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Phase Behavior of Poly(vinylpyrrolidone) Containing Amorphous Solid Dispersions in the Presence of Moisture

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Abstract: The objective of this study was to investigate the phase behavior of amorphous solid dispersions composed of a hydrophobic drug and a hydrophilic polymer following exposure to elevated relative humidity. Infrared (IR) spectroscopy, differential scanning calorimetry (DSC) and moisture sorption analysis were performed on five model systems (nifedipine−poly(vinylpyrrolidone) (PVP), indomethacin−PVP, ketoprofen−PVP, droperidol−PVP, and pimozide−PVP) immediately after production of the amorphous solid dispersions and following storage at room temperature and elevated relative humidity. Complete miscibility between the drug and the polymer immediately after solid dispersion formation was confirmed by the presence of specific drug−polymer interactions and a single glass transition (T_g) event. Following storage at elevated relative humidity (75−94% RH), nifedipine−PVP, droperidol−PVP, and pimozide−PVP dispersions formed drug-rich and polymer-rich amorphous phases prior to crystallization of the drug, while indomethacin−PVP and ketoprofen−PVP dispersions did not. Drug crystallization in systems exhibiting amorphous−amorphous phase separation initiated earlier (<6 days at 94% RH) when compared to systems that remained miscible (≥46 days at 94% RH). Evidence of moisture-induced amorphous−amorphous phase separation was observed following storage at as low as 54% RH for the pimozide−PVP system. It was concluded that, when an amorphous molecular level solid dispersion containing a hydrophobic drug and hydrophilic polymer is subjected to moisture, drug crystallization can occur via one of two routes: crystallization from the plasticized one-phase solid dispersion, or crystallization from a plasticized drug-rich amorphous phase in a two-phase solid dispersion. In the former case, the polymer is still present in the same phase as the drug, and can inhibit crystallization to a greater extent than the latter scenario, where the polymer concentration in the drug phase is reduced as a result of the amorphous−amorphous phase separation. The strength of drug−polymer interactions appears to be important in influencing the phase behavior.

Keywords: Solid dispersion; miscibility; moisture; amorphous; crystallization

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Introduction

Delivery of active pharmaceutical ingredients in the amorphous form can be exploited as a strategy to increase apparent solubilities and dissolution rates, which in turn may lead to higher bioavailability.[1−4] However, these enhanced

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properties come at the cost of decreased physical and chemical stability relative to their crystalline counterparts.[5−7] Compared to the corresponding crystalline solid, amorphous materials also have increased hygroscopicity, since water can be absorbed into their internal structure in addition to being adsorbed on the surface.[8] Studies have shown that crystallization rates of amorphous drugs are higher when exposed to moisture.[9,10] To prevent drug crystallization over pharmaceutically relevant time scales, a second component is often added. When the second component is intimately mixed with the drug at the molecular level, the system is typically referred to as an amorphous molecular level solid dispersion.[11] Often, the second component is a hydrophilic polymer, and the overall hygroscopicity of the system is increased relative to the pure amorphous drug.

The presence of water in amorphous solid dispersions (ASD) has many potential implications. Absorbed water decreases the glass transition temperature (T_g) of both small molecules and polymers.[9,10,12,13] Due to its large free volume and high molecular mobility, absorbed water has been shown to increase the overall molecular mobility leading to faster drug crystallization.[10,14] In addition, due to changing composition upon absorption of moisture (i.e., the addition of a third component), the thermodynamic properties of the system will be altered.[15] For solid dispersions composed of a hydrophobic drug and a hydrophilic polymer, the presence of water may drive the system toward immiscibility, in other words, induce amorphous−amorphous phase separation. In this instance, the drug and the polymer, which were initially intimately mixed, will separate into amorphous drug-rich and polymer-rich domains. This phenomenon has been reported previously for felodipine and poly(vinylpyrrolidone) (PVP)[16,17] and griseofulvin−PVP dispersions.[18]

Infrared (IR) spectroscopy offers several advantages for studying moisture induced changes in dispersions; specific interactions between the drug and the polymer molecules can be quickly and noninvasively characterized, and control of the sample temperature and atmosphere is relatively straightforward. Drug−polymer specific interactions provide information about the intimacy of mixing, or miscibility, between the drug and the polymer in the dispersions.[19−21] Disruption of drug−polymer interactions and the formation of drug−drug interactions indicate that phase separation has occurred, either as a result of crystallization of the drug or because of amorphous−amorphous phase separation. Examples of amorphous−amorphous phase separation include the indomethacin−citric acid system[22] as well as itraconazole−Eudragit E100 dispersions;[23] however, the effects of moisture on miscibility have not been extensively evaluated. The goal of this study was to test the hypothesis that certain drug−polymer amorphous solid dispersions will undergo moisture induced amorphous−amorphous phase separation

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prior to crystallization of the drug. IR spectroscopy was chosen as the primary technique of choice to monitor moisture-induced molecular level changes in the solid dispersions. PVP was selected as the model polymer to form dispersions with five model drugs, which in turn were selected to encompass a range of chemistries and potential interactions with PVP.

Experimental Methods

Dichloromethane (ChromAR grade) and chloroform (AR grade) were obtained from Mallinckrodt Baker, Inc., Paris, KY, while ethanol (200 proof) was obtained from Aaper Alcohol and Chemical Co., Shelbyville, KY. Poly(vinylpyrrolidone) (PVP) K29-32, pimozide, droperidol, ketoprofen, and indomethacin were purchased from Sigma-Aldrich Co., St. Louis, MO, and nifedipine was obtained from Hawkins, Inc., Minneapolis, MN. PVP K12 was obtained from BASF, Ludwigshafen, Germany. Prior to use, PVP was dried in a desiccator over powdered phosphorus pentoxide for at least one week.

Infrared Spectroscopy. Binary mixtures of the model drug and PVP were prepared at different weight ratios and dissolved in a common solvent. For nifedipine−PVP systems, the solvent used was a 1:1 w/w mixture of dichloromethane and ethanol. For droperidol−PVP and pimozide−PVP systems, chloroform was used, while for indomethacin−PVP and ketoprofen−PVP systems, the solvent was ethanol. All mixtures were visually inspected to confirm that the drugs and the polymer were fully dissolved, and the systems formed uniform one-phase solutions.

One to two drops of the solution were then placed on ZnS or KRS-5 substrates, which were immediately rotated on a KW-4A two-stage spin coater (Chemat Technology, Northridge, CA) at 500/2500 rpm for 18 and 30 s respectively. Immediately after spin-coating, the substrates were transferred onto a hot plate set to 90 °C for at least a minute to remove any residual solvents. Infrared spectra of the resulting thin films were obtained in absorbance mode using a Bio-Rad FTS 6000 spectrophotometer (Bio-Rad Laboratories, Hercules, CA) equipped with globar infrared source, KBr beamsplitter, and DTGS detector. The scan range was set from 500 to 4000 cm^{-1} with 4 cm^{-1} resolution, and 128 scans were coadded. Care was taken to ensure that the absorbance intensity of the spectral region of interest was between 0.6 and 1.0. During measurements, the spin-coated samples and the sample compartment of the spectrophotometer were flushed with dry air to minimize interference from absorbed and gas-phase moisture.

Samples of each system at a particular drug-to-polymer ratio were also prepared by spin coating, and then stored at room temperature in desiccators maintained at 54, 75, 84, or 94% relative humidity (RH) using saturated solutions of $Mg(NO_3)_2$, NaCl, KCl, and KNO_3. Periodically, the samples were removed from the desiccators, dried by flushing with dry air (RH < 10%) until no changes in the OH region was observed, and their infrared spectra were collected. The solid dispersion samples were rigorously dried before analysis so that absorbed moisture would not mask changes in the extent of the drug−polymer interactions. Preliminary experiments were conducted with nifedipine−PVP−H_2O dispersions following exposure to 75, 84 and 94% RH (data not shown).[24] Spectroscopic changes observed in the dried samples were also present in samples containing water, however, the water absorption peaks complicated the spectra as anticipated, making interpretation more complex. These results suggest that the drying stage did not cause disruption of drug−polymer interactions.

In a separate experiment, a pimozide−PVP sample containing 50% PVP (w/w) was prepared using the spin-coating technique mentioned, and then stored in a desiccator kept at 75% RH under refrigeration (4 °C). Periodically, the sample was removed, and the infrared spectrum of the sample was obtained as described above.

Reference spectra of the amorphous form of the drugs and pure PVP were collected using the same spin-coating technique described. The spectra of the crystalline forms of the drugs were obtained using a Golden Gate MII attenuated total reflectance sampling accessory with a diamond top-plate (Specac Inc., Woodstock, GA).

Differential Scanning Calorimetry (DSC). DSC measurements were carried out for droperidol−PVP and pimozide−PVP systems to confirm drug−polymer miscibility; for the other systems, literature data is available. For these measurements, samples at different drug−polymer weight ratios were dissolved in the same solvents as used for the spin-coating procedure. The solvent was then removed using a rotary evaporator apparatus, and the resultant solid was placed in sealed aluminum pans with pinholes (Perkin-Elmer Life and Analytical Sciences, Inc., Waltham, MA). The samples were then heated at 20 °C/min to 10 °C above the melting temperature of the drug, held isothermally for ∼12 s, cooled at >20 °C/min to −20 °C, and then reheated at 20 °C/min to the melting temperature of the drug. Upon completion of the test, the pans were opened and visually inspected to ensure no significant degradation of the samples had occurred. A Q10 or a Q2000 DSC (TA Instruments, New Castle, DE) equipped with a refrigeration cooling system (RCS) attachment was used to perform the measurements. The enthalpic response was calibrated using indium, while the temperature scale was calibrated using indium, tin, and benzophenone.

DSC measurements were also carried out on select model solid dispersion systems (prepared by rotary evaporation as described above) after storage at 94% RH, with or without drying. Solid dispersions in open aluminum pans were exposed to 25 °C/94% RH using an SGA-100 Symmetrical Gravimetric Analyzer instrument (VTI Corporation, Hialeah, FL) at a flow rate of 200 mL/min for 42−72 h. For samples that were dried, the sample was then exposed to dry air (RH < 5% at 25 °C) in the SGA-100 instrument until a plateau

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in the weight loss was observed. The pans were then hermetically sealed, and analyzed using DSC at a heating rate of 20 °C/min. Midpoint values of T_gs are reported.

Melting points and heats of fusion for the crystalline drugs were determined using aluminum pans with a pinhole and a heating rate of 10 °C/min. For droperidol, two overlapping thermal events were observed at this heating rate. The measurements were repeated at 0.5 °C/min to better resolve the events, and three thermal events were observed consistent with the melt of one polymorph, followed by recrystallization and melting of a second polymorph. To measure the melting point and heat of fusion of the first polymorph, the analysis was repeated at a heating rate of 200 °C/min, which suppressed recrystallization, and only one thermal event was recorded.

Data analyses for all measurements were performed using Universal Analysis 2000 software v. 4.1D (TA Instruments, New Castle, DE).

Moisture Sorption Measurements. Moisture sorption isotherms of the solid dispersions samples at select drug−polymer concentrations were collected using an SGA-100 symmetrical gravimetric analyzer instrument, as well as the moisture sorption isotherms for the amorphous drugs. For these measurements, the amount of moisture sorbed by the various systems at 95% RH was estimated from a plot of weight gain versus time and was taken as the value where a plateau was initially observed.

Results

Miscibility of Drug−Polymer Systems in the Absence of Moisture. Infrared spectroscopy has been widely used to investigate drug−polymer interactions in solid dispersion systems.[19−21] Essentially, when the drug and the polymer contain chemical moieties that interact through specific interactions, e.g. hydrogen bonding, the spectrum of the solid dispersion often contains peaks that are shifted relative to those found in the spectrum of a physical mixture of amorphous drug and polymer. Furthermore, infrared spectroscopy is well-suited to study solid-state phase transitions such as crystallization of the drug, since the spectrum is sensitive to changes in the local environment.[19,25,26]

For all the dry solid dispersion systems studied, evidence for drug−polymer interactions was found from analysis of the IR spectra, providing support for miscibility. In particular, changes in the infrared peaks assigned to the carbonyl moieties of the drug and polymer molecules, which act as hydrogen bond acceptors, or the −NH and −OH moieties in the drug molecules, which act as hydrogen bond donors, were observed. These functional groups can provide insight into the state of interactions among drug molecules and between the drug molecules and the polymer molecules. Peak assignments for these functional groups for the various pure amorphous systems and the solid dispersions are listed in Table 1, and their chemical structures are shown in Figure 1. Drug−PVP interactions have been reported previously for indomethacin[19] and nifedipine,[16,21] hence the results of this study serve to confirm that these systems can form miscible solid dispersions. IR results for ketoprofen−PVP, droperidol−PVP, and pimozide−PVP indicate that these molecules can also form molecular level dispersions with PVP.

Another parameter commonly used to evaluate drug−polymer miscibility is determination of the glass transition temperature (T_g). In binary systems where the components are miscible and a one-phase ASD is formed, only one T_g is typically observed. However, in systems where the components have limited miscibility, more than one T_g may be observed, for example as reported for PVP−dextran and PVP−PVP/vinyl acetate,[28] citric acid−indomethacin,[22] and itraconazole−Eudragit.[23] A single T_g has been reported for binary drug−polymer combinations of indomethacin−PVP,[29] nifedipine−PVP,[21] and ketoprofen−PVP.[30] Due to the lack of published data for droperidol−PVP and pimozide−PVP, drug−polymer miscibility was evaluated by DSC in this study. At polymer concentrations up to 50% (dry weight basis), only one glass transition event was observed for these systems, located between the T_gs of the pure amorphous drug and the pure polymer. These data support the conclusions from the IR results, namely that the initially dry systems are miscible over the range of drug−polymer composition studied.

Miscibility of Systems Following Exposure to Moisture. Having confirmed that a single phase mixture can be formed for all the model systems, the next step is to evaluate if immiscibility can be induced by exposure to moisture. If amorphous−amorphous phase separation occurs, a reduction in the intensity of IR absorbance peaks assigned to drug−polymer hydrogen bonding relative to those arising from drug−drug interactions is expected, since drug molecules will predominantly interact with other drug molecules in the amorphous drug-rich regions. The same is true for polymer−polymer interactions. If phase separation occurs because of crystallization,

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Table 1. Infrared Spectroscopy Peak Assignments for Systems Studied

systems	wavenumber (cm^{-1})[a]	assignment
poly(vinylpyrrolidone)/PVP	1681	νC=O, non H-bonded
	Nifedipine−PVP	
crystalline nifedipine	3317	νNH
amorphous nifedipine	3342	νNH
nifedipine−PVP solid dispersion	3288	νNH of nifedipine when H-bonded to PVP
	~1660	νC=O of PVP when H-bonded to nifedipine
	Pimozide−PVP	
crystalline pimozide	1693	νC=O
amorphous pimozide	1696	νC=O in dimers
	1709 $^{\text{sh}}$	νC=O, non H-bonded
pimozide−PVP solid dispersion	1661 $^{\text{sh,w}}$	νC=O of PVP when H-bonded to pimozide
	1709 $^{\text{sh}}$	νC=O, non H-bonded
	Droperidol−PVP	
crystalline droperidol	1682	νC=O
amorphous droperidol	1684	νC=O away from NH, non H-bonded
	1704	νC=O in dimers
	1718 $^{\text{sh}}$	νC=O next to NH, non H-bonded
droperidol−PVP solid dispersion	1657 $^{\text{sh,w}}$	νC=O of PVP when H-bonded to droperidol
	1684	νC=O away from NH, non H-bonded
	1718	νC=O next to NH, non H-bonded
	Indomethacin−PVP[b]	
crystalline indomethacin (γ-polymorph)	1717	asymmetric νC=O of a cyclic dimer
	1692	benzoyl C=O
crystalline indomethacin (α-polymorph)	1735	non H-bonded acid C=O
	1688	benzoyl C=O
	1681 $^{\text{sh}}$	H-bonded acid C=O
	1649	H-bonded acid C=O
amorphous indomethacin	1685	benzoyl C=O
	1710	acid C=O in dimers
	1735 $^{\text{sh}}$	non H-bonded acid C=O
indomethacin−PVP solid dispersion	1639	νC=O of PVP when H-bonded to indomethacin
	1680	acid C=O, non H-bonded
	1726	νC=O non H-bonded
	Ketoprofen−PVP[c]	
crystalline ketoprofen	1652	νC=O non H-bonded
	1690	H-bonded acid C=O
amorphous ketoprofen	1659	νC=O non H-bonded
	1708	acid C=O in dimers
	1739	acid C=O, non H-bonded
ketoprofen−PVP solid dispersion	1637	νC=O of PVP when H-bonded to ketoprofen

[a] sh (shoulder), w (weak). [b] Peak assignments based on work by Taylor et al.[19] [c] Peak assignments partially based on work by Gupta et al.[39]

drug−drug interactions will also increase, at the expense of drug−polymer interactions. The spectrum of the amorphous phase separated dispersion, however, would be expected to bear a greater resemblance to the spectrum of a physical mixture of amorphous drug and polymer, but be different from the spectrum of a physical mixture of crystalline drug and polymer or the molecularly mixed amorphous solid dispersion. In making these comparisons, it is important to eliminate spectral interference from water. Therefore, systems described below are binary systems from which water has been removed by drying.

Systems Exhibiting Amorphous−Amorphous Phase Separation Prior to Drug Crystallization. Spectra showing the νNH region for nifedipine−PVP system (50% PVP w/w) and the carbonyl region for pimozide−PVP (30% PVP w/w) and droperidol−PVP (30% PVP w/w) before and after exposure to moisture for different time periods are shown in Figures 2−5. The spectra of the amorphous and crystalline drugs are included for comparison, as well as the theoretically calculated spectra of physical mixtures (amorphous drug and PVP) at the same weight ratios (see Appendix for details of the calculation method used to produce these spectra). It

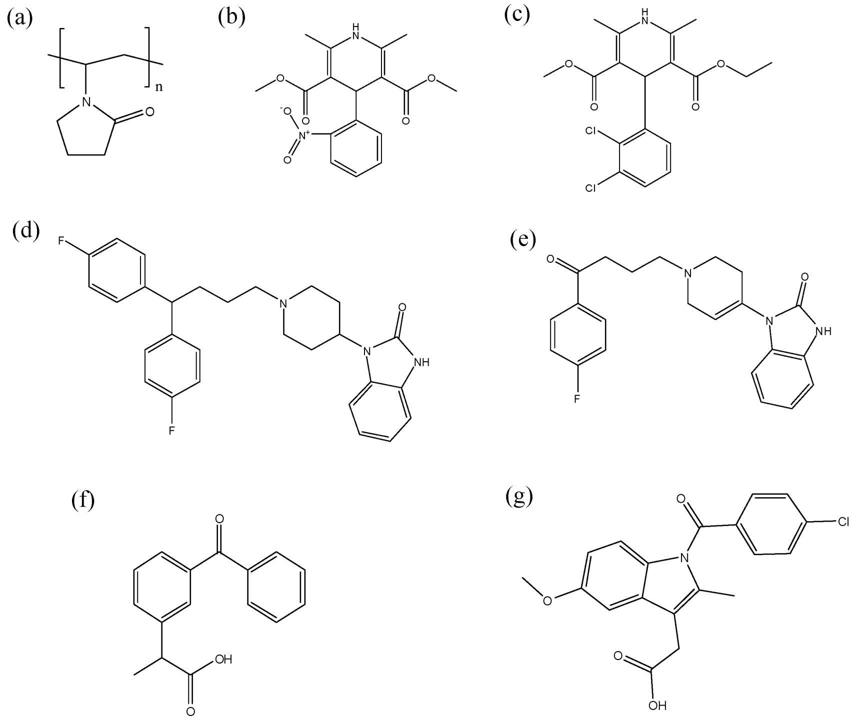

Figure 1. Chemical structures of (a) the repeating unit of PVP, (b) nifedipine, (d) pimozide, (e) droperidol, (f) ketoprofen, and (g) indomethacin. The chemical structure of felodipine (c), model drug where moisture-induced amorphous−amorphous phase separation was previously reported,[17,27] is also included.

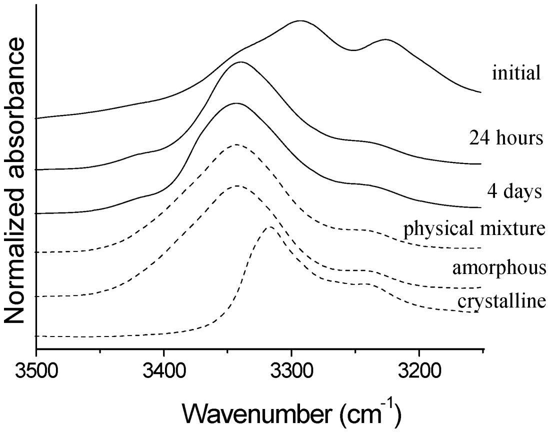

Figure 2. Infrared spectra of the υNH region of nifedipine−PVP solid dispersion samples containing 50% (w/w) PVP after storage at 94% RH for different amounts of time and subsequent drying. The calculated spectra of amorphous nifedipine−PVP physical mixture at the same weight ratio, amorphous nifedipine, and crystalline nifedipine (dashed lines) are included for comparison.

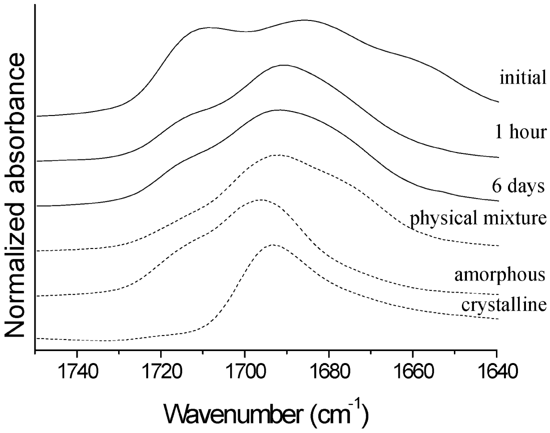

Figure 3. Infrared spectra of the carbonyl region of pimozide−PVP solid dispersion samples containing 30% (w/w) PVP after storage at 94% RH for different amounts of time and subsequent drying. The calculated spectra of amorphous pimozide−PVP physical mixture at the same weight ratio, amorphous pimozide, and crystalline pimozide (dashed lines) are included for comparison.

should be noted that the samples were dried before analysis so that absorbed moisture would not interfere with the spectroscopic interpretation.

Several observations can be made from Figures 2−5. First, initially formed solid dispersions have spectra that were different from those of the physical mixtures, as expected for systems forming specific drug−polymer interactions. The solid dispersion spectra were also different from the reference crystalline spectra. Second, significant changes occurred in the IR spectra of these systems after storage at high RH for relatively short periods of time. It is apparent that, following exposure to moisture and subsequent drying, the spectra of the solid dispersion samples became similar to the physical mixture spectra.

For nifedipine−PVP system, the peak at 3288 cm^{-1}, assigned to the −NH moiety of the drug when hydrogen bonded to PVP, decreased in relative intensity after only one hour storage at 94% RH. There was a concurrent increase

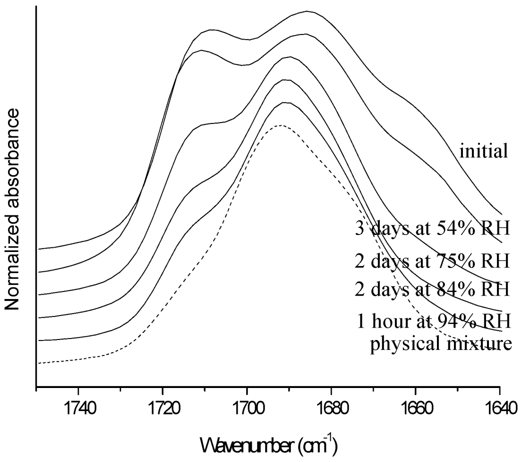

Figure 4. Infrared spectra of the carbonyl region of pimozide−PVP solid dispersion samples containing 30% (w/w) PVP after storage at different RHs and subsequent drying. A reduction in the intensity of peaks assigned to free pimozide carbonyl (1709 cm^{-1}) and PVP carbonyl when hydrogen bonded to pimozide (1661 cm^{-1}) was observed as the storage RH was increased, and the resulting spectra looked progressively similar to the theoretically calculated spectrum of the physical mixture composed of amorphous drug and PVP (dashed line).

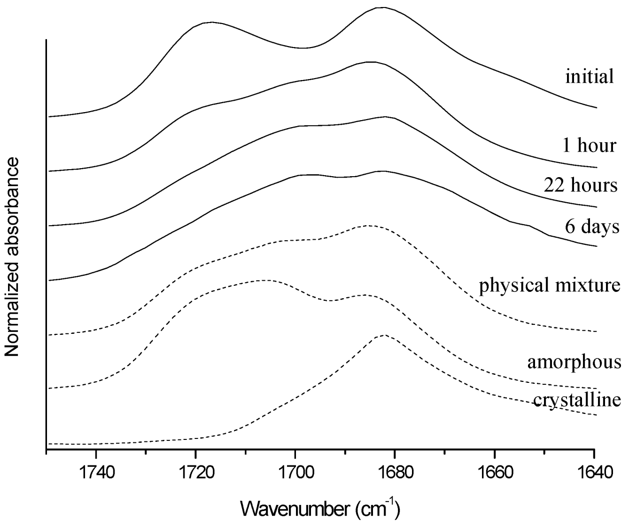

Figure 5. Infrared spectra of the carbonyl region of droperidol−PVP solid dispersion samples containing 30% (w/w) PVP after storage at 94% RH for different amounts of time and subsequent drying. The calculated spectra of droperidol−PVP physical mixture at the same weight ratio, amorphous droperidol, and crystalline droperidol (dashed lines) are included for comparison.

in the peak at 3345 cm^{-1}, indicating an increased level of amorphous drug−drug interactions, consistent with phase separation and the formation of a drug-rich amorphous phase. In the carbonyl region, a concurrent decrease in the intensity of the peak at ∼1660 cm^{-1} (assigned to the carbonyl moiety of PVP when hydrogen bonded to nifedipine; data not shown) was also observed. Furthermore, the absence of a peak at 3317 cm^{-1} (found in the crystalline reference spectrum) indicated that the observed reduction in drug−polymer hydrogen bonding was not caused by drug crystallization. Evidence of drug crystallization was observed after 48 h storage at 94% RH, whereby IR peaks correlated to the crystalline form of nifedipine were observed to develop. Similar trends consistent with amorphous−amorphous phase separation into drug-rich and polymer-rich regions prior to drug crystallization, albeit to a lesser extent, were also observed following storage at 75% RH.

For pimozide−PVP, following storage at high RH, the relative intensity of the peak centered at 1709 cm^{-1} (assigned to free carbonyl moiety of the drug) decreased, suggesting an increase in drug−drug hydrogen bonding. A concurrent decrease in the intensity of the peak centered 1661 cm^{-1}, assigned to the carbonyl moiety of PVP when hydrogen bonded to drug molecules, was also observed. These observations are again consistent with phase separation of the system to form drug-rich and polymer-rich amorphous regions prior to drug crystallization. The changes were observed following storage at RH as low as 54% (see Figure 4). Similar trends consistent with the formation of drug-rich and amorphous-rich polymer phases were also observed for a pimozide−PVP sample (50% PVP w/w) which was stored at 4 °C/75% RH. After 6 days storage at 22 °C/94% RH, signs of drug crystallization were apparent, whereby the peak centered at 1690 cm^{-1} began to shift to 1693 cm^{-1}; a peak at this position is indicative of the presence of crystalline material.

For the droperidol−PVP system, a reduction in the relative intensity of the peak assigned to the free carbonyl moiety of the drug, centered at 1717 cm^{-1}, was also observed, again suggesting an increase in drug−drug hydrogen bonding and amorphous−amorphous phase separation. Subsequent to this, a shift of the peak at 1685 cm^{-1} to 1683 cm^{-1} after storage at 94% RH for 22 h indicated the occurrence of drug crystallization, which was more prevalent after 6 days. Similar trends consistent with amorphous−amorphous phase separation into drug-rich and polymer-rich regions were also observed following storage at 75% RH (data not shown).

Systems Not Exhibiting Amorphous−Amorphous Phase Separation Prior to Drug Crystallization. For indomethacin−PVP and ketoprofen−PVP, the carbonyl region of the spectrum proved most useful in understanding changes in the system following exposure to moisture. This spectral region is shown for solid dispersions of indomethacin−PVP (25% PVP w/w, Figure 6) and ketoprofen−PVP (30% PVP w/w, Figure 7) before and after storage at 94% RH. The spectra of the pure amorphous and crystalline forms are also shown for comparison.

From Figures 6 and 7, it can be seen that initially formed solid dispersions again have spectra that were different from those of the physical mixtures. However, in contrast to the systems described above, no significant changes were observed in the carbonyl region of indomethacin−PVP and ketoprofen−PVP solid dispersion samples following storage at 94% RH for 40 days and 68 days respectively. Peaks assigned to the hydrogen-bonding interaction between the drug and the carbonyl of PVP were still present at the same

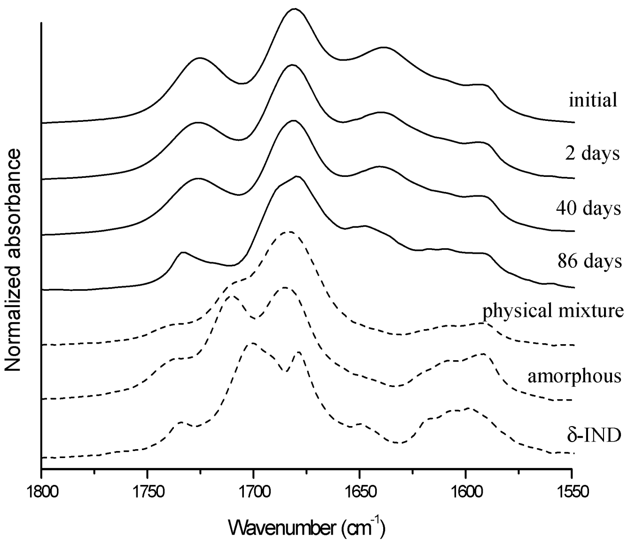

Figure 6. Infrared spectra of the carbonyl region of indomethacin−PVP solid dispersion samples containing 25% (w/w) PVP after storage at 94% RH for different amounts of time and subsequent drying. Theoretically calculated spectra of amorphous indomethacin−PVP physical mixture at the same weight ratio, amorphous indomethacin, and δ-polymorph of indomethacin (dashed lines) are included for comparison.

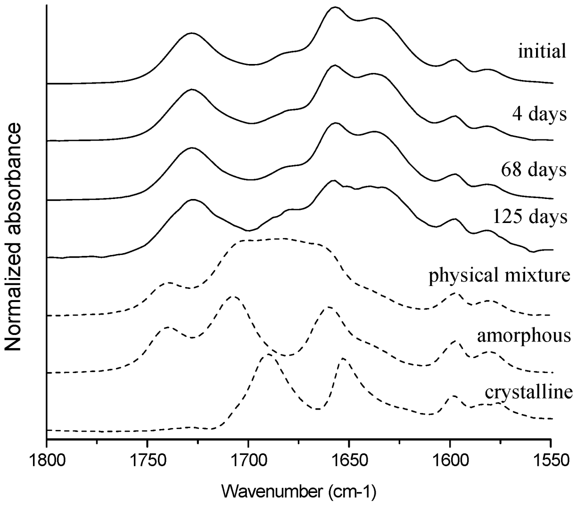

Figure 7. Infrared spectra of the carbonyl region of ketoprofen−PVP solid dispersion samples containing 30% (w/w) PVP after storage at 94% RH for different amounts of time and subsequent drying. Theoretically calculated spectra of amorphous ketoprofen−PVP physical mixture at the same weight ratio, amorphous ketoprofen, and crystalline ketoprofen (dashed lines) are included for comparison.

relative intensity and position, indicating no detectable molecular level changes in the systems due to the formation of different amorphous regions or drug crystallization. After 46 days, changes in the IR spectrum of indomethacin−PVP system consistent with indomethacin crystallization were identified. Visual signs of crystallization were also apparent. Based on the presence of a peak at 1357 cm^{-1}, the resulting crystalline form is assigned to the δ-polymorph (the spectrum of this polymorph is shown for reference in Figure 6). Similar IR measurements with dispersions of indomethacin and PVP K12 yielded identical results in that no evidence of amorphous−amorphous phase separation was observed prior to crystallization (data not shown). In the ketoprofen−PVP system, a shoulder developed at around 1688 cm^{-1} and a small peak appeared at 1651 cm^{-1}, with these spectroscopic changes again coinciding with visual observation crystallization after storage at 94% RH for 125 days.

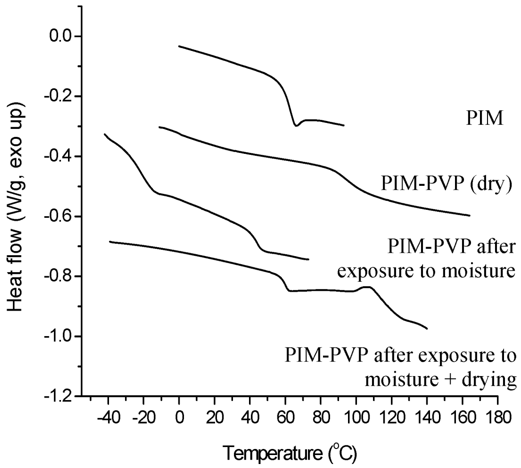

Figure 8. Glass transition temperatures (T_gs) of pimozide−PVP (50% PVP w/w) solid dispersion samples before and after exposure to 94% RH with and without drying. The T_g of pure amorphous pimozide (top) is also included for comparison.

Confirmation of Amorphous−Amorphous Phase Separation Using DSC. To further confirm the presence or absence of amorphous−amorphous phase separation upon exposure to moisture at high relative humidity, DSC measurements were conducted on pimozide−PVP and indomethacin−PVP samples, and the results are presented in Figures 8 and 9. Following storage at room temperature and 94% RH for 42 h, pimozide−PVP (50:50 wt.%) samples (T_g of the initial solid dispersion was 94 °C) showed two glass transition events, recorded at −21 and 44 °C. After drying this sample, the two glass transition events persisted but had shifted to 61 and 112 °C. It should be noted that the lower T_g event in the dried sample occurs at a similar temperature to the T_g of pure amorphous pimozide (60 °C) supporting the IR results which suggested that moisture sorption leads to the formation of a drug-rich amorphous phase. Similar results were observed with a pimozide dispersion containing 30% PVP, whereby the T_g of the dry dispersion was 81 °C, and two T_g events were observed in the wet dispersion at 13 and 48 °C (which shifted to 59 and 109 °C in the dried dispersion).

Similar measurements performed with the indomethacin−PVP system showed only a single T_g around 62 °C after storage at 94% RH for 72 h followed by drying, which coincides with the T_g of the dispersion prior to exposure to moisture (see Figure 9a). It is known from the literature that, even after exposure to high RH, the T_g of indomethacin−PVP dispersions prepared with high molecular-weight PVP do not fall below room temperature.[29] Therefore, in order to study

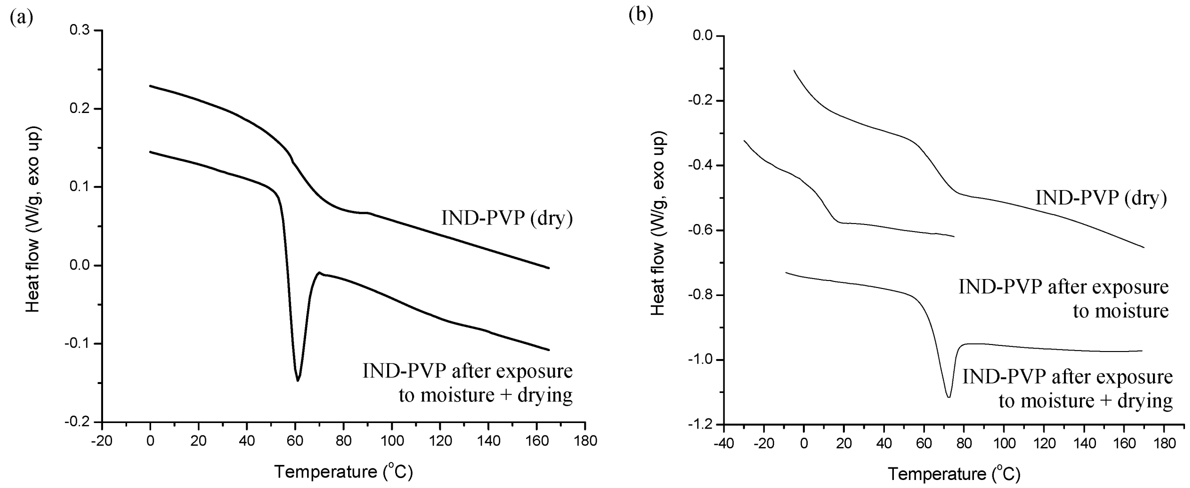

Figure 9. (a) T_gs of indomethacin–PVP K29-32 (25% PVP w/w) solid dispersion samples before and after exposure to 94% RH and subsequent drying. (b) T_gs of indomethacin–PVP K12 (50% PVP w/w) solid dispersion samples before and after exposure to 94% RH.

Table 2. Amounts of Moisture Sorbed by PVP, Amorphous Drugs, and the ASD Systems at 25 °C and 95% Relative Humidity

variable	experimentally measured % moisture sorbed (dry wt basis)	predicted % moisture sorbed by physical mixtures (dry wt basis)	% difference
	Pure Components		
poly(vinylpyrrolidone)/PVP	77.7		
indomethacin (amorphous)	3.0		
ketoprofen (amorphous)	2.8		
nifedipine (amorphous)	2.2		
pimozide (amorphous)	1.0		
droperidol (amorphous)	2.2		
	Binary Systems		
75% indomethacin–25% PVP	4.9	21.7	341.5
70% ketoprofen–30% PVP	11.4	25.3	121.7
50% nifedipine–50% PVP	42.5	39.9	5.9
70% pimozide–30% PVP	22.4	24.0	7.4
70% droperidol–30% PVP	24.8	24.9	0.2

a more highly plasticized system, an indomethacin–PVP dispersion prepared with a lower molecular weight grade of PVP (PVP K12) was exposed to high RH, and DSC results are shown in Figure 9b. It can be seen that this system has a dry T_g of 68 °C, which drops to 11 °C following storage at 94% RH. In contrast to the pimozide system, only one T_g event can be observed in the wet sample.

Moisture Sorption. The amount of moisture sorbed by PVP, amorphous drugs, and the solid dispersion samples at 25 °C and 95% (±1%) RH is shown in Table 2. The predicted moisture uptake for a physical mixture of the same composition was calculated using weighted contributions of the moisture sorption results for the pure components.

For amorphous solid dispersions composed of PVP and poorly water-soluble drugs, for example indomethacin, ursodeoxycholic acid and indapamide, it has been reported that the amount of water sorbed is significantly lower than for the corresponding physical mixtures.[29] Similar results were also obtained with indomethacin–PVP and ketoprofen–PVP systems, where the amount of moisture sorbed at 95% RH is very different (more than 100%) from that predicted to be absorbed by a physical mixture at the same weight ratios. In contrast, the amount of moisture sorbed by pimozide–PVP, droperidol–PVP, and nifedipine–PVP at 95% RH, is similar (less than 10% difference) to the theoretically predicted amounts that would be absorbed by physical mixtures of amorphous drug and PVP at the same weight ratios. This result is again consistent with phase separation since in a phase separated system it would be anticipated that moisture sorption would be closer to additive due to the reduced opportunity for drug–polymer interactions.

Discussion

Amorphous solid dispersion systems composed of a poorly water-soluble drug and a polymer are formulated with the intention of maintaining the drug as an amorphous solid over the lifetime of the product, thereby ensuring higher and reproducible dissolution rates. It is generally thought that, for the polymer to act as an effective crystallization inhibitor,

Table 3. Selected Physical Properties of the Model Drugs Used

	MW[a] (g/mol)	aqueous solubility[b] (g/L)	calcd log P[d]	T_m[e] (K)	ΔH_f[e] (kJ/mol)	$\Delta G_c^{25°C}$ (kJ/mol)[f]	ρ (g/cm^3)
nifedipine	346.34	3.9×10^{-2} (298 K)[c]	2.31	445.3 (0.2)	37.2 (0.5)	8.2	1.20[g]
felodipine	384.26	2.7×10^{-3} (298 K)[c]	2.24	416.5 (0.6)	29.9 (0.2)	6.1	1.28[g]
droperidol	379.44	4.1×10^{-3} (303 K)	1.92	417.1 (0.2)	44.9 (0.1)	9.2	1.18[h]
pimozide	461.56	2.9×10^{-3} (303 K)	5.34	490.9 (0.9)	46.0 (1.4)	11.0	1.13[h]
indomethacin	357.81	$4{-}14 \times 10^{-3}$ (298 K)	3.58	432.2 (0.6)	38.0 (0.2)	8.1	1.34[g]
ketoprofen	254.3	0.1436 (298 K)	3.31	366.9 (0.1)	27.2 (0.7)	4.1	1.13[h]

[a] As reported in ref 40. [b] As reported in ref 41 at the temperatures stated unless otherwise specified. [c] As reported in ref 15. [d] As reported in ChemBioDraw Ultra v 11.0, CambridgeSoft Corp., Cambridge, MA. [e] Values reported as average (standard deviation), $n = 3$, measured using DSC as described in the *Experimental Methods* section. [f] Calculated from eq *3*. [g] As reported for nifedipine and felodipine[21] and for indomethacin.[42] [h] Approximated as 0.9 of the density of crystalline drugs as reported for droperidol,[43] pimozide,[44] and ketoprofen[45] respectively.

the drug and the polymer should be intimately mixed in a one-phase system; this is usually inferred by the presence of a single T_g event. All of the binary drug−polymer systems investigated in this work form miscible amorphous systems displaying a single T_g, as well as evidence of drug−polymer (adhesive) intermolecular interactions. Interestingly, it appears that sorption of moisture promotes amorphous−amorphous phase separation for some systems prior to crystallization of the drug, but not for others.

It is obviously of interest to understand the physicochemical properties of drug molecules which may make them susceptible to this phenomenon. The compounds used in this study can be grouped into different categories based on their physical properties and chemical structure. All dispersions were prepared using PVP, a hydrophilic polymer with one hydrogen bond acceptor per repeating unit, but no hydrogen bond donors. All the model compounds are relatively hydrophobic (log P values are listed in Table 3) but differ in their chemistry. Nifedipine and pimozide each contain an NH group capable of acting as a hydrogen bond donor and several acceptor groups. Ketoprofen and indomethacin both contain a carboxylic acid functionality that can engage in dimer or catemer type cohesive hydrogen bonding, and other functional groups that could potentially function as acceptors. Selected properties of the various drugs are listed in Table 3.

Log P can be used as an indicator of the hydrophobicity.[31] In addition to values obtained experimentally, different calculation methods can be used to predict log P values for different compounds. In this study, log P values calculated using ChemBioDraw Ultra version 11.0 (CambridgeSoft, Cambridge, MA) were used. All the model drugs have different positive log P values indicative of varying degrees of hydrophobicity. It is clear that log P is not predictive of either the amount of moisture absorbed by the pure amorphous solid or the tendency to undergo moisture induced amorphous−amorphous phase separation, in that droperidol, felodipine and nifedipine are all more hydrophilic than indomethacin or ketoprofen, based on reported log P values, but undergo moisture-induced immiscibility in PVP solid dispersions.

Another way to assess the relative hydrophobicity of these compounds is by examination of the activity coefficients, which describe how mixing between the drug and water deviates from ideal mixing.[31] The activity coefficients for low concentrations of water sorbed in the amorphous drug can be calculated from the moisture sorption isotherms using eq 1:

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$$a_{\text{water}} = \frac{P}{P_0} = \gamma_{\text{water}} X_{\text{water}} \tag{1}$$

where a_{water} is the activity of the solute (water), P/P_0 is the relative vapor pressure of water (equivalent to relative humidity/100), γ_{water} is the activity coefficient of water in the mixture (=1 in ideal mixtures), and X_{water} is the mole fraction of water in the amorphous solid. The values of γ_{water} mixed with the hydrophobic model compounds used in this study were calculated from the amount of moisture sorbed by the amorphous drugs at 95% RH and are listed in Table 4.

Alternatively, the activity coefficients for the drugs in dilute aqueous solution can be estimated by comparing the experimental solubility with the ideal solubility.[31] Approximating the free energy difference between the crystal and the supercooled liquid using the Hoffman approach,[32] the activity coefficient can be estimated using eq 2:

$$\ln \gamma_{\text{drug}} = \Delta G_{\text{c}} - \ln X_{\text{drug}} \tag{2}$$

where X_{drug} is the mol fraction solubility of the drug and γ_{drug} is the activity coefficient of the drug in the solution. Here, ΔG_{c} is the difference in the free energies of the drug in the supercooled liquid and the crystalline states (also considered as the driving force for crystallization of the drug), and its value is estimated from:

$$\Delta G_{\text{c}} = \Delta H_{\text{f}} \frac{(T_{\text{m}} - T)T}{{T_{\text{m}}}^2} \tag{3}$$

where ΔH_{f} is the heat of fusion, T_{m} is the melting temperature, and T is the experimental temperature. The values of ΔG_{c} and γ_{drug} calculated from this method are listed in Tables 3 and 4 respectively.

Results shown indicate nonideal mixing between water and the drugs, and the positive values of the activity coefficient suggest unfavorable adhesive interactions, as expected for hydrophobic drugs mixed with water. However, no trends between estimated activity coefficients and the tendency for amorphous−amorphous phase separation can be discerned. Based on activity coefficients calculated from water vapor sorption data, water has the least favorable interactions with felodipine, droperidol, and pimozide, while the interactions with indomethacin, nifedipine, and ketoprofen are somewhat less unfavorable (assuming that nonidealities of mixing entropy do not contribute significantly to the differences in the activity coefficients). From solubility data, mixing of water with felodipine and pimozide are most nonideal, while indomethacin and droperidol have the smallest activity coefficients. It can also be seen from Table 3 that there is no correlation between experimental evidence of amorphous−amorphous phase separation and various parameters which describe differences between the crystal and the supercooled liquid states, including the melting point, heat of fusion, and estimated free energy difference between supercooled liquid and crystal at 25 °C.

Table 4. Calculated Values of Activity Coefficients and Drug−Water Interaction Parameters

	γ_{water}[a]	γ_{drug}[b]	$\chi_{\text{drug-water}}$[c]
nifedipine	3.19	4.95×10^5	2.84
felodipine	4.13	7.71×10^6	3.18
droperidol	3.00	5.16×10^6	2.85
pimozide	4.65	8.88×10^6	3.58
indomethacin	2.54	1.99×10^6	2.50
ketoprofen	3.35	9.85×10^4	2.71

[a] From method 1, moisture sorption data. [b] From method 2, solubility equation. [c] At 25 °C and 95% RH.

Given the lack of correlation between properties of the drug alone or various estimates of drug−water compatibility, and the observed behavior, it appears necessary to examine the properties of the ternary systems more closely. In order for moisture-induced amorphous−amorphous phase separation to occur, there must be a thermodynamic driving force (i.e., the phase separated systems must have lower free energy compared to the one phase ternary mixture) as well as sufficient molecular mobility to allow diffusion of molecules over the time scale of observation. The addition of water will influence both the kinetic and thermodynamic properties of the system. Figure 10 provides a schematic describing a purely kinetic route to phase separation compared with a thermodynamic route. It is our opinion that moisture induced amorphous−amorphous phase separation is a thermodynamically driven event which requires some level of enhanced molecular mobility. Thus systems that simply have enhanced molecular mobility will not undergo moisture induced immiscibility in the presence of moisture if the thermodynamics are not favorable.

If moisture-induced immiscibility was purely a kinetic phenomenon, then this suggests that the drug−PVP mixtures are kinetically trapped as a one-phase dispersion at room temperature which cannot undergo amorphous−amorphous phase separation due to the low molecular mobility in the glassy state. The introduction of water has a plasticizing effect, increasing molecular mobility and allowing the system to undergo amorphous−amorphous phase separation that was precluded in the dry glassy matrix. In this mechanism, illustrated schematically as route II in Figure 10, water plays a purely kinetic role, and the implication is that the binary drug−polymer systems are not thermodynamically miscible at room temperature.

In a purely thermodynamic route, single phase drug−PVP mixtures are thermodynamically favored at room temperature relative to a two-phase amorphous mixture (Figure 10). When water molecules are introduced into the system, interaction with the polymer chains is favorable and the polarity of the matrix is increased. The hydrophobic drug has unfavorable interactions with the polymer−water "cosolvent" system and a lower free energy is achieved by phase separation into drug-rich and polymer-rich regions.

Evidence against a purely kinetic route is provided by the ketoprofen−PVP system. When these amorphous solid dispersions were exposed to high RH, no evidence of

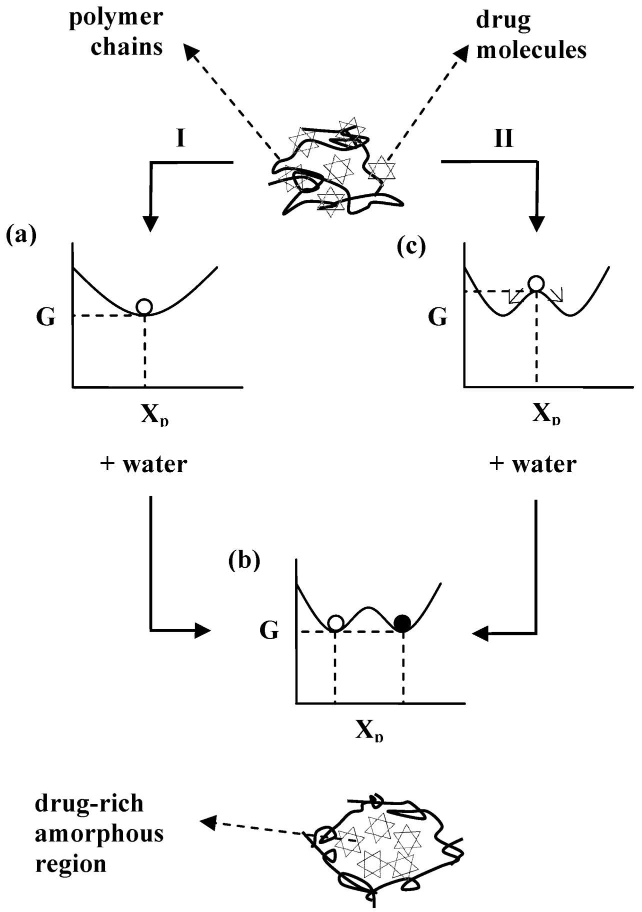

Figure 10. Illustration explaining (I) purely thermodynamic and (II) purely kinetic contributions of water when sorbed into a solid dispersion composed of a hydrophobic drug and a hydrophilic polymer. Just considering thermodynamics as the basis for moisture-induced amorphous−amorphous phase separation prior to drug crystallization, the dry solid dispersion is at a global free energy minimum (a), and absorption of water creates two minima in the free energy versus composition diagram, such that the system can lower its free energy by forming drug-rich and polymer-rich regions (b). In a purely kinetic reasoning, the dry solid dispersion is trapped at a local free energy maximum (c), and the system can lower its free energy by forming drug-rich and polymer-rich regions (b). However, molecular motions to form these amorphous regions are kinetically hindered in the glassy state. Absorption of water results in increased molecular mobility, enabling this event to occur. In reality, it is likely that water impacts both the thermodynamic and kinetic aspects of the system.

moisture induced immiscibility was observed (Figure 7). However, the T_g of the ketoprofen−PVP (70:30 wt %) system stored at 94% RH is very low (midpoint value is −23 °C, data not shown), indicating that the system was well above the T_g at room temperature, and sufficient molecular mobility exists to enable amorphous−amorphous phase separation. Rather, the thermodynamics of the system appears to be such that the formation of a one-phase system was favored at all times, even in the presence of moisture. In addition, indomethacin dispersions prepared with PVP K12 (this molecular weight grade has a much lower T_g than PVP K29-32, therefore the corresponding dispersion has a lower T_g in the presence of moisture) had a midpoint T_g of 11 °C following storage at 94% RH (Figure 9b), but showed very similar IR results to those shown in Figure 6, i.e. no evidence of amorphous−amorphous phase separation. Therefore, being above T_g did not drive phase separation in indomethacin−PVP and ketoprofen−PVP systems. Furthermore, the purely kinetic argument suggests that the binary dispersions should already have a thermodynamic driving force for amorphous−amorphous phase separation, whereas thermodynamic analysis of nifedipine−PVP and indomethacin−PVP systems suggest that the mixing of these binary systems is energetically favorable in the absence of moisture,[33] and the formation of a one-phase drug−polymer system in the absence of moisture is favored.

Molecular mobility is clearly important to enable thermodynamically favorable phase separation to occur. Thus when pimozide−PVP samples were exposed to high RH at 4 °C, moisture-induced amorphous−amorphous phase separation still occurred, but at a much slower rate than at 22 °C (data not shown). Similar results have also been observed for felodipine−PVP systems.[27] These results suggest that thermodynamic factors play an important role in determining whether moisture will induce drug−polymer miscibility in amorphous molecular level solid dispersion system, but the rate at which amorphous−amorphous phase separation occurs is (at least partially) dependent on molecular mobility.

The thermodynamic analysis of the absorption of water by a solid dispersion can be further considered as follows: following the absorption of water, a ternary one-phase system composed of water (W), drug (D), and polymer (P) is initially formed. During the formation of this ternary system, both the entropy (ΔS_{mix}) and enthalpy (ΔH_{mix}) of mixing are affected. When a new component is introduced, the value of ΔS_{mix} is typically favorable to mixing.[34] However, ΔH_{mix} can either be favorable or unfavorable, depending on the balance of interactions between the various components. Since the entropy of mixing is favorable, phase separation in a ternary system must therefore be caused by a positive $\Delta H_{\mathrm{mix.}}$ This can be seen from eq 4 (Flory−Huggins equation[35]), which describes the free energy of mixing (ΔG_{mix}) for a ternary system:

$$\frac{\Delta G_{\mathrm{mix}}}{RT} = n_{\mathrm{W}} \ln \phi_{\mathrm{W}} + n_{\mathrm{D}} \ln \phi_{\mathrm{D}} + n_{\mathrm{P}} \ln \phi_{\mathrm{P}} + n_{\mathrm{W}}\, \phi_{\mathrm{D}} \chi_{\mathrm{WD}} + n_{\mathrm{W}} \phi_{P}\, \chi_{\mathrm{WP}} + n_{\mathrm{D}} \phi_{\mathrm{P}}\, \chi_{\mathrm{DP}} \qquad (4)$$

where R is the gas constant, T is temperature (in kelvins), n and ϕ are the mole fraction and volume fraction respectively of each component, and χ is the binary interaction parameter between components W, D and P[36] and also includes any nonidealities in the entropy of mixing. The first three terms on the right-hand side of the equation represent the combinatorial entropy of mixing. The latter three terms on the right-hand side represent the enthalpy of mixing. If we describe three binary interaction parameters in a system composed of the drug, the polymer, and water, to represent the interactions between the pairs of components in ternary systems (χ_{WD}, χ_{WP}, and χ_{DP} as shown in eq 4), then the values of all three parameters will affect ΔH_{mix}, and hence the overall free energy of mixing. Complete miscibility is expected in systems where ΔH_{mix} is either negative or not substantially positive due to the balance of interactions between W−D, W−P, and D−P, resulting in a negative value of ΔG_{mix} for the ternary system, and only one minimum is observed in the profile of ΔG_{mix} when plotted as a function of composition.

When the pairwise interaction energies between the components are very different, as anticipated for ternary systems composed of water, PVP, and a hydrophobic drug, absorption of moisture into the system will potentially create a thermodynamically unfavorable environment, leading to phase separation into drug-rich and polymer-rich regions prior to crystallization of the drug. An alternative way to consider this is as follows: due to the favorable interactions between water and the hydrophilic polymer, the water and the polymer form a "cosolvent" system. As the amount of water in this cosolvent system is increased, the miscibility of the hydrophobic amorphous drug with the more hydrophilic system is decreased, leading to amorphous−amorphous phase separation. This phenomenon has been documented for ternary solvent systems,[37] and also reported for the felodipine−PVP−water system.[17,27]

Using methods described in the literature, the interaction parameters between water and the amorphous drugs used in this study can be calculated from moisture sorption isotherm data collected at 95% RH[8,38] and are listed in Table 4. All of the values are large and positive, reflecting the unfavorable drug−water interactions. In contrast, the interaction parameter between PVP and water has been reported to be much more favorable.[8,38] Comparing the different systems, it is interesting to note that moisture-induced immiscibility was observed for the four drugs with the highest χ_{WD} values (most unfavorable drug−water interactions), but not for systems containing two drugs with the lower χ_{WD} values.

The strength of drug−polymer interactions also has to be considered since these will affect the magnitude and sign of the drug−polymer interaction parameter. In the case of nifedipine, felodipine, droperidol, and pimozide (susceptible to moisture-induced phase separation), drug−polymer hydrogen bonds are formed between the NH moiety of the drug and the carbonyl moiety of the polymer. For ketoprofen and indomethacin (no experimental evidence of moisture-induced phase separation), hydrogen bonds were formed between the COOH moiety of the drug and the carbonyl moiety of the polymer. Due to the potential for electron sharing in COOH hydrogen bond donor moieties, the bond between the O and the H is relatively weaker, compared to the bond between the N and H in NH hydrogen bond donor moieties. Thus the hydrogen atom in the COOH moiety is a better hydrogen-bond donor compared to the hydrogen atom in the NH moiety. This in turn leads to stronger hydrogen bonds between $COOH_{drug}-CO_{PVP}$ compared to the hydrogen bonds between $NH_{drug}-CO_{PVP}$.

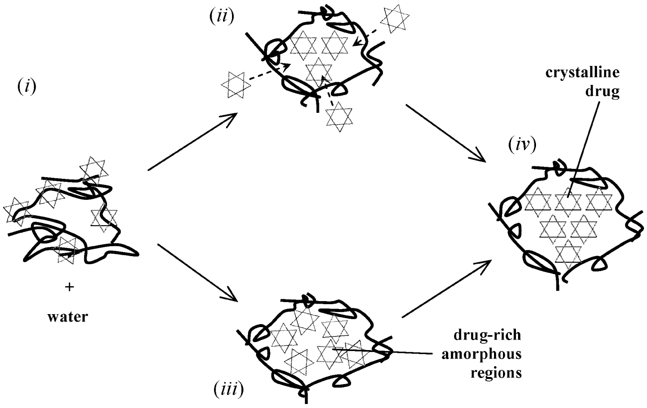

Figure 11. Schematic representation of the different routes to drug crystallization from solid dispersions when exposed to moisture. It is proposed that when (i) a solid dispersion composed of a drug and a polymer is exposed to moisture, drug crystallization can occur (ii) immediately from the one-phase ternary (water−drug−polymer) systems, or (iii) amorphous−amorphous phase separation can first occur, resulting in the formation of drug-rich and polymer-rich regions, until ultimately (iv) the formation of crystalline drug happens.

Evidence for the relative strength of drug−polymer interactions in PVP-containing systems can be obtained by analyzing the red shift experienced by the carbonyl peak of PVP when hydrogen bonded to the different drugs. In PVP−indomethacin and PVP−ketoprofen systems, 42−44 cm^{-1} shifts to lower wavenumbers were observed, much greater than the 20−24 cm^{-1} shifts observed for PVP−nifedipine, PVP−droperidol, and PVP−pimozide systems (calculated from values listed in Table 1). Stronger hydrogen bonding interactions are expected to result in more favorable drug−polymer interactions; it has been reported that PVP−indomethacin systems have a more negative (favorable) interaction parameter than PVP−nifedipine systems (χ for indomethacin and PVP was reported as −0.8 versus 0.0 for nifedipine and PVP),[33] and this in turn might lead to a greater resistance to moisture induced immiscibility. Clearly more work needs to be done to investigate the dependence of moisture induced immiscibility on drug and polymer chemistry.

Consequences of Moisture-Induced Immiscibility on Crystallization Tendency. Moisture-induced immiscibility in amorphous solid dispersion systems composed of a poorly water-soluble drug with PVP would be expected to have drastic consequences on the physical stability of the dispersions. As shown in Figure 11, there are two potential routes for drug crystallization from amorphous molecular level solid dispersion: directly from the miscible dispersion, and through the formation of a phase-separated system. It would be anticipated that drug crystallization would be much faster following amorphous−amorphous phase separation, since the inhibitory influence of the polymer would be reduced. This supposition is supported by our experimental observations, where PVP−nifedipine and PVP−pimozide dispersions all showed signs of crystallization after a few days at high RH in contrast to the indomethacin and ketoprofen systems that were stable for a few weeks, even at a relatively high RH.

These observations underscore the importance of drug−polymer miscibility for achieving physical stability in solid dispersion systems. Furthermore, the observations of moisture induced immiscibility at RHs as low as 75 or 54% RH highlight some of the problems associated with using accelerated stability testing conditions to predict physical stability. For susceptible systems, the route of crystallization may be altered at high RH leading to reduced physical stability, which may not be representative of the phase behavior at lower RHs.

Finally, the potential for phase separation during the dissolution process can be postulated. During hydration of the solid dispersion, a very high water activity will be reached which can potentially lead to phase separation prior to dissolution. This may promote crystallization of the drug in the hydrated matrix, and would potentially be of greater concern for controlled release formulations containing dispersions.

Conclusions

Select hydrophobic drug−PVP solid dispersions were found to undergo amorphous−amorphous phase separation upon exposure to high relative humidities. For these systems, water was found to disrupt drug−polymer interactions, which coupled with the ability of water to increase molecular mobility, led to phase separation. This phenomenon was observed at a RH as low as 54% in the case of one drug. Other hydrophobic drug−PVP solid dispersions remained miscible following equilibration at the highest RH employed, 94% RH. It is speculated that the strength of the drug−polymer interactions, which in turn will influence the mixing enthalpy, is important in determining which systems will be susceptible to moisture induced immiscibility. Thus the model drugs with NH moieties were sensitive to moisture induced immiscibility while those containing COOH functions did not undergo this phenomenon. Other factors of likely importance include the strength of drug−water interactions and the total amount of moisture sorbed. This phenomenon may have several implications for solid dispersion characterization including prediction of the long-term stability of dispersions sensitive to moisture induced immiscibility.

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Appendix

To produce the theoretically calculated spectra of physical mixtures of amorphous drug and PVP, the spectra of the pure amorphous drug and PVP were first collected. For any given drug-to-polymer weight ratio, the molar ratio can be determined from the molecular weight of the drug and the polymer, and from this, the molecular ratio can be determined. Assuming the infrared absorbencies of the C−C bonds in the mixtures are constant in terms of location and relative intensity relative to those in the pure drug and polymer, the ratio of the C−C peaks in the mixture can be calculated, and the theoretically calculated spectra can be produced by adding and multiplying the spectra of the pure compounds with the appropriate weighting factor (done using GRAMS/32 AI v 6.00, Thermo Fisher Scientific, Waltham, MA).

For example, consider a mixture of 70 g of pimozide and 30 g of PVP. The number of moles for the two components can be calculated by dividing their respective masses with their molecular weights: $n_{\text{pimozide}} = 0.152$ mol ($\text{MW}_{\text{pimozide}}$ is 461.56 g/mol), and $n_{\text{PVP}} = 7.5 \times 10^{-4}$ mol (MW_{PVP} is assumed to be 40,000 g/mol). The number of molecules for the two components is then calculated by multiplying the number of moles by Avogadro's number, giving $N_{\text{pimozide}} = 9.13 \times 10^{22}$, and $N_{\text{PVP}} = 4.52 \times 10^{20}$. Since the number of C−C bonds per pimozide molecule is 9, and assuming the number of C−C bonds per PVP molecule is 1440, the total number of C−C bonds for 70 g of pimozide is 8.22×10^{23}, and the total number of C−C bonds for 30 g of PVP is 6.5×10^{23}. The ratio of the IR absorbance intensity for $\text{C−C}_{\text{pimozide}}$ to that of C−C_{PVP} peaks should be ∼1.26. The C−C bond selected for amorphous pimozide is the peak centered at 1223 cm^{-1}, and the C−C bond peak selected for PVP is centered at 1286 cm^{-1}. Experimentally acquired spectra of amorphous pimozide and PVP can then be added following multiplication by the appropriate constants to give the correct ratio of the two C−C peaks, study.

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