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Research Paper

Ability of Different Polymers to Inhibit the Crystallization of Amorphous Felodipine in the Presence of Moisture

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Purpose. To investigate the ability of various polymers to inhibit the crystallization of amorphous felodipine from amorphous molecular dispersions in the presence of absorbed moisture.
Methods. Spin coated films of felodipine with poly(vinylpyrrolidone) (PVP), hydroxypropylmethylcellulose acetate succinate (HPMCAS) and hydroxypropylmethylcellulose (HPMC) were exposed to different storage relative humidities and nucleation rates were measured using polarized light microscopy. Solid dispersions were further characterized using differential scanning calorimetry, infrared spectroscopy and gravimetric measurement of water vapor sorption.
Results. It was found that the polymer additive reduced nucleation rates whereas absorbed water enhanced the nucleation rate as anticipated. When both polymer and water were present, nucleation rates were reduced relative to those of the pure amorphous drug stored at the same relative humidity, despite the fact that the polymer containing systems absorbed more water. Differences between the stabilizing abilities of the various polymers were observed and these were explained by the variations in the moisture contents of the solid dispersions caused by the different hygroscopicities of the component polymers. No correlations could be drawn between nucleation rates and the glass transition temperature (T_g) of the system. PVP containing solid dispersions appeared to undergo molecular level changes on exposure to moisture which may be indicative of phase separation.
Conclusions. In conclusion, it was found that for a given storage relative humidity, although the addition of a polymer increases the moisture content of the system relative to that of the pure amorphous drug, the crystallization tendency was still reduced.

KEY WORDS: amorphous; crystallization; FTIR; solid dispersion; water sorption.

INTRODUCTION

The importance of solid dispersions as a means of improving the kinetic solubility of poorly water soluble drugs has been thoroughly reviewed (1–4). Since amorphous solids are metastable relative to the crystalline form, crystallization during storage can potentially occur, effectively negating any solubility enhancement for solid dispersions that rely on this mechanism. Polymers are commonly used to stabilize the amorphous state during storage, with both synthetic polymers such as polyvinylpyrrolidone (PVP) (5,6) and natural derivatives such as hydroxypropylmethylcellulose (HPMC) (7,8), being employed. The stabilizing effect of polymers has been attributed to their antiplasticization effect following observations that solid dispersions typically possess higher glass transition temperatures (T_g) than the pure amorphous drug, suggesting that a lower molecular mobility may be achieved (6,9). It has also been suggested that the formation of specific drug-polymer interactions such as hydrogen bonds can contribute to physical stabilization (6,10).

In a previous study, we investigated the effectiveness of three different polymers as nucleation inhibitors for amorphous felodipine, formulated as a solid dispersion (11). The three polymers, PVP, HPMC and hydroxypropylmethylcellulose acetate succinate (HPMCAS), all showed a significant initiatory effect on crystallization. However, no discrimination could be made between the three polymers with the nucleation rate of felodipine being reduced by the same extent for a given concentration of additive.

In the aforementioned study, water was rigorously excluded from the systems. However, it is well known that amorphous materials are more hygroscopic than their crystalline counterparts due to the ability to absorb moisture into their bulk structure in addition to surface adsorption. (12,13). The presence of absorbed moisture will result in plasticization and enhanced molecular mobility which can lead to crystallization (5,14,15). It is therefore of interest to examine the ability of different polymers to inhibit crystallization in ternary systems consisting of drug, polymer and water. The number and type of polar functional groups capable of hydrogen bonding with water will affect the amount of moisture absorbed by a system. For example, it has been reported that the larger magnitude of moisture

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absorption into PVP compared to poly(vinylacetate) correlates with the stronger water-pyrrolidone hydrogen bond relative to the water-acetate hydrogen bond (16). Because the active component of a molecular dispersion is typically hydrophobic, then the amount of water sorbed by these systems is likely to be largely dependent on the properties of the polymer. Furthermore, the types of polymers used in solid dispersions for bioavailability enhancement are generally hydrophilic, hence the level of moisture in a solid dispersion may actually be higher for a given storage relative humidity relative to the drug alone. Therefore, it is of interest to probe the ability of a polymer to inhibit crystallization in the presence of absorbed moisture. In other words, how well does a polymer compete as a crystallization inhibitor against the crystallization promoting effects of absorbed moisture and how is this related to the hygroscopicity of the polymer?

In this study, we have investigated nucleation kinetics in thin films of felodipine molecularly dispersed in a polymer and exposed to different storage relative humidities. Three different polymers were studied, PVP, HPMC and HPMCAS. Solid dispersions were also characterized using differential scanning calorimetry to measure the glass transition temperature, gravimetric measurement of water vapor sorption and Fourier Transform Infrared Spectroscopy to probe intermolecular interactions.

MATERIALS

Felodipine was generous gift from AstraZeneca, Södertälje, Sweden. Poly(vinylpyrrolidone) K29/32 (PVP) was purchased from Sigma-Aldrich Co., St. Louis, MO, USA. Hydoxypropylmethylcellulose acetate succinate (HPMCAS: Shin-Etsu AQOAT®, Type AS-MF) and hydoxypropylmethylcellulose USP (HPMC: Pharmacoat® type 606) were generous gifts from Shin-Etsu Chemical Co., Niigata, Japan. Dichloromethane and ethanol were obtained from Mallinckrodt Baker, Inc., Paris, KY, USA and Aaper Alcohol and Chemical Co., Shelbyville, KY, USA, respectively.

METHODS

Preparation of Spin-coated Films

For the analysis of nucleation rate and infrared (IR) measurement, samples were prepared by a spin-coating method. The spin-coating operations were performed using a commercially available spin-coater KW-4A (Chemat Technology Inc., Northridge, CA, USA). Felodipine and polymer were dissolved together in a mixed solvent (dichloromethane:ethanol=1:1), and then the solution was dropped onto a clean substrate spinning at about 2,500 rpm. During spinning, the solution spread out onto the substrate and the solvent was evaporated. The thin film obtained was heated to 90°C for several seconds to remove residual solvent from the film. The preparation was performed under dry conditions (glove box purged with N_2 gas, RH<10%) to minimize contact with water vapor.

Preparation of Bulk Solid Dispersions

Bulk samples of solid dispersion were prepared using solvent evaporation under reduced pressure. Felodipine and polymer were dissolved together in a mixed solvent (dichloromethane:ethanol, 1:1 volume ratio), and then the solvent was removed using a rotary evaporator immersed in a water bath held at 60°C. In order to remove residual solvent, the prepared samples were subsequently left under vacuum for several hours.

Evaluation of Nucleation Sites with Microscopic Observation

For the evaluation of nucleation sites, spin-coated films were prepared on glass cover slips. The spin-coated samples were stored in desiccators over saturated solutions of various relative humidity at 22°C. Salts were used to prepare saturated salt solutions for control of relative humidity (RH) and were of analytical grade. The following saturated salt solutions were used: phosphorous pentoxide (0% RH), lithium chloride (11%RH), magnesium chloride (33% RH), sodium bromide (58% RH), sodium chloride (75% RH). The samples were removed from the desiccators for microscopic observation. At the end of the evaluation (approximately 5 min) they were returned to the desiccators until the next sampling time, when the same samples were reevaluated.

The number of nucleation sites was determined using polarized light microscopy (Olympus BHS system microscope, Olympus Co., Tokyo, Japan). This method relied on the growth of each nucleation site to a size which was detectable using the microscope (approximately 1 μm). A total of 12 individual areas were evaluated for every sample at each time point in order to determine the number of nucleation sites. The site number of density per unit volume was calculated by multiplying the site number density per unit area (17), by the depth of field of the appropriate lens. The depth of field (D_{tot}) as a function of the wavelength of the light used (λ=550 nm) and the numerical aperture (NA) of the lens is given by the following equation (18).

$$D_{tot} = \frac{\lambda n}{\mathrm{NA}^2} + \frac{n \times e}{M \times \mathrm{NA}} \quad (1)$$

Where n is the refractive index of the medium (n_{air}=1.000), e is the smallest distance that can be resolved by a detector (e=14 μm) and M is lateral magnification (M=10×). Based on these calculations, the D_{tot} in this study was 0.0144 mm for the 10× objective.

In some cases, preferential nucleation and growth appeared at the periphery of the films but these sites were not included in our analysis. Triplicate experiments were performed using the procedure described above.

Infra-red Spectroscopy

For FT-IR measurements, spin-coated samples were prepared on ZnS discs in a glove box purged with dry N_2 using a method similar to that described for the preparation of the microscopy samples. Samples were then stored at 75% RH for various time periods and the absorbed moisture was removed by setting samples in a glove box purged with dry N_2 prior to spectroscopic analysis. Following exposure to moisture, no evidence of crystallization was seen either visually or from the resultant spectrum. FT-IR spectra were collected on a Bio-Rad FTS-6000 (Bio-Rad, Cambridge, MA,

USA). One hundred twenty-eight scans were collected at a resolution of 4 cm^{-1} for each sample over the wavenumber region 6,000–400 cm^{-1}. The optics and sample compartment were purged with dry N_2 gas to prevent absorption of moisture into the sample and other spectral interference from water vapor. Win-IR Pro v3.3 software (Digilab, Randolph, MA, USA) was used for the analysis of spectra.

Thermal Analysis

For thermal analysis, samples were prepared using the bulk preparation method described above. Differential scanning calorimetry (DSC) measurements were performed on a TA 2920 modulated DSC (TA Instruments, New Castle, DE, USA). Indium and benzophenone were used to calibrate the temperature scale and indium was employed to calibrate the enthalpic response.

Approximately 5 mg of the sample was weighed into an aluminum sample pan (Perkin Elmer, Boston, MA), equilibrated in a desiccator at the desired RH for 2 days at 25°C and then hermetically sealed. The glass transition temperature (T_g) was determined at a heating rate of 20 K/min, and the onset temperature was reported. All values of the T_g were determined from the second scan after heating the sample to 20 K above T_g followed by cooling to 50 K below T_g in order to erase the previous thermal history. Experiments were performed in triplicate using fresh samples for each run.

Dynamic Moisture Sorption

Vapor sorption isotherms of bulk solid dispersions were generated using a Symmetrical Gravimetric Analyzer (SGA-100) (VTI Corporation, Hialeah, FL) at 25°C. For all samples the total weight was in the range of 7–10 mg. Prior to exposure to increasing RH, samples were dried at 50°C under a stream of dry nitrogen in the sorption analyzer. The equilibrium criterion for the drying step was 0.01% w/w in 2 min with a maximum drying time of 60 min. During the experiment, the sample was exposed to increasing RH from 5 to 95% RH at 10% intervals, 25°C. For samples containing HPMC and HPMCAS, the step isotherm equilibrium criterion was 0.01% w/w in 15 min with a maximum step time of 90 min. For samples containing PVP, it took longer to attain equilibrium hence samples were exposed to each RH for 1,000 min.

RESULTS

Nucleation Rate from Amorphous Solid Dispersions

In a previous study (11), it was found that in absence of moisture, the polymers dramatically reduced nucleation rates in amorphous solid dispersions with the reduction in nucleation rate being dependent on the polymer concentration. These results are reproduced in Fig. 1a. In addition it can be seen that there was very little difference in the stabilizing ability of the three different polymers as a function of concentration when moisture was absent (Fig. 1a). In contrast, on exposure to water vapor (Fig. 1b, c), the stabilizing ability of the polymers starts to differ, with PVP being a less effective nucleation inhibitor than the cellulose polymers at the same storage relative humidity. This is seen most clearly in Fig. 1c, where it is apparent that the divergence in stabilizing ability is greatest at low polymer

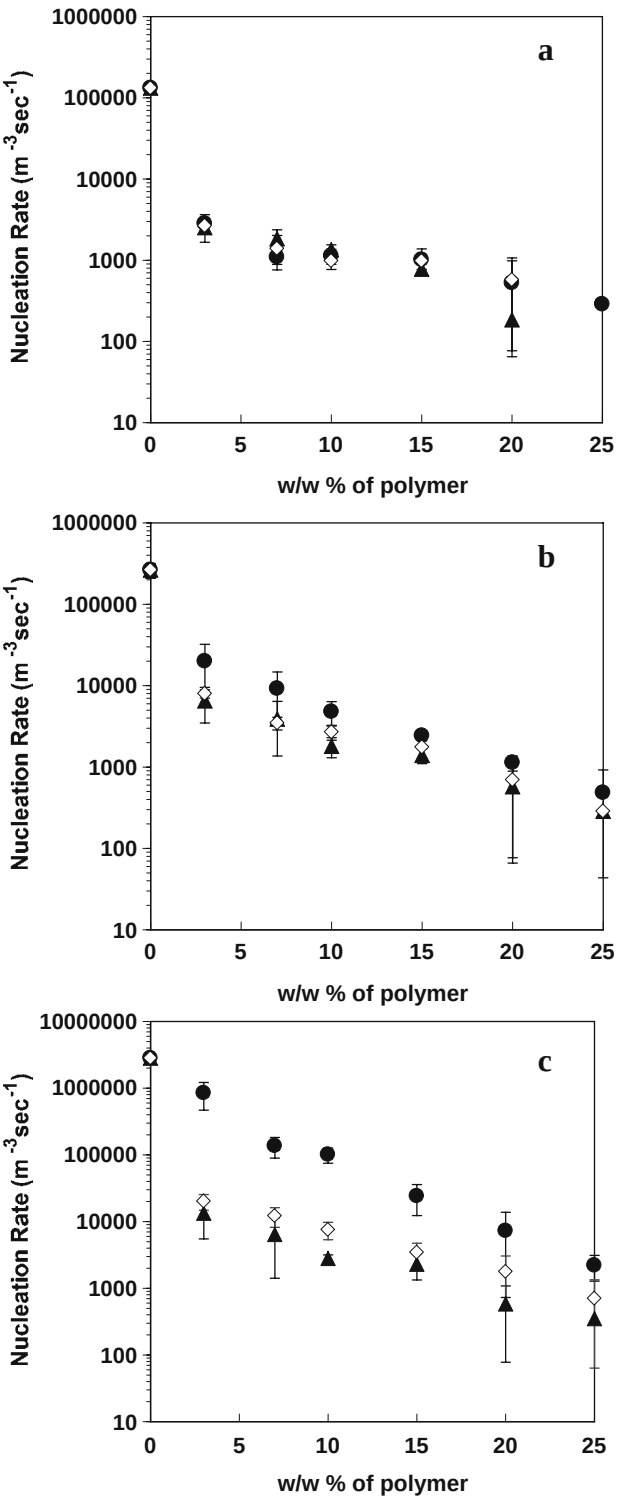

Fig. 1. Nucleation rate as a function of polymer concentration for solid dispersions stored at **a** 0% RH, **b** 33% RH and **c** 75% RH. Symbols represent data for felodipine with PVP (*closed circle*), HPMCAS (*closed triangle*) and HPMC (*open diamond*). Error bars represent the standard deviation, n=3.

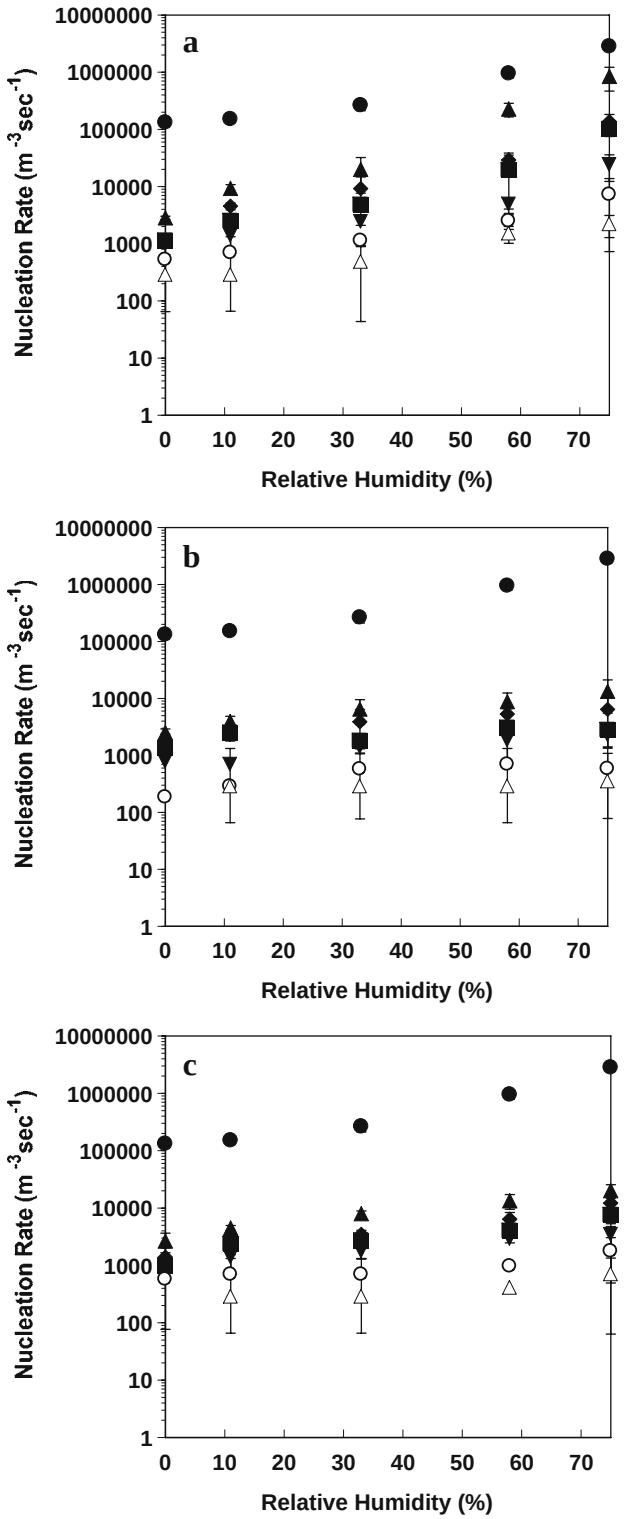

Fig. 2. Nucleation rate as a function of storage relative humidity: Felodipine with **a** PVP, **b** HPMCAS and **c** HPMC. Symbols represent data for samples which contain 0% (*closed circle*), 3% (*closed triangle*), 7 % (*closed diamond*), 10% (*closed square*), 15% (*inverted closed triangle*), 20% (*open circle*) and 25% (*open triangle*) of polymers. Error bars represent the standard deviation, n=3.

contents, while the polymers start to converge as the polymer content increases.

Figure 2 shows more clearly the effect of exposure to increasing relative humidity on the nucleation rate. In all cases, the nucleation rate increases as a function of the storage relative humidity, with the fastest nucleation rates being seen for drug alone. Increasing the concentration of polymer mitigates the influence of relative humidity on nucleation rate. This is particularly apparent for the cellulose polymers where it can be seen that, for the systems containing 25 wt% polymer, the slope of the nucleation rate versus relative humidity plot is close to zero. In contrast, for the systems containing very low percentages of PVP (in particular 3 wt% PVP), the dependence of nucleation rate on

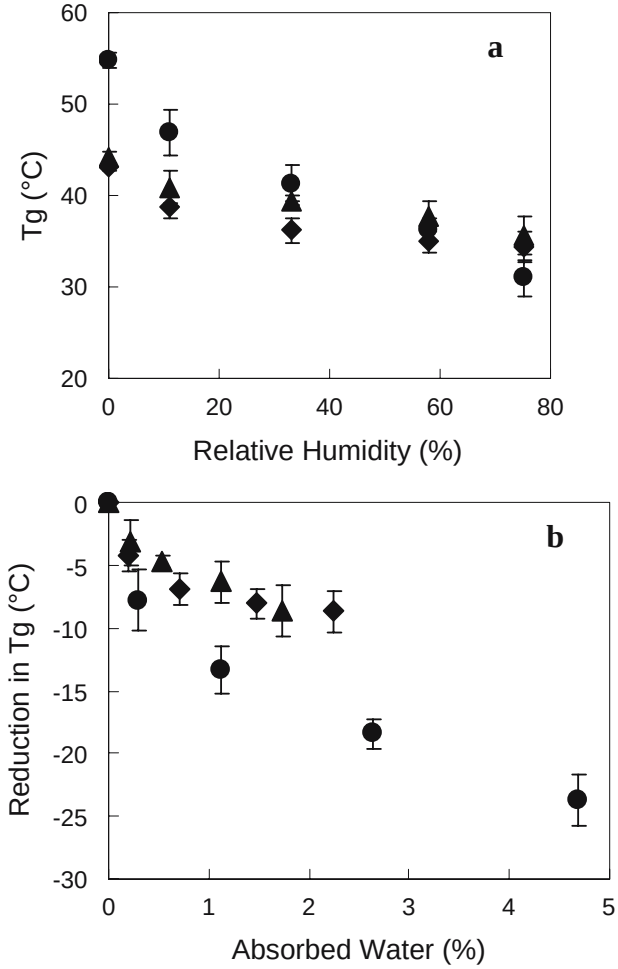

Fig. 3. **a** T_g values for solid dispersions of felodipine containing 25% polymer as a function of relative humidity. **b** Reduction in T_g values for solid dispersions of felodipine containing 25% polymer as a function of moisture content (as estimated from the isothermal moisture sorption data shown in Fig. 5). It can be seen that water is a more efficient plasticizer for PVP than the cellulose polymers. PVP (*closed circle*), HPMCAS (*closed triangle*) and HPMC (*closed diamond*). Error bars represent the standard deviation, n=3.

RH is actually greater than for the pure drug, even though the actual nucleation rate is less for all storage RHs (Fig. 2a).

Glass Transition Temperature of the Solid Dispersions

Figure 3a shows the T_g of the solid dispersions containing 25% polymer following exposure to various storage RHs. It can be seen that, as expected, the T_g values of the felodipine–polymer systems decreased with increasing storage relative humidity. The rate of decrease for the PVP containing system, which had a significantly higher T_g value in the dry state, was greater than for HPMCAS and HPMC as shown in Fig. 3b where the relationship between T_g and moisture content (as estimated from the moisture sorption data presented in a later section) is shown. Here it is apparent that water is a more efficient plasticizer for the PVP containing system. Because of the higher initial T_g, a solid dispersion containing 25% PVP maintains a higher T_g than the equivalent HPMC/HPMCAS systems until about 60% RH, where the curves intersect leading ultimately to a slightly lower T_g at 75% RH for the PVP containing dispersion (Fig. 3a).

The relationship between T_g and polymer concentration in the absence of moisture has been reported previously for felodipine solid dispersions (11). Figure 4 compares T_g values for the dry systems (11) with those obtained following storage at 75%RH, as a function of polymer concentration. In the absence of moisture, T_g increased as a function of polymer concentration. However, the antiplasticization effect of each polymer was counteracted by absorbed moisture. In the presence of moisture and at low polymer concentrations, T_g is reduced below that of pure amorphous (dry) felodipine.

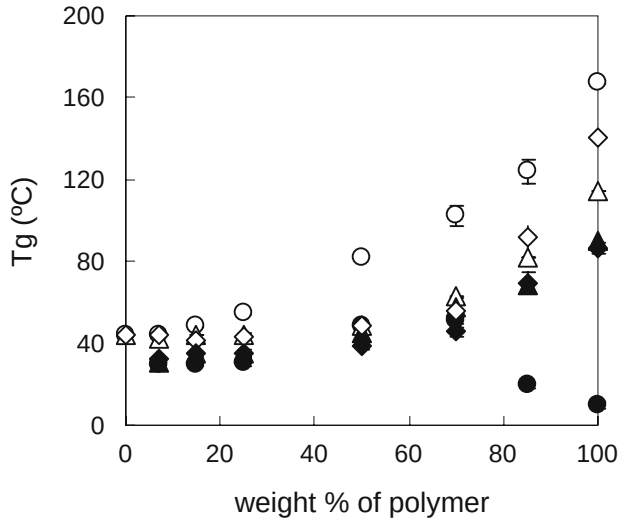

Fig. 4. T_g values for dry solid dispersions and solid dispersions stored at 75% RH as a function of polymer content. Open symbols are for samples stored at 0%RH, closed symbols are for samples stored at 75% RH. PVP (circle), HPMCAS (*triangle*) and HPMC (*diamond*). Error bars represent the standard deviation, n=3.

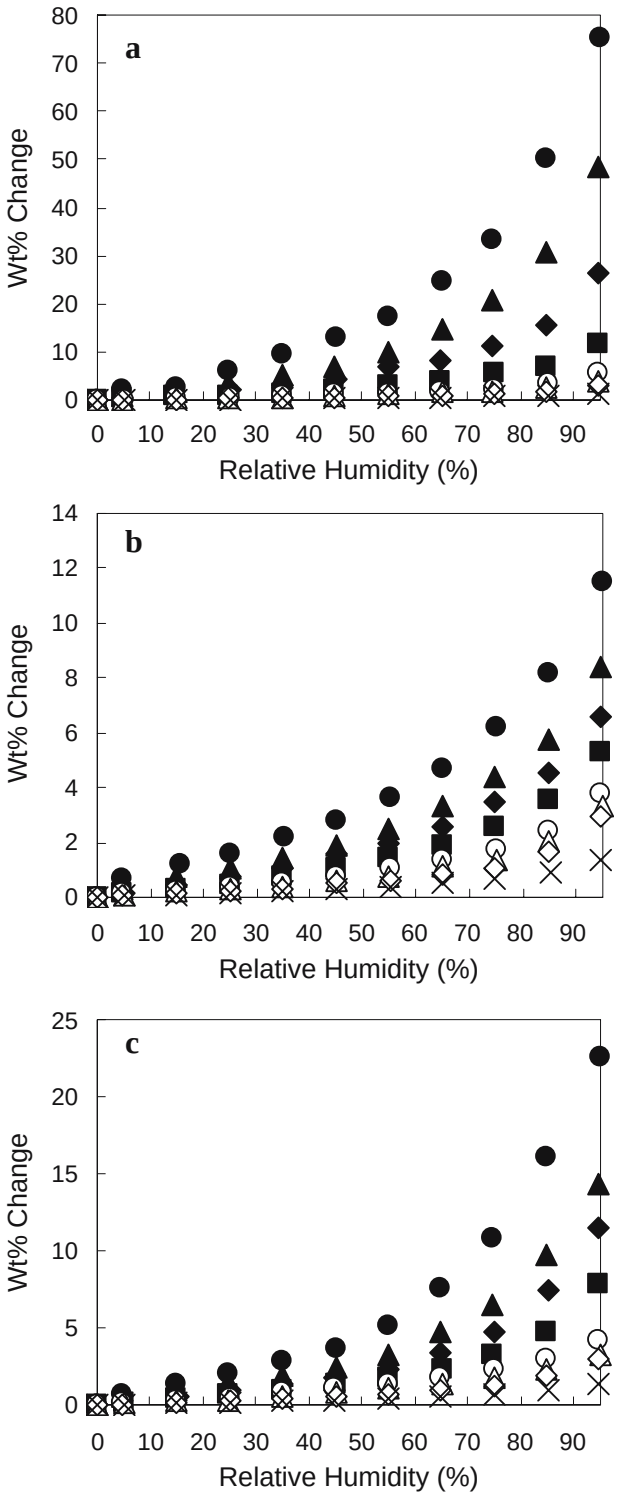

Fig. 5. Moisture sorption profiles for solid dispersions of felodipine obtained at 25°C; **a** PVP, **b** HPMCAS and **c** HPMC. Symbols represent the concentration of polymer; 100% (*closed circle*), 85% (*closed triangle*), 70% (*closed diamond*), 50% (*closed square*), 25% (*open circle*), 15% (*open triangle*), 7% (*open diamond*) and 0% (pure amorphous felodipine) (×).

For the cellulose polymers, as the polymer content increases, T_g starts to increase. For PVP solid dispersions, a maximum T_g value is obtained around 70% polymer followed by a sharp decrease for higher concentrations. It is relevant to note at this point that all samples stored at 75% RH and containing up to 25% polymer (the maximum amount of polymer used for the nucleation studies) had lower T_g values than pure dry amorphous felodipine.

Analysis of Isothermal Water Vapor Absorption

Although the influence of storage RH on crystallization tendency is of practical importance, it is also important to understand the relationship between RH and water content. Therefore, moisture sorption isotherms were determined for amorphous felodipine, each polymer and the various solid dispersions with the results presented in Fig. 5. Felodipine is a hydrophobic substance and as an amorphous solid, absorbs very low amounts of moisture. The three pure polymers show large variation in the amount of moisture absorbed with PVP being the most hygroscopic and HPMCAS the least hygroscopic. The amounts of water sorbed by the solid dispersions increased with increasing polymer content over the entire relative humidity for all polymers, indicating that adding a polymer increases the hygroscopicity of the system. The solid dispersions with PVP absorbed more moisture than those containing HPMC or HPMCAS.

Figure 6 shows the amount of moisture absorbed by the solid dispersions following storage at 75% RH and the difference in the T_g between the dry state and after storage at 75% RH as a function of polymer content. Figure 6 shows more clearly that the amounts of water absorbed by the solid dispersions increased with increasing polymer concentration in the solid dispersions and that the solid dispersions containing PVP absorbed more water than the other polymers with the difference becoming particularly noticeable at higher polymer contents. It can be also seen that the difference in T_g between the dry state and after storage at 75% RH was greater as the polymer content increased, with the PVP containing dispersions showing the biggest moisture induced decrease in T_g. Based on the data shown in Fig. 6, it is obvious that the plasticization of the solid dispersions by water is directly related to the hygroscopicity of polymer used to form the dispersion.

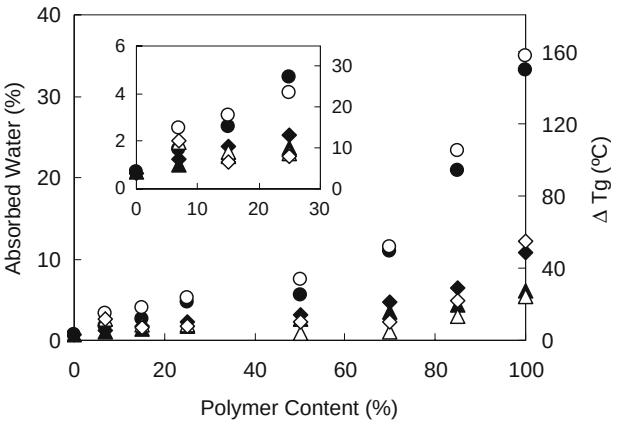

Fig. 6. Difference in T_g values (ΔT_g) for dry samples and samples exposed to 75% RH as a function of polymer concentration (*open symbol*) and the amount of absorbed water in solid dispersions as a function of polymer concentration (*closed symbol*). PVP (*circle*), HPMCAS (*triangle*) and HPMC (*diamond*). The insert data for low concentrations of polymer.

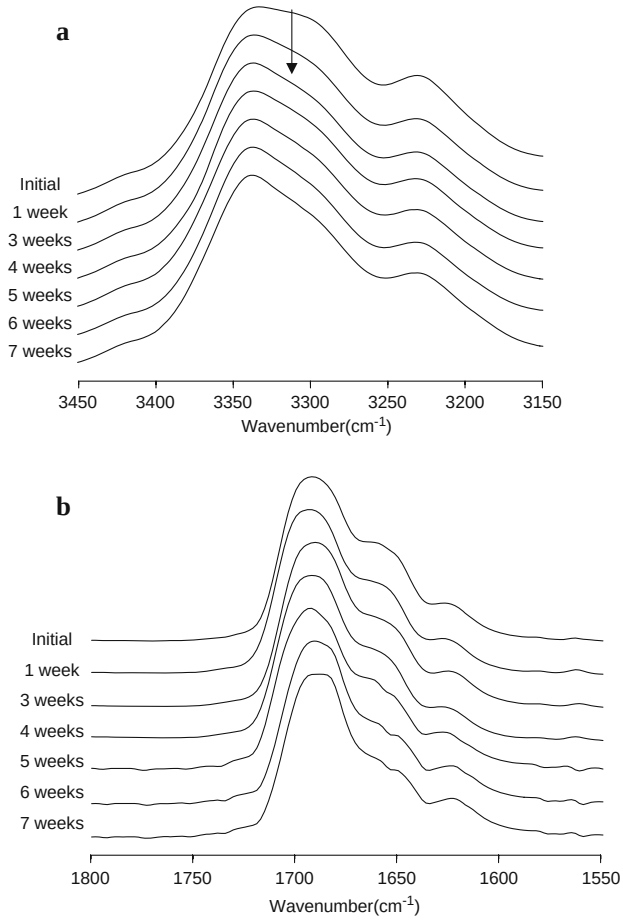

Fig. 7. Infrared spectra of solid dispersions of felodipine with 25% PVP showing **a** the NH stretching region (3,150–3,450 cm^{-1}) and **b** the carbonyl stretching region (1,550–1,800 cm^{-1}) following exposure for various periods of time (up to 7 weeks) to 25°C 75% RH. Residual moisture was removed from samples prior to analysis. The arrow shows the decrease in intensity of the shoulder assigned to drug-polymer interactions.

FTIR Spectroscopy

Figures 7, 8 and 9 show FTIR spectra of the NH and C=O stretching regions for solid dispersions containing 25% polymer that were stored at 25°C 75% RH for various periods of time and then dried prior to analysis. For the solid dispersions containing PVP, shown in Fig. 7, the peaks at around 3345 cm^{-1} (higher wavenumber shoulder) and 3,291 cm^{-1} (lower wavenumber shoulder) correspond to felodipine–felodipine interactions and felodipine–PVP interactions, respectively, as described previously (11). It is clear from Fig. 7a, that the peak assigned to drug–polymer interactions decreases in intensity relative to the peak arising from drug–drug interactions as the time of exposure to high RH increased (note that the absorbed moisture was removed prior to obtaining the IR spectra, so that the only interactions being detected are between drug and

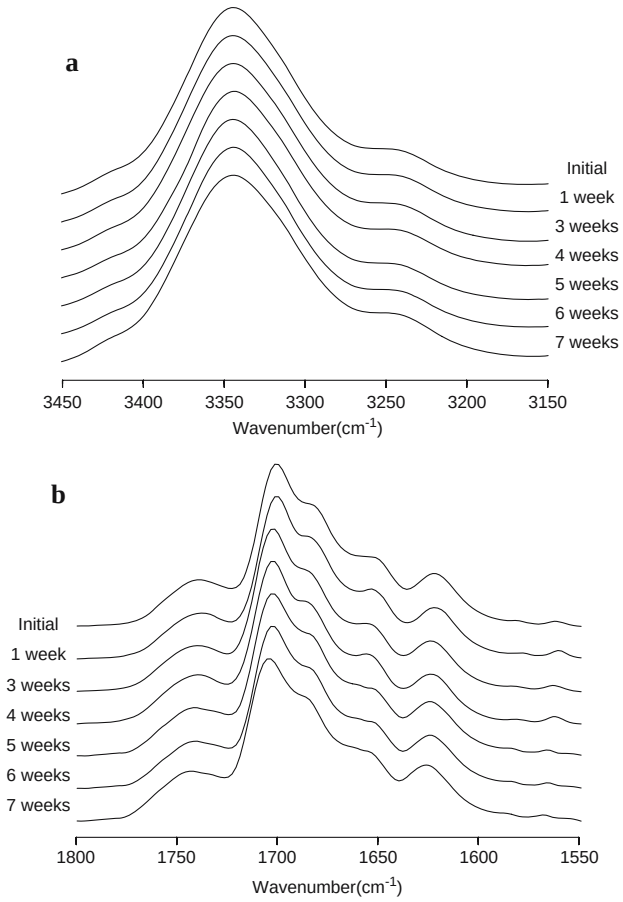

Fig. 8. Infrared spectra of solid dispersions of felodipine with 25% HPMCAS showing **a** the NH stretching region (3,150–3,450 cm^{-1}) and **b** the carbonyl stretching region (1,550–1,800 cm^{-1}) following exposure for various periods of time (up to 7 weeks) to 25°C 75% RH. Residual moisture was removed from samples prior to analysis.

polymer). These results suggest that absorbed moisture disrupts drug–polymer interactions and that this disruption persists even after moisture is removed. The changes in the carbonyl region (felodipine contains two and PVP contains one carbonyl function) are consistent with the disruption of drug–polymer interactions whereby the shoulder at around 1,655 cm^{-1}, which is assigned to the PVP carbonyl hydrogen bonded with the drug (19), decreases in intensity following exposure to water vapor followed by drying. In contrast, solid dispersions prepared with HPMCAS and HPMC show no notable differences in the spectra following exposure to water vapor and drying, in either in the NH or the C=O region as shown in Figs. 8 and 9.

Figure 10 shows the FTIR spectra obtained from solid dispersions containing 3% of polymer (either PVP or HPMCAS) after storage at 75% RH followed by drying. For the PVP containing solid dispersion, Fig. 10a clearly shows that the NH peak shifts to a higher wavenumber, from 3,345 cm^{-1} in the initial solid dispersion to 3,373 cm^{-1} after 2 weeks of exposure to 75% RH. The peak at 3,373 cm^{-1} corresponds to the NH stretching peak of crystalline felodipine and indicates that the sample has crystallized. The solid dispersion with HPMCAS shows less change in the NH peak over the same exposure time, suggesting that a lower extent of crystallization has occurred (Fig. 10b). Results for HPMC were similar to for HPMCAS. These observations are consistent with the nucleation rate data shown in Fig. 1c and also serve to demonstrate that the changes observed in a dispersion containing 25% PVP cannot be accounted for by crystallization (Fig. 7a)

DISCUSSION

There have been many studies which demonstrate increased crystallization rates for single component amorphous systems exposed to moisture (3,20–24) and decreased crystallization rates in binary drug–polymer amorphous solid dispersions (6,9,10,14,25). Such results are often ascribed to water acting as a plasticizer while the polymeric additive serves as an antiplasticizer (26–28). However, there are very few reports describing crystallization rates in ternary systems consisting of a hydrophobic drug, a hydrophilic polymer and absorbed water. Ternary systems are of practical relevance since it is virtually impossible to completely exclude moisture from a formulation. In this study it was observed that there is

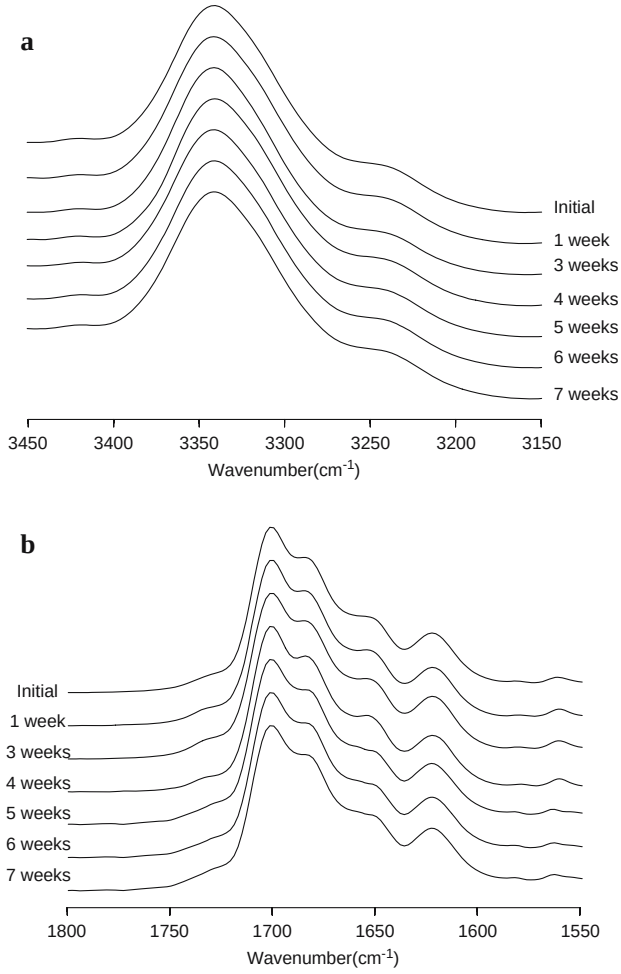

Fig. 9. Infrared spectra of solid dispersions of felodipine with 25% HPMC showing **a** the NH stretching region (3,150–3,450 cm^{-1}) and **b** the carbonyl stretching region (1,550–1,800 cm^{-1}) following exposure for various periods of time (up to 7 weeks) to 25°C 75% RH. Residual moisture was removed from samples prior to analysis.

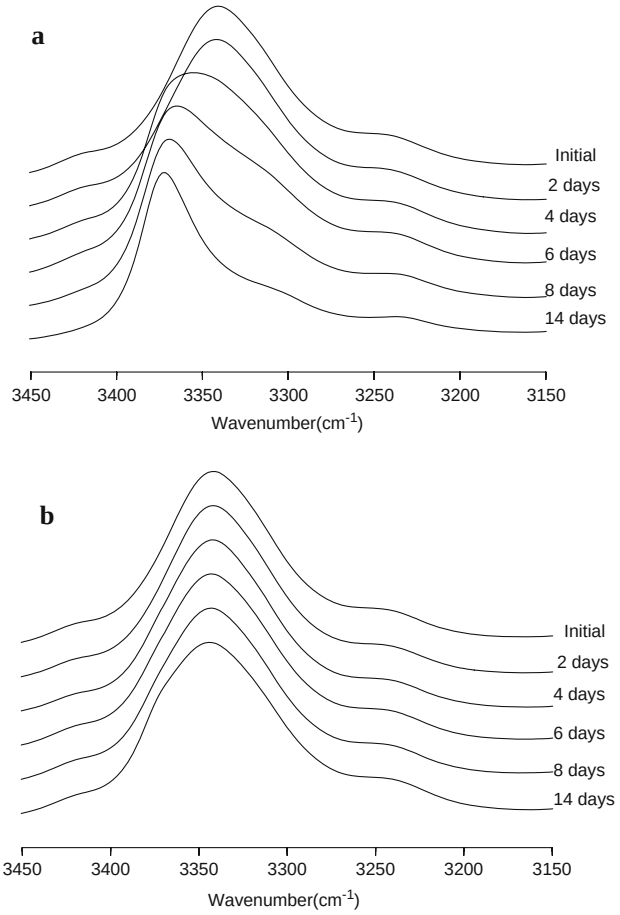

Fig. 10. Infrared spectra of solid dispersions of felodipine with 3% **a** PVP and **b** HPMCAS showing the NH stretching region (3,150–3,450 cm^{-1}) following exposure for various periods of time (up to 2 weeks) to 25°C 75% RH. Residual moisture was removed from samples prior to analysis.

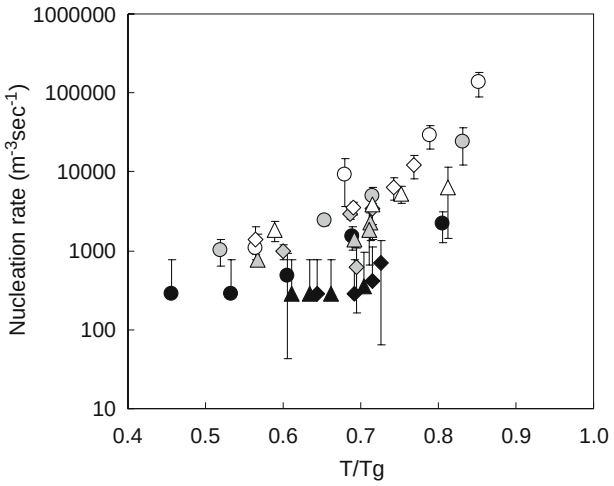

Fig. 11. Nucleation rate as a function of T/T_g.where T was 22°C Symbols indicate the type of polymer in solid dispersions; PVP (*circle*), HPMCAS (*triangle*) and HPMC (*diamond*) and polymer content; 7% (*open*), 15% (*grey*) and 25% (*black*). Error bars represent the standard deviation, n=3.

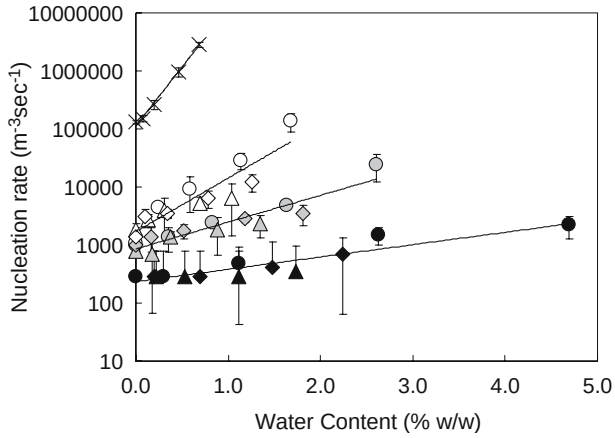

Fig. 12. Nucleation rate as a function of water content. Symbols indicated the type of polymer in solid dispersions; PVP (*circle*), HPMCAS (*triangle*) and HPMC (*diamond*) and polymer content; 0% (amorphous felodipine) (×), 7% (*open*), 15% (*grey*) and 25% (*black*). Error bars represent the standard deviation, n=3. The solid line represents the linear-regression curve (R^2 values are 0.9942 (0% polymer), 0.8463 (7% polymer), 0.8873 (15% polymer) and 0.8592 (25% polymer).

a competing effect between the polymer which acts as a crystallization inhibitor, and water which enhances crystallization. As shown in Fig. 2, nucleation rates were enhanced by absorbed moisture, however, for any given storage RH, systems containing polymer had a lower nucleation rate than drug alone (Figs. 1 and 2). Furthermore, in the presence of moisture, the ability of different polymers to inhibit crystallization of felodipine from the amorphous solid dispersion varied quite considerably, even though each polymer had a similar inhibitory ability in the absence of moisture (11). The disparity in stabilizing ability between the polymers was greatest at low polymer concentrations. For example, it can be seen from Fig. 1c that the nucleation rate of a sample stored at 75% RH is only slightly decreased by the addition of 3% PVP, whereas the same amount of either HPMC or HPMCAS resulted in a more dramatic decrease in nucleation rate. However, when the polymer concentration reached 25%, the stabilizing abilities of the various polymers were similar (Fig. 1c). These results are difficult to rationalize based on changes in T_g. At the polymer concentrations employed and in the absence of moisture, the T_gs of the solid dispersions are not very different from that of pure felodipine (11). As expected, absorbed moisture results in a decrease in T_g. However, since felodipine is extremely hydrophobic, dispersions containing low amounts of polymer do not absorb very much water and therefore are only slightly plasticized as shown in Fig. 4. In addition, the T_g of the dispersions containing the various polymers are not very different from each other. The lack of a systematic correlation between nucleation rate and T_g is clearly shown by Fig. 11. The relationship between nucleation rate and T_g is even more interesting if Figs. 1 and 4 are compared. Figure 4 indicates that the T_gs of the solid dispersion systems (0–25% polymer) that have been exposed to moisture are all lower that of dry amorphous felodipine (about 43°C). However, the dispersions containing the cellulose polymer and dispersions

containing PVP at a concentration greater than 7%, have lower nucleation rates than dry amorphous felodipine. Thus, the polymers are still able to act as crystallization inhibitors even when T_g is reduced.

As shown in Fig. 5, the individual polymers and hence solid dispersions prepared with the various polymers, have an increased tendency to absorb moisture relative to pure amorphous felodipine. Each polymer has a different affinity for water and, for any given storage RH, the PVP containing dispersions have much higher water contents than dispersions prepared with cellulose polymers. It is therefore relevant to consider the relationship between the nucleation rate and the water content and these data are presented in Fig. 12. Presenting the data in this manner reveals some extremely interesting trends. Firstly, it can be seen that although the pure amorphous drug picks up the least amount of water, the nucleation rate is very sensitive to small amounts of absorbed moisture as reflected by the steepness of the slope. A similar tendency for enhanced nucleation rates in the presence of moisture has been observed for another hydrophobic drug, indomethacin (17). As the amount of polymer in the solid dispersion increases, the amount of sorbed water at any given RH increases, however the dependence of nucleation rate on water content decreases. Thus for systems containing 25% polymer, considerable amounts of water are absorbed, but the nucleation rate does not increase very dramatically. In addition, it can be seen, that within experimental error, for a given concentration of polymer, the ability of each polymer to influence the nucleation rate appears to be dependent on the water content of the system. That is, the variation in the stabilizing ability of the different polymers at a particular concentration appears to be reasonably explained by their different tendencies to absorb moisture, although it must be conceded that there is considerable scatter in the nucleation rate data. These results suggest that the chemistry of the polymer is only important to its stabilizing ability in so far as it affects the moisture sorption properties of the solid dispersion. In other words, it is unlikely that the stabilizing ability of the polymers in the presence of absorbed moisture can be attributed to any specific drug–polymer interactions. A similar conclusion was reached for these solid dispersion systems in the absence of moisture (11). This apparent non-specific stabilization against crystallization by polymers of quite different chemistries clearly needs to be investigated more thoroughly.

As well as being more hygroscopic than the cellulose polymers, a solid dispersion prepared with PVP appears to undergo molecular level changes on exposure to a high RH (Fig. 7). The spectroscopic changes observed are consistent with the disruption of intermolecular interactions between the drug and polymer leading to more drug–drug interactions. These results suggest that the system maybe undergoing a partial phase separation induced by the absorbed moisture. On removal of the moisture, the solid dispersion does not remix at room temperature indicating that the system has been kinetically trapped as a partially phase separated system. This type of behavior was not observed for dispersions prepared with the cellulose polymers. The PVP containing systems may be more susceptible to moisture induced phase separation either because they simply absorb more moisture or for more complex reasons relating to relative polarities of each of the three components in the ternary system. This is clearly a phenomenon that needs to be explored in more detail since phase separation would be expected to affect the performance of the solid dispersion.

CONCLUSIONS

Amorphous felodipine does not absorb large quantities of water on exposure to high RH due to the hydrophobicity of the drug. However, small amounts of absorbed moisture result in a dramatic increase in the nucleation rate. Forming a solid dispersion with a hydrophilic polymer increases the hygroscopicity of the system and results in a decrease in T_g, whereby the amount of moisture absorbed depends both on the type and amount of polymer employed. However, in spite of the increased hygroscopicity of the system, the nucleation rate is reduced relative to the drug alone. In addition, the dependence of nucleation rate on moisture content becomes less sensitive as the concentration of polymer increases. Differences between the stabilizing ability of the three model polymers could be accounted for by differences in water content, but no correlation could be made with T_g. PVP containing systems showed evidence of a tendency to phase separate when stored at high RH.

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REFERENCES

1. W. L Chiou and S. Riegelman. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* **60**:1281–1302 (1971).
2. J. L Ford. The current status of solid dispersions. *Pharm. Acta Helv.* **61**:69–88 (1986).
3. A. T. M. Serajuddin. Solid dispersions of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs. *J. Pharm. Sci.* **88**:1058–1066 (1999).
4. C. Leuner and J. Dressman. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* **50**:47–60 (2000).
5. M. Yoshioka, B. C Hancock, and G. Zografi. Inhibition of indomethacin crystallization in poly(vinylpyrrolidone). *J. Pharm. Sci.* **84**:983–986 (1995).
6. L. S Taylor and G. Zografi. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.* **14**:1691–1698 (1997).
7. T. Hino and J. L. Ford. Characterization of the hydroxypropylmethylcellulose–nicontinamide binary system. *Int. J. Pharm.* **219**:39–49 (2001).
8. K. Yamashita, T. Nakate, K. Okimoto, A. Ohike, Y. Tokunaga, R. Ibuki, K. Higaki, and T. Kimura. Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int. J. Pharm.* **267**:79–91 (2003).
9. T. Matsumoto and G. Zografi. Physical properties of solid dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl acetate) in relation to indomethacin crystallization. *Pharm. Res.* **16**:1722–1728 (1999).

10. T. Miyazaki, S. Yoshioka, Y. Aso, and S. Kojima. Ability of poly(vinylpyrrolidone) and polyacrylic acid to inhibit the crystallization of amorphous acetaminophen. *J. Pharm. Sci.* **93**:2710–2717 (2004).
11. H. Konno and L. S. Taylor. Influence of different polymers on the crystallization tendency of molecularly dispersed amorphous felodipine. *J. Pharm. Sci.* **95**:2692–2705 (2006).
12. G. Zografi. States of water associated with solids. *Drug Dev. Ind. Pharm.* **14**:1905–1926 (1988).
13. C. Ahlneck and G. Zografi. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int. J. Pharm.* **62**:87–95 (1990).
14. S. L. Shamblin and G. Zografi. The effects of absorbed water on the properties of amorphous mixtures containing sucrose. *Pharm. Res.* **16**:1119–1124 (1999).
15. C. A. Oksanen and G. Zografi. The relationship between the glass transition temperature and water vapor absorption by poly(vinylpyrrolidone). *Pharm. Res.* **7**:654–657 (1990).
16. L. S. Taylor, F. W. Langkilde, and G. Zografi. Fourier transform Raman spectroscopic study of the interaction of water vapor with amorphous polymers. *J. Pharm. Sci.* **90**:888–901 (2001).
17. V. Andronis and G. Zografi. Crystal nucleation and growth of indomethacin polymorphs from the amorphous state. *J. Non-Cryst. Solids* **271**:236–248 (2000).
18. S. Inoue and R. Oldenbourg. Microscopes. Handbook of Optics, Volume II, Bass, M. (ed), McGraw-Hill, New York, 1995.
19. L. S. Taylor and G. Zografi. Sugar–polymer hydrogen bond interactions in lyophilized amorphous mixtures. *J. Pharm. Sci.* **87**:1615–1621 (1998).
20. B. C. Hancock and G. Zografi. Characteristics and significance of amorphous state in pharmaceutical systems. *J. Pharm. Sci.* **86**:1–12 (1997).
21. B. Makower and W. C. Dye. Equilibrium moisture content and crystallization of amorphous sucrose and glucose. *J. Agric. Food Chem.* **4**:72–77 (1956).
22. H. Imaizumi, N. Nambu, and T. Nagai. Stability and several physical properties of amorphous and crystalline forms of indomethacin. *Chem. Pharm. Bull.* **28**:2565–2569 (1980).
23. C. Schimitt, C. W. Davis, and S. T. Long. Moisture-dependent crystallization of amorphous lamotrigine mesylate. *J. Pharm. Sci.* **85**:1215–1219 (1996).
24. V. Andronis, M. Yoshioka, and G. Zografi. Effects of sorbed water on the crystallization of indomethacin from the amorphous state. *J. Pharm. Sci.* **86**:346–351 (1997).
25. F. Tanno, Y. Nishiyama, H. Kokubo, and S. Obara. Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions. *Drug Dev. Ind. Pharm.* **30**:9–17 (2004).
26. A. Saleki-Gerhard and G. Zografi. Non-isothermal and isothermal crystallization of amorphous state. *Pharm. Res.* **11**:1166–1173 (1994).
27. B. C. Hancock and G. Zografi. The relationship between glass transition temperature and water content of amorphous pharmaceutical solids. *Pharm. Res.* **11**:471–477 (1994).
28. G. Van den Mooter, M. Wuyts, N. Blaton, R. Busson, P. Grobet, P. Augustijns, and R. Kinget. Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur. J. Pharm. Sci.* **12**:261–269 (2001).