resolution of the Wollaston wire based probes used in SThM is approximately 1 μm, although the use of thinner wires (Pollock and Hammiche, 2001) or the addition of diamond tips (Brown et al., 2008) has achieved a resolution of around 100 nm. In nano-TA the conventional silicon based AFM tip is replaced by a specialised microfabricated silicon-based probe with a miniature heater that has a topographic spatial resolution of around 5 nm and a thermal property measurement resolution of up to 20 nm (Sedman et al., 2009). Importantly this probe enables a surface to be studied with the most widely applied AFM imaging mode, tapping mode, enabling the analysis of softer samples, such as polymers, without damage from the imaging probe. As in SThM, nano-TA can be used to map thermal properties during imaging, or to carry out local thermal analysis (LTA) at defined points on a surface. LTA, where the probe is heated in a temperature cycle not dissimilar to DSC whilst in contact with the sample, can provide quantitative information on thermally induced phase transitions.

Here we describe a case study using nanothermal analysis to characterise a model nano-dispersed pharmaceutical system containing carbamazepine (CBZ) and hydroxypropyl methyl cellulose (HPMC).

2. Materials and methods

Solid dispersions of CBZ in HPMC were prepared by a gel-entrapment method (Bhise and Rajkumar, 2008). HPMC (Sigma, UK) was first dissolved in dichloromethane (DCM) to prepare a clear

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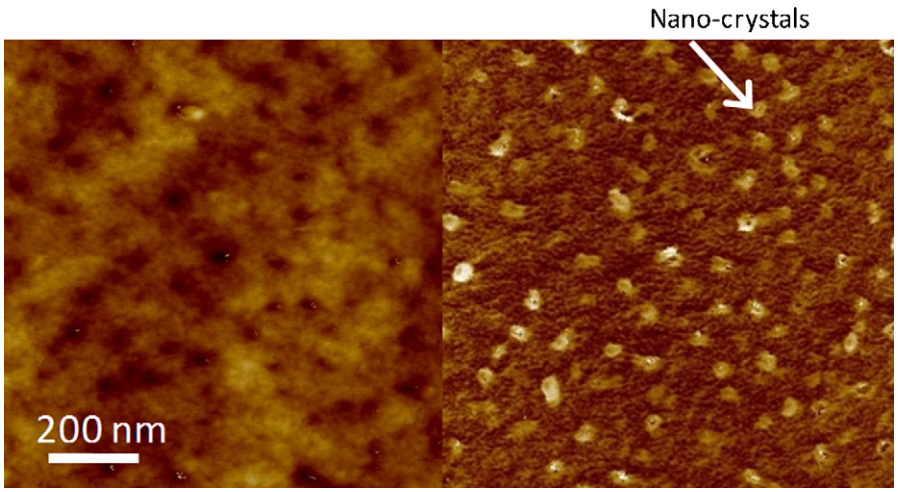

Fig. 1. AFM tapping mode image of 50% CBZ–HPMC using a nanothermal probe. Left: topography image (z-scale = 20 nm). Right: phase image.

and transparent gel, 5% (wt./vol.). CBZ Form III (Acros, UK) was then dissolved into the gel to give a 50/50 polymer/drug ratio. This was repeated to give a second sample containing a 95/5 polymer/drug ratio. Small quantities of the samples were spread onto clean silicon wafers. The DCM was allowed to evaporate overnight under ambient conditions. The thin films thus formed were further conditioned in a vacuum for 6 h to remove residual DCM.

Crystals of CBZ Form III were prepared for LTA measurements by heating a 100 mg ml^{-1} solution of CBZ in ethanol to 80 °C. The solution was allowed to slowly cool at room temperature and left for a further 24 h. The resultant crystals were collected by vacuum filtration. The crystals were confirmed to be Form III by powder X-ray diffraction (PXRD). To help, analyse and validate the findings from nanothermal LTA, DSC (TA Instruments Q2000) analysis was performed on the dispersions and pure samples.

Nanothermal experiments were carried out using a Multimode Nanoscope V (Veeco, Santa Barbara) equipped with a nano-TA module and a nano-TA probe (Anasys Instruments, Santa Barbara). All images were recorded in tapping mode. LTA was performed by first bringing the probe into contact with the sample surface. The probe was then heated at a controlled rate of 2 °C s^{-1}. Thermal events such as melting and glass transitions produce a downward deflection of the cantilever. Temperature calibration of the probe was performed against the known T_m of three polymers, polycaprolactone, high-density polyethylene and polyethyleneterephthalate (Harding et al., 2007; Ye et al., 2007; Dai et al., 2008).

3. Results and discussion

The surfaces of the two CBZ/HPMC formulations were examined using tapping mode imaging with the nano-TA probe. Fig. 1 presents topographic (left) and phase (right) images obtained from the sample containing 50% CBZ. The topography indicates that the imaging spatial resolution of the nanothermal probe is comparable to that of conventional AFM tips, which is higher than its predecessor, microthermal analysis which used a Wollaston wire based probe (Bond et al., 2002). The phase image contrast observed highlights the presence of heterogeneity. The bright phase-separated domains are attributed to the presence of CBZ nano-crystals (later confirmed by LTA and DSC analysis), approximately 50 nm in size. However, the sample containing only 5% CBZ showed no prominent phase contrast (data not shown), indicating a homogeneous surface with the absence of nano-crystals. This result is not unexpected since drug re-crystallisation is inhibited by the interaction between the drug and polymer molecules (Douroumis and Fahr, 2007). In contrast, at 50% CBZ some molecules were able to re-organise themselves during solvent evaporation leading to a phase separated system. Similar observations have occurred in solid dispersions of other systems (Naima et al., 2001; Layre et al., 2005).

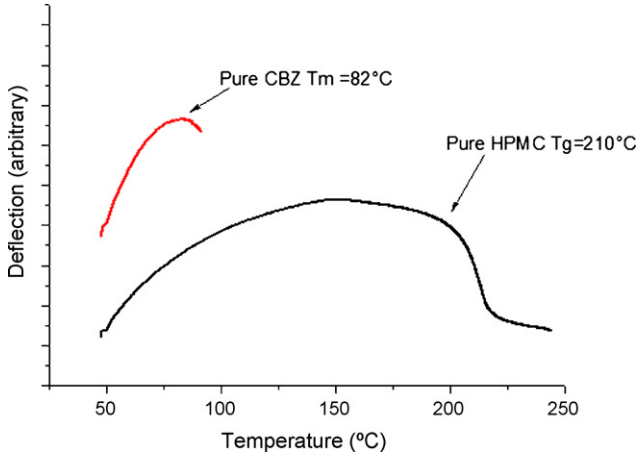

Fig. 2. LTA data of control samples (CBZ and HPMC).

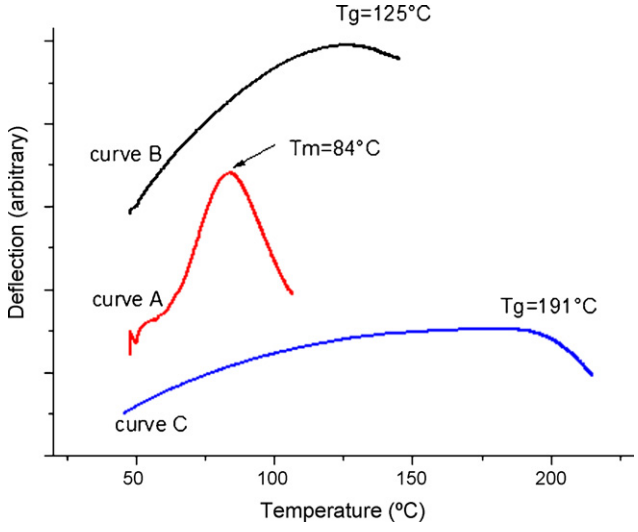

Fig. 3. LTA data of 50% CBZ–HPMC (traces A and B), and 5% CBZ–HPMC (trace C).

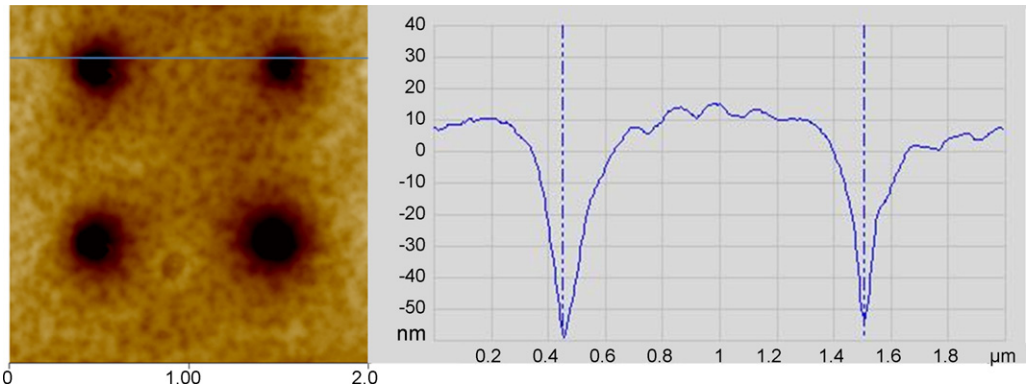

Fig. 4. Craters generated on the 50% CBZ–HPMC sample surface after LTA measurements and corresponding cross-section (*z*-scale = 50 nm).

As a control, LTA was performed on samples of the pure crystalline drug and the polymer (Fig. 2). The HPMC glass transition temperature (T_g) was determined from the trace to be approximately 210 °C which is comparable to the value from DSC (174 °C, Fig. 5), within the expected variations due to very different heating rates and method of analysis. However, the T_m of pure CBZ Form III was estimated from LTA to be 82 °C, significantly lower than the value determined from DSC (171 °C, Fig. 5) and the literature values (Grzesiak et al., 2003). This suggest that the use of a calibration scale based on polymers is not appropriate to measure melting transitions of CBZ. This point has been noted previously by the authors (Zhang et al., 2003) and others (Gorbunov et al., 2009). In addition to calibration issues, it is suggested that the thermal behaviour of different classes of materials (here low molecular weight organic crystals and crystalline polymers) may not be comparable at the nanometer scale. At present the reasons for this discrepancy are not fully understood, however, surface confinement effects due to the extremely small scale of the measurement may be one contributing factor (Bergese et al., 2004; Alcoutlabi and McKenna, 2005). We also note that as measurements are recorded from individual faces of the CBZ crystals, they may not reflect a single bulk value as determined say by DSC, as different crystalline faces are known to have different melting points (Pluis et al., 1987). Finally, we note that this apparently reduced melting point may be related to the phenomenon of pre-melting (or surface melting) where a quasi-liquid film can form on crystalline surfaces well below the bulk melting point (Pluis et al., 1987; Dash, 2006). Despite this difficulty with absolute determination of transitions, LTA has demonstrated the capability for identifying, differentiating and characterising the thermal properties of multi-component systems.

LTA analysis was performed on the CBZ/HPMC samples and results are shown in Fig. 3. Two distinctive kinds of LTA curves were observed in the 50% CBZ sample (denoted as curves A and B). It is reasonable to assign curve A (T_m = 82 °C) as a nano-crystalline region as its profile is similar to that of the pure CBZ in Fig. 2. This is despite the very small size of these crystals, suggesting that they have sufficient long-range order to behave as a bulk crystal under nano-LTA analysis. Curve B can be assigned the tip's thermal response to the HPMC-CBZ solid solution, with a lower T_g than the pure HPMC. This reduction from approximately 210 °C to 125 °C, is attributed to the plasticizing effect of the drug molecules (Matsumoto and Zografi, 1999). In contrast to the 50% CBZ sample, the 5% CBZ sample consistently shows a single type of LTA trace with a T_g of approximately 191 °C (curve C), suggesting homogeneity. As expected, the T_g is depressed compared to the pure HPMC, but less so than in the 50% CBZ sample.

Fig. 4 displays an AFM image of the craters formed after a series of LTA measurements on the 50% CBZ sample. Cross-sectional measurements show a spot size of approximately 300 nm, however it is believed that this may underestimate the true LTA spatial resolution. The fact that nano-crystalline regions approximately 50 nm in size were identified by LTA suggests that the effective spot size of the measurement is less than that of the remaining crater. Recent work by Sedman et al. (2009) has shown features as small as 20 nm on peptide nanotubes following LTA supporting this suggestion.

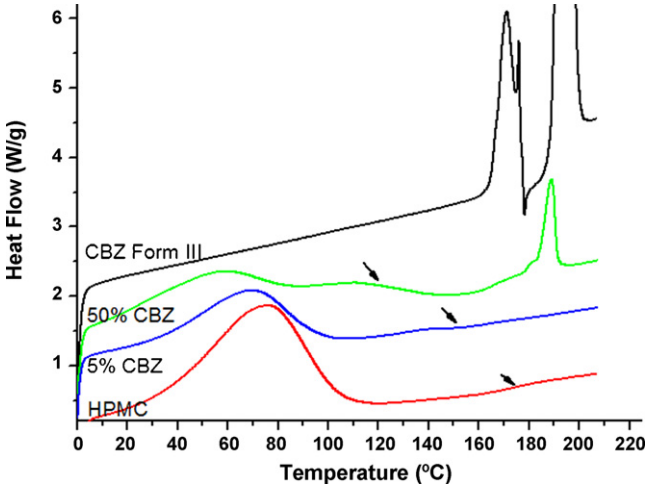

Fig. 5. DSC thermographs of CBZ Form III (black), 5% CBZ–HPMC (blue), 50% CBZ–HPMC (green) and HPMC (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 5 presents DSC data of the two formulations together with the pure CBZ and HPMC. The pure CBZ is confirmed as crystalline Form III by T_m = 171 °C with a small shoulder at 176 °C, followed by a Form I T_m at 193 °C (Grzesiak et al., 2003). The sharp endothermic peak in the 50% CBZ sample is consistent with the presence of crystals, whereas there is no such peak present in the 5% sample, again consistent with the nano-TA data. DSC data also confirms the reduction of the HPMC T_g as more CBZ is added to the system (indicated by arrows). Note that the large and broad endothermic peak in the low temperature range is related to the dehydration of the HPMC.

4. Conclusions

Model samples containing 5% and 50% solid dispersions of CBZ in HPMC were characterised using nanothermal analysis. This revealed that in the 5% sample, a solid solution is formed, however, in the 50% sample, some of the CBZ precipitates into nano-crystals, visible through phase imaging as 50 nm domains and through direct

observation of thermal transitions with localised thermal analysis. In the surrounding matrix, CBZ and HPMC mix molecularly, causing a measurable reduction of the T_g.

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