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The stability of solid dispersions of felodipine in polyvinylpyrrolidone characterized by nanothermal analysis

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ABSTRACT

Nanothermal analysis (NTA) supported by atomic force microscopy imaging has been used to study the changes that occur at the surfaces of solid dispersions of the drug felodipine and the water soluble polymer, polyvinylpyrrolidone (PVP) on exposure to standard pharmaceutical environmental stress conditions. Exposure to relative humidities above 75% (at 40 °C) was sufficient to achieve phase separation of the drug and polymer into areas which displayed a glass transition temperature consistent with pure drug and polymer over a period of a few days. Higher values of humidity at 25 °C (e.g. 95%RH) were also sufficient to cause such phase separation within a day. Extended studies of up to two months showed an eventual crystallization of the drug. NTA is shown to be effective at the early detection of instabilities in solid dispersions and the quantifiable identification of the relative composition of phase separated domains based upon their glass transition temperatures. The combined nanoscale analytical approach employed here is able to systematically study the influence of storage conditions and different drug loadings and to evaluate physical stability as a function of environmental conditions.

1. Introduction

The production of a solid-solution or solid dispersion of a drug in a water-soluble polymer is a well known formulation route for potentially enhancing the dissolution of poorly water-soluble drugs. The need to improve dissolution arises from the extensive use of drug discovery methods based upon high throughput screening approaches that tend to select for compounds with lower water-solubilities, higher lipophilicities and higher molecular weights (Lipinski, 2000). Whilst providing for a potentially increased oral bioavailability through an increased drug dissolution rate, solid solutions can suffer from physical stability problems. In particular, crystallization of the drug from the solid solution with consequent reduction in dissolution and bioavailability is a critical issue. Characterizing the onset of crystallization can be challenging for bulk techniques such as Powder-X-ray Diffraction (P-XRD) and Differential Scanning Calorimetry (DSC) due to their sensitivity limits, meaning that the onset of such transformations of form may remain un-detected. The recent case of the crystallization of the active ingredient (rotigotine) in Neupro patches causing a withdrawal of the product (Rascol and Perez-Lloret, 2009) highlights the continuing challenge of this area.

Clearly, the development of sensitive methods and strategies suitable for the assessment of formulation stability early in development programs will be important to allow the rapid establishment of the critical design features of a dosage form (Weuts et al., 2011) and map out formulation design space (Yu, 2007). Amongst analytical approaches that can assist in this process, those based upon probe microscopy and analysis have a number of potentially advantageous features, including the ability to analyse very small amounts of material and to detect the onset of physical changes through nanoscale resolution of a formulation under suitable environmental stress conditions (Turner et al., 2007). For example, we have previously demonstrated the application of nanothermal analysis (NTA) to the characterization of a nano-dispersed pharmaceutical system containing 5% and 50% loadings of carbamazepine (CBZ) in a hydroxypropyl methyl cellulose (HPMC) matrix (Zhang et al., 2009). A solid solution was formed for the 5% sample, however, at 50% loading some of the CBZ precipitated into nano-crystals, visible through atomic force microscopy (AFM) imaging as 50 nm domains and through NTA measurements of the melting of these domains. Localized thermal measurements on the matrix of these formulations also confirmed the ability of NTA to observe the reduction of the glass transition temperature

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(T_g) of the HPMC with loading of the CBZ. NTA has also been used to map amorphous and crystalline lactose at the nanoscale in simulated tablet formulations (Dai et al., 2009). The phase separation of solid dispersions of drug and polymers has also been studied using the related probe-based technique of scanning thermal microscopy (SThM) (Six et al., 2003). Qi et al. (2008) employed SThM, supported by spectroscopic and imaging techniques to characterize solid dispersions of paracetamol in EUDRAGIT® E, showing that such formulations may be complex in physical form and spatial distribution. In addition as part of a programme of complementary analysis including traditional bulk approaches such as DSC, TGA, FT-IR and P-XRD, atomic force microscopy (AFM) has been used to establish the critical range of weight to weight ratio of the drug etravirine in HPMC required to form a solid solution (Weuts et al., 2011).

In NTA the conventional silicon tip used in AFM is replaced by a microfabricated silicon-based probe with a miniature heater that has an imaging spatial resolution of around 5 nm and a thermal property measurement spatial resolution of up to 20 nm (Sedman et al., 2009). NTA can be used to map thermal properties during imaging, or to carry out local thermal analysis at defined points on a surface. In such analysis, the probe is heated in a temperature cycle not dissimilar to DSC whilst in contact with the sample, providing quantitative information on thermally induced phase transitions. The use of a microfabricated levers to sense thermal transitions is advantageous because of their ability to measure samples down to femtograms and nanoliters rapid heating and cooling rates exceeding 100 °C s^{-1}, and high sensitivity to small temperature changes and heat flows (Olson et al., 2000; Sedman et al., 2009).

Here, we explore the application of NTA to the understanding of the physical state of felodipine dispersed in the soluble polymer, polyvinylpyrrolidone (PVP) and the effect of humidity and temperature stress on this system. The use of PVP with felodipine, a poorly soluble antihypertensive drug is a recognized and extensively studied method of improving the bioavailability of this drug (Konno and Taylor, 2006). It has been proven that the main factor which affects the release profile of felodipine is hydrogen bonding with the PVP, with dissolution improving with the intensity of this hydrogen bonding (Karavas et al., 2006). Infrared spectroscopy, supported by electron microscopy, AFM and DSC have also been used to study the effect of humidity and temperature on the felodipine–PVP system (Marsac et al., 2010). In this work the drug-polymer intermolecular hydrogen bonding interactions were proposed to be reversibly reduced with increasing temperature, whereas water irreversibly disrupted such interactions leading to crystallization above a relative humidity of 75%. Further work from the same group has shown that PVP–felodipine dispersions were very sensitive to changes in storage RH, whilst hypromellose acetate succinate–felodipine dispersions were less so (Rumondor et al., 2009). Here we further explore the stability of the PVP–felodipine system to long-term exposure to temperature and humidity stress using NTA to reveal the nanoscale architecture and structure of these materials and the early onset of physicochemical changes under stress.

2. Materials and methods

2.1. Materials

Predetermined proportions of Felodipine (AK Scientific, Ahern Avenue Union City, CA) and PVP (Kollidon30, BASF AG, Ludwigshafen, Germany) were dissolved in anhydrous ethanol (99.5%). Solid dispersions containing 10%, 25% and up to 75% (w/w) drug were prepared from solution by spin coating, whereby 30 μl of solutions were deposited onto the central portion of a spinning glass slide (approximately 16,000 rpm). As the solution spread due to centrifugal force, the solvent evaporated depositing a thin and uniform film. The speed of rotation and concentration of solution were chosen to ensure a uniform film displaying complete surface coverage was achieved. These spin coated films were stressed under different humidity and temperature combinations over varying periods of time.

2.2. Methods

2.2.1. Sample conditioning

In this project, prepared formulations were exposed to two stressing conditions with different combinations of temperature and humidity; 75% RH/40 °C and 95% RH/25 °C. The former condition was created by placing an airtight container (1 L in volume) containing an appropriate quantity of saturated NaCl solution in an oven (Memmert UFB 400, Germany) at 40 °C. Likewise, the latter condition used saturated Potassium Nitrate solution, and an oven temperature of 25 °C. The samples were exposed to such environments for different periods of time before they were subjected to analysis.

2.2.2. Nanothermal analysis and atomic force microscopy

Nanothermal experiments and AFM imaging were carried out using a Multimode Nanoscope V (Bruker Surface Nano, Santa Barbara, CA) equipped with a nano-TA module and a nano-TA probe (Anasys Instruments, Santa Barbara, CA). All images were recorded in tapping mode. Localised thermal analysis (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. At least three measurements were taken for transition temperature determination. Temperature calibration of the probe was performed against the known melting temperature (T_m) of three polymers, polycaprolactone (T_m = 55 °C), high density polyethylene (T_m = 116 °C) and polyethylene terephthalate (T_m = 238 °C).

2.2.3. Theoretical analysis

A comparison was made between the T_g as determined by NTA and the theoretical T_g of a mixture as predicted by the Gordon–Taylor equation (Eq. (1)). This equation assumes that the

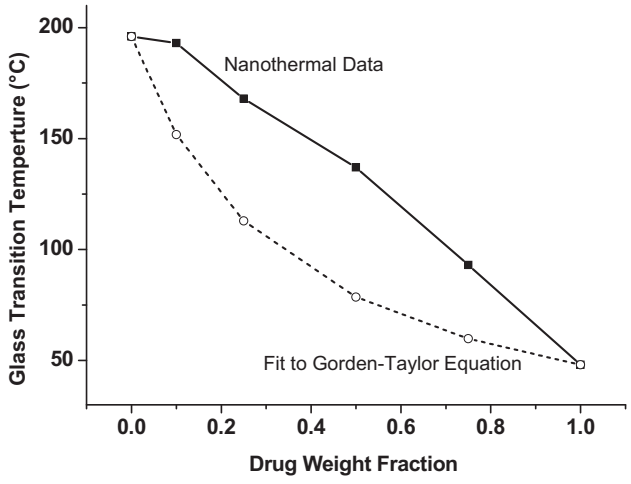

Fig. 1. Plot of the glass temperature of varying weight fractions of felodipine in PVP as determined by local nanothermal measurements (±1 °C) recorded at the surface of films compared with a theoretical prediction of glass transition temperature of comparable solid dispersions as predicted using the Gordon–Taylor relationship.

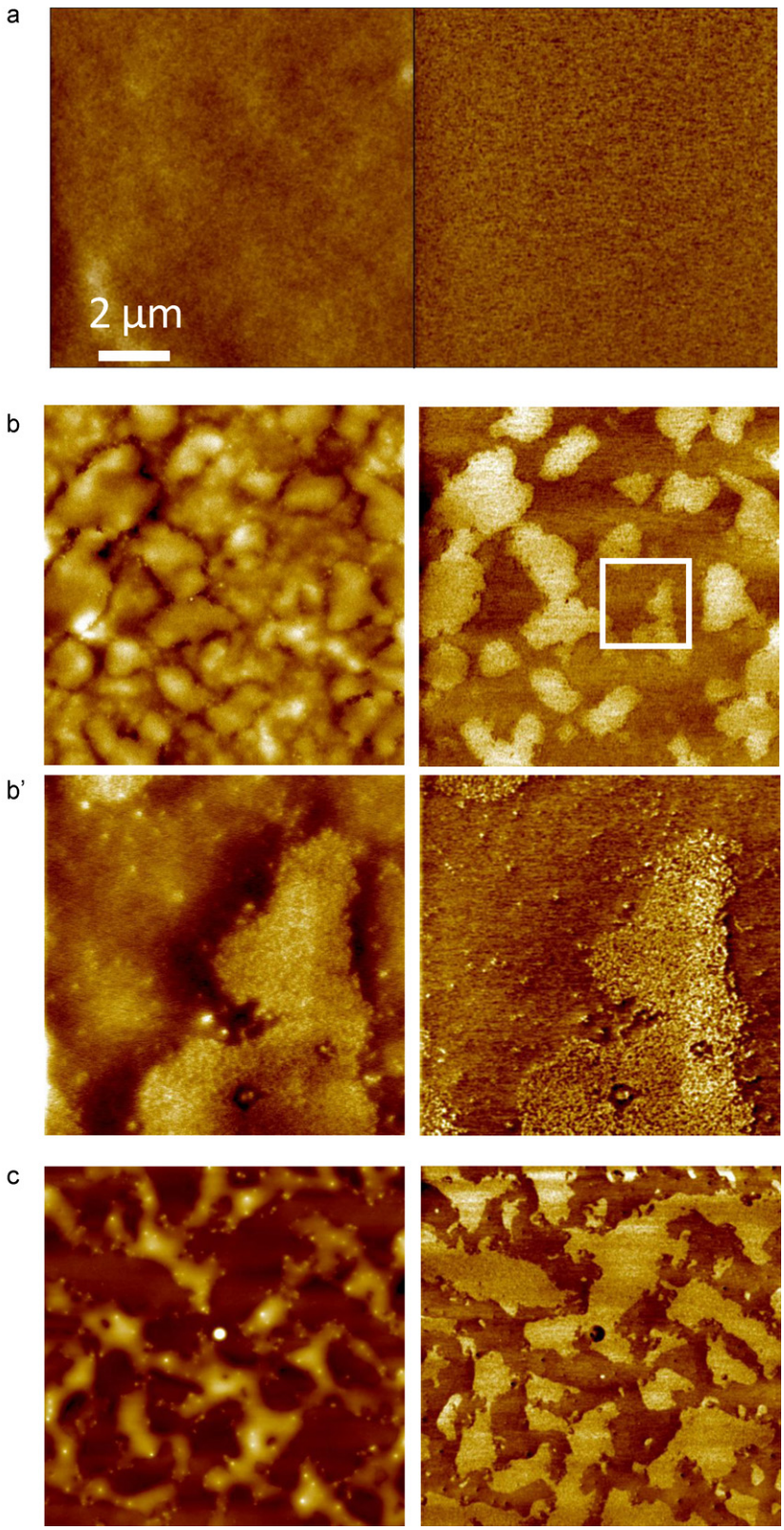

Fig. 2. (a) 10 μm × 10 μm height (left) and phase (right) AFM images of a 25/75 drug-PVP sample as-prepared. (b) The same sample after 1 day (topography and phase) at 95% RH. (b') Higher resolution images (topography and phase) of the boxed region in (b) (2 μm × 2 μm). (c) Sample after 3 days at 95% RH shown in topography (left) and phase (right). Vertical *z*-scale: (a) 5 nm, 5° (b) 17 nm, 36°, (b') 12 nm, 32° and (c) 75 nm, 47°.

two components are miscible and that mixing is not accompanied by volume changes.

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \quad (1)$$

where the constant k is defined as,

$$k = \frac{p_1 t_{g1}}{p_2 T_{g2}} \quad (2)$$

where w_1, w_2, T_{g1} and T_{g2} are the mass fraction and the glass transition of felodipine and PVP respectively and p_1 and p_2 the densities of felodipine and PVP as measured by Konno et al. (2008) and are equal to 1.33 mg/ml and 1.28 mg/ml respectively.

3. Results and discussions

The T_g of formulations containing different concentrations of felodipine in PVP were measured following preparation with NTA (Fig. 1). A single thermal transition was observed for each sample, proposed to be associated with the T_g (the softening point which would occur after the T_g was not observed within the measured range). In NTA the small load on the heated probe causes it to indent a surface as molecular mobility increases at the T_g. The observed thermal transition was found to decrease in an approximately linear fashion with increasing drug content between the values for pure PVP (196 °C) and pure felodipine (48 °C), consistent with this transition being a T_g and suggesting the miscibility of these two components. The nanothermal traces collected at different locations across the sample surface were highly reproducible, indicating that all the samples were homogeneous solid solutions immediately after preparation. This is an important requirement when moving forward to understand subsequent changes after storage in different conditions. The comparison of NTA data with the theoretical values predicted by the Gordon–Taylor relationship for the PVP–felodipine mixtures (based upon the NTA values of the pure materials) in Fig. 1 reveals that the formulations display higher than expected values for T_g. This indicates that the assumption that there is no interaction between the components of the formulation required by Gordon–Taylor is not valid. This is consistent with the known hydrogen bonding that occurs between felodipine and PVP in such mixtures (Konno and Taylor, 2006). It should be noted that the reported T_g for felodipine determined by the bulk method DSC is in the range 40–50 °C (Kerc et al., 1991) and is hence consistent with the NTA result. The reported bulk T_g for dry Kollidon30 PVP is 168 °C (Kolter and Flick, 2000) and was determined by DSC for the samples here to be 161 °C (data not shown) indicating minimal water content. These values are lower than the observed NTA value but within the expected variations due to very different heating rates and the temperature dependence of structural relaxation rates associated with material changes at the T_g. (Zhang et al., 2003, 2009). The miscibility and homogeneity of felodipine and PVP as indicated by the NTA is consistent with AFM imaging (Fig. 2a) which showed a uniform material at the nanoscale before the sample was stressed.

Fig. 2 shows AFM imaging of the evolution of the surface morphology of a 25% drug loaded formulation before and after exposure to 95%RH and 25 °C for 1 and 3 days. Note that the left-hand images are height (topography) and the right hand images present AFM phase data where the contrast is derived from local differences in material properties. Such differences are detected through variations in the degree and nature of the AFM probe interactions over these regions. The darker phase indicates more energy lost by the vibrating AFM cantilever, which can be due to, for example, increased probe-sample contact area, a softer surface or a more adhesive interaction compared to the brighter phase (Chen et al., 1998). Such phase imaging has been used extensively in the characterization of pharmaceuticals, for example in the identification of polymorphic forms (Danesh et al., 2000), to study the variations in the physico-mechanical properties of salbutamol sulfate crystals due to milling (Begat et al., 2003) and drug enriched regions within a polymeric coating of a drug eluting stent (Wu et al., 2010).

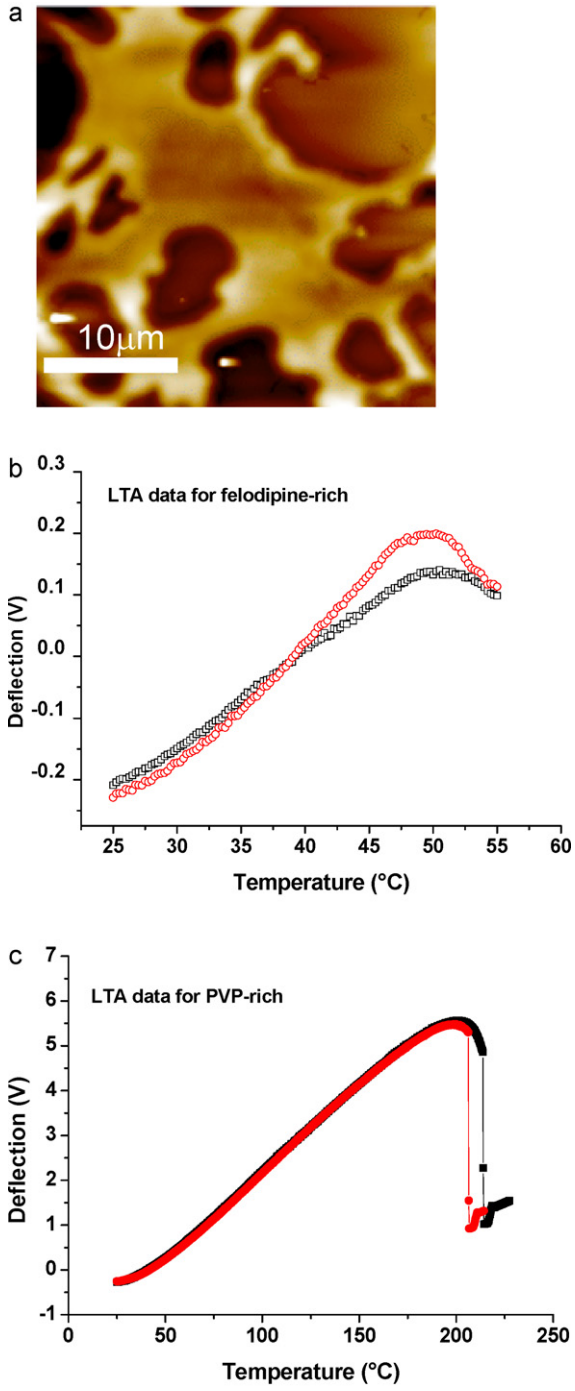

Fig. 3. (a) AFM topographic image (z-scale: 400 nm) of a following exposure to 75% RH and 40 °C for three days. (b) Nano-TA traces from the bright region in (a) determined to be felodipine-rich domains and (c) from the dark regions in (a) determined to be PVP-rich areas.

Exposure to high humidity has clearly driven a phase separation of the sample induced by water absorption (Fig. 2b). The development of this heterogeneity continues over the observed time period (3 days) (Fig. 2c). High resolution imaging as in Fig. 2b'

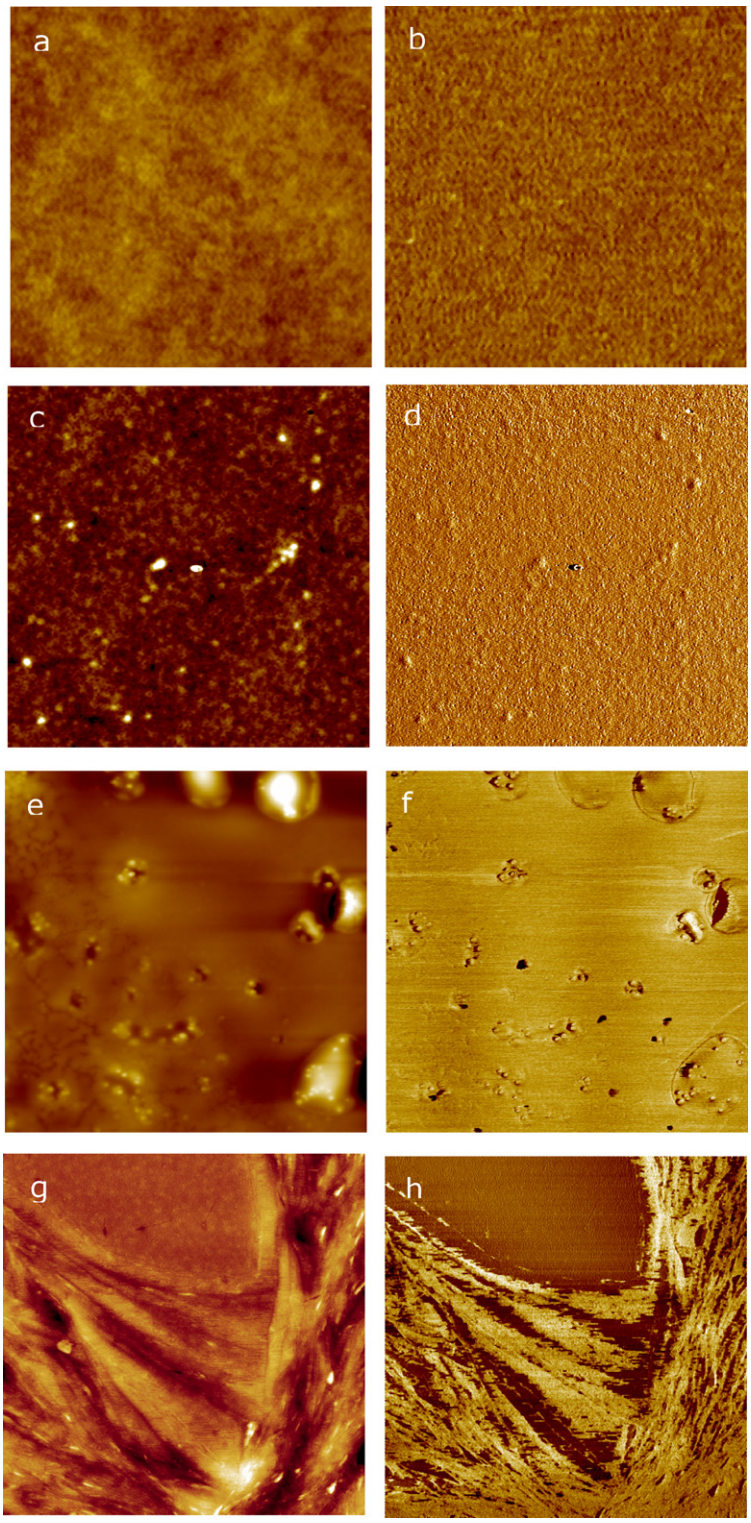

Fig. 4. 5 μm × 5 μm topography and phase images after exposure to 40 °C/75% RH for two months for 25/75% felodipine/PVP. (a, b) 1 day (*z* 1.7 nm, 2°) (c, d) 3 days (*z* 19 nm, 55°) (e, f) 5 days (*z* 136 nm, 75°), (g, h) 20 μm × 20 μm images after 2 months (*z* 80 nm, 96°).

of the sample at 1 day exposure clearly indicates the ability of AFM to visualize this process occurring. For example, the phase image in Fig. 2b' shows that the brighter area in this image has a fine reticulated structure. Surrounding this growing domain small 'threads' of material with a similar phase shift (and therefore likely similar composition) can be seen becoming associated with this domain or in its close proximity. These demonstrate that the AFM is able to visualize at the molecular scale such processes and indicates that the material is locally phase separating and displaying mobility to allow the growth of phase separated domains.

Whilst it is possible to speculate as to the nature of the material changes that have led to this nanoscale heterogeneity it is not generally possible with AFM to provide unequivocal identification of

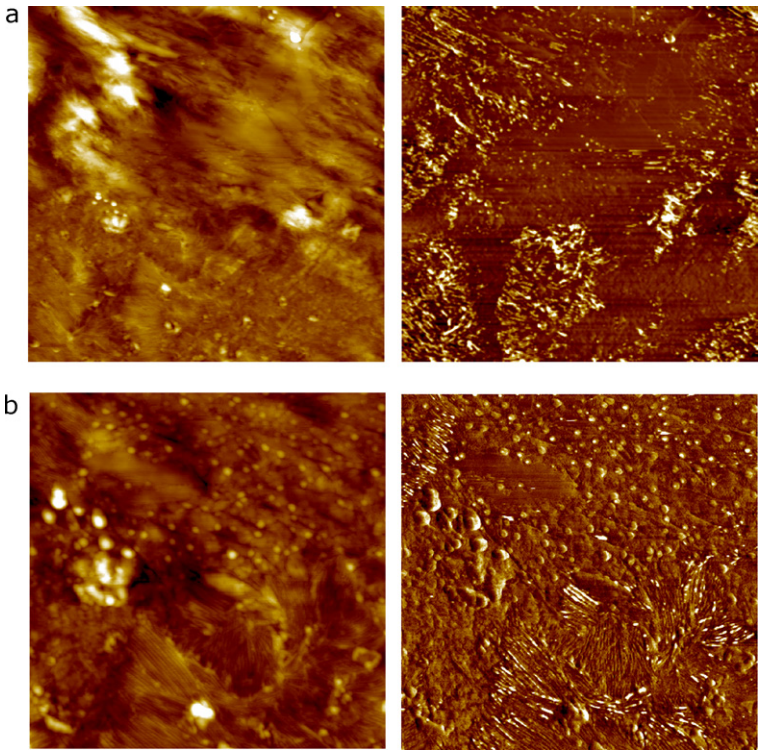

Fig. 5. AFM topography and phase images after exposure to 40 °C/75% RH for two months of a 75/25% felodipine/PVP sample; (a) 5 μm × 5 μm, *z* 54 nm, 68° (b) 2 μm × 2 μm, *z*-scale: 27 nm, 34°.

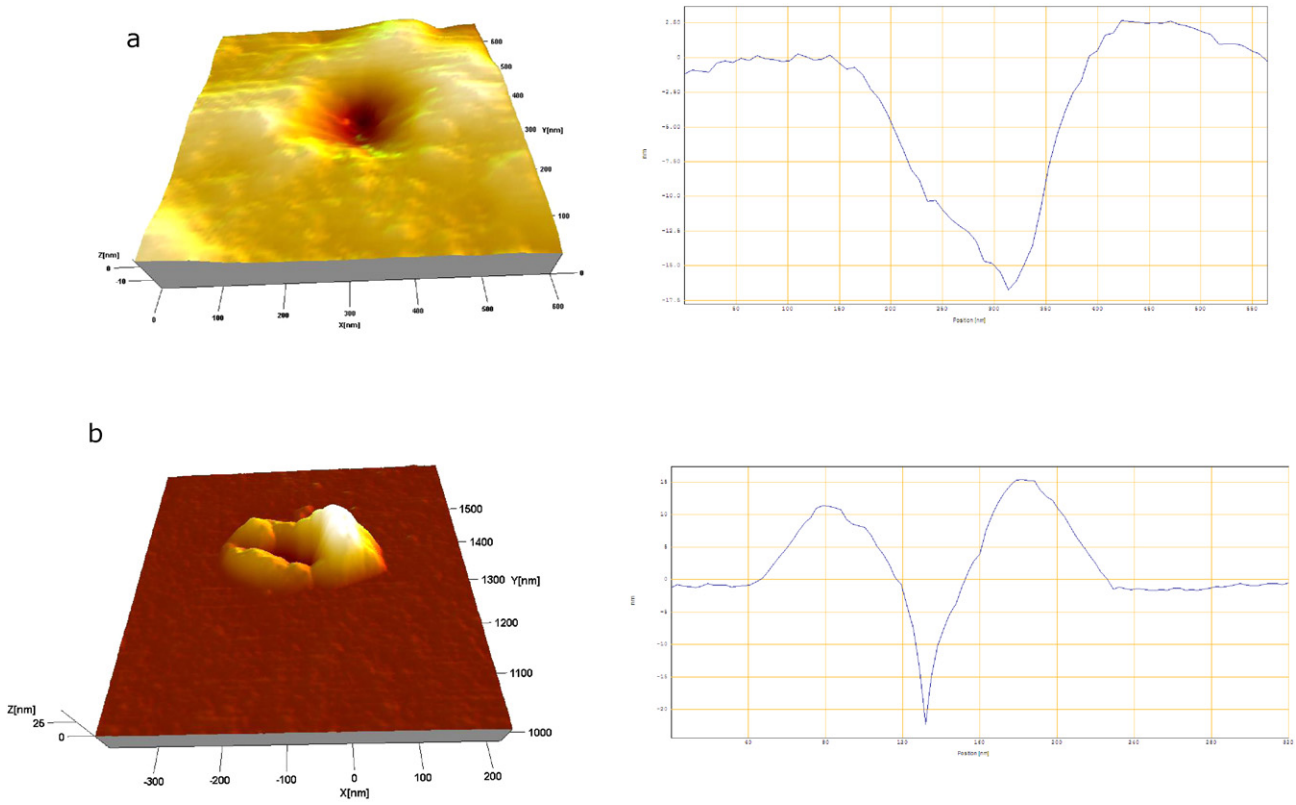

Fig. 6. 3D 600 nm × 600 nm AFM images of indentations following a single NTA measurement (left) and corresponding cross-sectional profile (right) for (a) a felodipine rich region and (b) PVP rich region.

materials or their form. It is therefore, common practice to employ complementary techniques, such as FT-IR, Raman, DSC and P-XRD to assist in this identification. However, these techniques lack the spatial resolution and often the sensitivity to provide identification of materials at the same scale as AFM. NTA analysis, however, can be used to characterize the thermal properties of the different phase separated regions at almost the same spatial resolution as AFM. In Fig. 3, a sample which has been exposed to 75%RH and 40 °C for 3 days is shown along with NTA traces from the different regions. NTA has identified that the raised (brighter in topography) domains as being drug rich, the T_g measured is approximately 50 °C, close to the T_g of the pure drug (48 °C). In contrast, the darker (lower) areas in the topography are PVP-rich, showing a $T_g \approx 200$ °C, close to that of the pure polymer. This thermal data strongly suggest that the sample has effectively completely phase separated, as if mixtures of the drug and polymer still remained T_g measurements should reveal intermediate values (as seen in Fig. 1). Hence, whilst AFM is able to visualize some level of molecular scale heterogeneity (see Fig. 2b'), the lower spatial resolution of NTA (ca. 50 nm) is not sensitive to this.

These data are consistent with previous observations that humidity above 75%RH is sufficient to promote phase separation to enriched domains and eventually to crystallization of the felodipine (Marsac et al., 2010). In this work the water was proposed to decrease drug-polymer hydrogen bonding interactions in a irreversible manner leading to immiscibility, however, it was not possible to unequivocally confirm that individual domains were drug or polymer rich as have been shown here with NTA.

The results shown in Figs. 2 and 3, and in the literature have not explored the nanoscale effect of extended exposure to standard GMP, FDA and ICH guidelines environmental stress conditions for extended periods of time. To address this the development of the morphology of 25% and 75% felodipine loaded samples exposed to 40 °C/75% RH for up to two months was studied (Figs. 4 and 5 respectively). Again the development of a phase separated system is evident at day 1. For the 25% felodipine loaded system less bright regions can be seen in the topography than in Fig. 2 (75% loading) as would be expected if these were related to drug rich areas as identified by NTA. These data demonstrate that further prolonged exposure to high humidity and temperature has led to extensive drug recrystallization. Previously it has been reported that the mechanical stress involved in contact mode AFM is able to locally accelerate the crystallization of amorphous felodipine not stabilized within a polymer (Trojak et al., 2001). No evidence of such an effect was observed here, presumably due to the presence of the PVP and the use of AFM tapping mode as opposed to the more mechanically disruptive contact mode. Although the conditions used here are different to the work of Marsac et al. (2010) the observation of crystallization is consistent with literature, where AFM imaging has shown crystallization of felodipine from PVP for formulations with a drug loading of 50% exposed to a humidity of 94%RH.

To further investigate the localized effect of an NTA measurement on the different components of the sample Fig. 6 shows high-resolution images and topographic cross-section profiles through indents left in the sample after a single NTA measurement at these positions. Fig. 6a was recorded from a drug rich region and Fig. 6b from a PVP rich region. These localized disruptions of the sample clearly demonstrate different features, with the polymer rich region showing an uplifted ring of material around the crater created by the heated NTA probe. This possibly indicates that the PVP when above its T_g and hence in the rubbery state is more adhesive to the AFM probe as it is withdrawn from the surface than the felodipine or that the material is more easily ejected around the indent edge during compression. It should also be noted that the temperature of the probe which reaches 200 °C during a NTA measurements is well beyond the melting point of felodipine (forms I, II and III, 145, 141.8 and 144.0 °C) and hence this material may be vaporized and dispersed during a measurement. Such evidence is further support of the different nature of the separated domains.

4. Conclusions

NTA on felodipine/PVP solid dispersions at various drug loadings was able to identify the expected trend in decreasing glass transition temperature with increased drug loading. Allowing for expected differences due to heating rate the values determined are in agreement with known values from bulk DSC analysis. AFM imaging clearly identifies both the process and the result of phase separation of the solid dispersions under environmental stress conditions of 75%/40 °C and 95%/25 °C. NTA was able to identify the relative composition of the sub-micron scale domains. Exposure to relative humidities above 75% (at 40 °C) was sufficient to initiate phase separation of the drug and polymer into areas of effectively pure drug and polymer over a period of a few days. High values of humidity at a 25 °C (e.g. 95%RH) were also sufficient to cause phase separation within a day. Extended studies of up to two months showed eventual crystallization of the drug.

Nanothermal analysis is shown to be effective at the early detection of instabilities in solid dispersions at the nanoscale and the quantifiable identification of the relative composition of phase separated domains based upon their glass transition temperatures. Such nanoscale phenomena would produce too little change in crystallinity to be detected by bulk techniques such as DSC or XRD (typically at least a ca. 1% (w/w) change is required for detection) and hence can be beneficially supported by nanothermal analysis. It should also be noted that when able to detect such changes techniques such as DSC and XRD provide a more quantitative assessment of factors such as degree of crystallinity and are less subject to sampling variability in heterogeneous samples than NTA.

The combined nanoscale analytical approach employed here is able to systematically study the influence of storage conditions and different drug loadings and to evaluate stability as a function of environmental conditions. This approach may be extended to different drugs in polymer matrices in order to evaluate and screen stability as a function of environmental conditions and to map out formulation design space.

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