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Research Paper

Effects of Polymer Type and Storage Relative Humidity on the Kinetics of Felodipine Crystallization from Amorphous Solid Dispersions

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Purpose. The objective of this study was to investigate the effects of polymer type and storage relative humidity (RH) on the crystallization kinetics of felodipine from amorphous solid dispersions.
Methods. Crystallization of the model drug felodipine from amorphous solid dispersion samples containing poly(vinyl pyrrolidone) (PVP) and hypromellose acetate succinate (HPMCAS) were evaluated. Samples at three different drug–polymer weight ratios (10, 25, and 50 wt. % polymer) were prepared and stored at six different RHs (0%, 32%, 52% or 66%, 75%, 86%, and 93%). Periodically, the fraction of the drug that had crystallized from the samples was quantified using powder X-ray diffractometry (PXRD).
Results. Felodipine crystallization rates from PVP-containing dispersions were found to be very sensitive to changes in storage RH, while crystallization rates from HPMCAS-containing dispersions were not. PVP and HPMCAS were similar in terms of their ability to inhibit crystallization at low RH, but when the storage RH was increased to 75% or above, felodipine crystallization from PVP-containing solid dispersions proceeded much faster. It is hypothesized that this trend was caused by moisture-induced drug–polymer immiscibility in PVP-felodipine system. For PVP-containing solid dispersion samples stored at 75% RH and above, crystallization of the model drug felodipine seemed to approach a kinetic plateau, whereby a fraction of the drug still remained amorphous even after storage for 500 days or more.
Conclusions. The physical stability of solid dispersions as a function of RH is highly dependent on the polymer used to form the solid dispersion, with PVP-containing dispersions being much less physically stable at high RH than HPMCAS-containing dispersions.

KEY WORDS: crystallization; felodipine; hygroscopicity; powder X-ray diffractometry; relative humidity.

INTRODUCTION

An amorphous solid dispersion is defined as a mixture of an amorphous active pharmaceutical ingredient (API) with a second amorphous component which is typically a polymer (1–4). Since it has been shown that the crystallization rate of many APIs is retarded in the presence of the polymer (5–11), this method is commonly considered as a viable strategy to produce amorphous formulations with adequate physical stability. Oral delivery of an API in the amorphous form is highly attractive for some compounds and exploits the differences in physical properties of the amorphous solid compared to its crystalline counterpart(s). In particular, due to higher free energy, the amorphous form of an API has a higher aqueous solubility than the crystalline form of an API (12,13). This property can potentially be exploited to improve bioavailability of drugs with low aqueous solubility, for example as shown with ritonavir (14).

Different polymers have been shown to be beneficial in inhibiting drug crystallization when used as a solid dispersion carrier; examples include poly(vinyl pyrrolidone) (PVP), poly (vinyl pyrrolidone-co-vinyl acetate) (PVPVA), hypromellose (HPM), and hypromellose acetate succinate (HPMCAS) (7,10,11,15–21). However, due to their chemistry and polarity, the polymers used in solid dispersion formulations are often hygroscopic in nature. As a result, absorption of water by the resulting solid dispersion either during manufacturing or on storage may occur.

The absorption of water has been shown to negatively impact physical stability both for single component and binary amorphous systems. For example, absorption of water during storage at increasing relative humidity (RH) promoted crystallization from amorphous indomethacin (22) and in amorphous sucrose-PVP systems (23). Konno and Taylor found that the nucleation rate of felodipine in various solid dispersions increased with increasing moisture content (16). The growth rate of felodipine has also been studied in the presence and absence of polymers as a function of storage RH, and in general has been found to increase with moisture content (24). However, studies that systematically investigate

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the effect of polymer type and storage RH on the bulk crystallization rate of solid dispersions are lacking. This study aims to address this knowledge gap.

Quantification of the extent of drug crystallization from amorphous solid dispersions as a function of time was performed using powder X-ray diffractometry (PXRD), a well-established method for quantification of crystallinity (25–27). Felodipine was selected as the model hydrophobic compound, since the effects of moisture on the nucleation and growth rates for this compound from amorphous solid dispersion systems containing different polymers have been separately studied as mentioned. Two model polymers with differing hygroscopicity, PVP and HPMCAS, were selected as carriers.

MATERIALS AND METHODS

Materials

Dichloromethane (ChromAR grade) and ethanol (200 proof) were obtained from Mallinckrodt Baker, Inc., Paris, KY, USA, and PHARMCO-AAPER, Brookfield, CT, USA, respectively. Felodipine was a generous gift from AstraZeneca, Södertälje, Sweden. Poly(vinyl pyrrolidone) PVP K29-32, was purchased from Sigma-Aldrich Co., St. Louis, MO, USA, and hypromellose acetate succinate (HPMCAS AQOAT® AS-MF) was obtained from Shin-Etsu Chemical Co., Tokyo, Japan. The polymers were kept in desiccators filled with P_2O_5 for at least one week prior to use to remove any moisture.

Sample Preparations

Felodipine and the polymer (PVP or HPMCAS) were combined at three different ratios (90:10, 75:25, and 50:50 dry weight basis), then dissolved in a 1:1 (by weight) mixture of dichloromethane and ethanol. The solvent was removed using a rotary evaporator apparatus (Brinkman Instruments, Westbury, NY, USA). For each drug–polymer ratio, three replicate samples were prepared independently. After storage under vacuum for at least 72 h to remove any residual solvents, the resulting material was cryo-milled in a liquid nitrogen bath for a total milling time of 4 min. The resulting powder was sieved, and only particles smaller than 150 μm were retained. The samples were analyzed using PXRD to ensure that no detectable amount of crystalline material was present.

Subsequently, the samples were stored at room temperature (22–25°C) in glass desiccators filled with saturated salt solutions. Seven different salts were used to control the RH: P_2O_5 (0% RH), $MgCl_2$ (33% RH), $Mg(NO_3)_2$ (52% RH—all samples except 10% PVP), $NaNO_2$ (66% RH–10% PVP only), NaCl (75% RH), KCl (86% RH), and KNO_3 (93% RH) (28,29). Periodically, the samples were removed from storage and analyzed using a Shimadzu XRD-6000 (Shimadzu Corporation, Kyoto, Japan) equipped with a Cu-Kα source and set in Bragg-Brentano geometry between 5–35° 2θ at 8°/min with a 0.04° step size. The accuracy of the 2θ angle was checked by first verifying that the [111] peak of a Si-standard sample was between 28.423 and 28.463° before each day of measurement, while the measured photon intensity for this peak was used to normalize data collected from samples analyzed on the same day.

For the bulk crystallization samples, three consecutive readings were taken of each sample to ensure that felodipine crystallization was not influenced by the analysis method. A preliminary experiment conducted on dry amorphous solid dispersion samples and those containing moisture following equilibration at 93% RH yielded identical X-ray diffractogram profiles, indicating that sorbed moisture did not noticeably affect the diffraction patterns.

Samples containing 25% PVP and 25% HPMCAS were also separately prepared with 50% of the drug added as crystalline powder. These samples were cryo-milled together for total milling times of 2, 4, and 6 min, and were analyzed using PXRD and infrared (IR) spectroscopy to ensure that the cryo-milling procedure did not result in significant sample alteration. IR spectra of the samples were obtained in absorbance mode using a Bio-Rad FTS 6000 spectrophotometer (Bio-Rad Laboratories, Hercules, CA, USA) equipped with a globar infrared source, KBr beamsplitter, and DTGS detector. The spectra of each sample milled for 2, 4, and 6 min (obtained using a Golden Gate™ Mk II ATR with diamond top-plate, Specac Inc., Woodstock, GA, USA) overlapped with one another, indicating that the processing steps did not induce the formation of amorphous solid dispersions for felodipine-PVP and felodipine-HPMCAS systems. The PXRD diffractograms of the samples milled for different amounts of time were also almost identical. Slight decreases in the height of the Bragg peaks characteristic of crystalline felodipine were detected from the diffractograms, indicating that cryo-milling may have introduced some crystalline defects. However, the difference in calculated crystallinity between samples cryo-milled for 2 min and 6 min was less than 3%, well within the error of the quantification method.

Quantification of Felodipine Crystallinity in the Samples and Statistical Analysis of Results

Standard samples containing known amounts of crystalline drugs were prepared by first mixing a portion of the drug and the polymer, dissolving the powder mixture in dichloromethane-ethanol solvent, and then removing the solvent through rotary-evaporation. Following storage under vacuum, the samples were verified to be X-ray amorphous. Crystalline felodipine was then added to the dispersions, and the resultant powder mixture was cryo-milled and sieved. Five different crystalline-to-amorphous felodipine ratios were prepared for each drug-to-polymer ratio. A Partial Least-Squares (PLS) model was then built using SIMCA-P+ v.11 software (Umetrics Inc., Kinnelon, NJ, USA). For all cases, a model that adequately described the % crystalline felodipine in the samples could be constructed, with R^2 values of 0.975 or greater, and Q^2 values of 0.973 or greater. The root-mean-squared error-of-prediction (RMSEP) for systems containing 10%, 25%, and 50% PVP are calculated as 4.0, 5.3, and 4.5 respectively, while the RMSEP for systems containing 25% and 50% HPMCAS are 3.7 and 5.3 respectively. The percent crystallinity of the drug in samples stored at different RHs was then determined by fitting their measured diffractograms into the respective PLS models.

To evaluate if differences in % crystallinity values obtained from the various samples were significant, statistical analyses were performed using *F*-test with a 95% confidence interval. Samples were typically compared at the final common assay time-point. In instances where the RMSEP of the prediction model was larger than the sample-to-sample variability, this value was used as the denominator in the *F*-test equation to best reflect the largest source of experimental error within a sample group.

RESULTS

Felodipine Crystallization from PVP-Containing Amorphous Solid Dispersions

Diffractograms of solid dispersions containing different levels of polymer after storage at 75% RH are shown in Fig. 1. Fitting of such diffractograms into the appropriate PLS model yielded the percentage of felodipine that crystallized as a function of time from the amorphous solid dispersions. The results are summarized in Figs. 2, 3 and 4 for samples containing 10%, 25%, and 50% PVP. Several trends can be seen from these plots. It is apparent that the crystallization rate of felodipine, as judged from the slope of the % crystallinity *versus* time plots, increased as the storage RH was increased. In particular, crystallization from samples stored at 93% RH occurred rapidly during the first 20 days of storage, before reaching what appears to be a steady-state value. Crystallization from samples stored at 66%, 75%, and 86% RH was also relatively fast and extensive. In contrast, crystallization from samples stored at 0%, 33%, and 52% RH proceeded at a much slower pace, resulting in extremely low levels of crystallinity, even after long storage periods. At 0% RH there was minimal crystallization of samples containing any concentration of PVP (no statistically significant difference was found between the different levels of PVP). At 33% RH, some effects of polymer level were observed, with the extent of felodipine crystallization at long time periods being statistically lower for samples containing 25% and 50% PVP relative to samples containing 10% PVP. However, no statistically significant difference was observed in the extent of crystallization between samples containing 25% and 50% polymer stored under low RHs (0%, 33% and 52% RH), with all samples showing extremely low levels of crystallization. All dispersions stored at high RH (66% RH and above) had a statistically significant higher extent of crystallization than the corresponding samples stored at lower RHs.

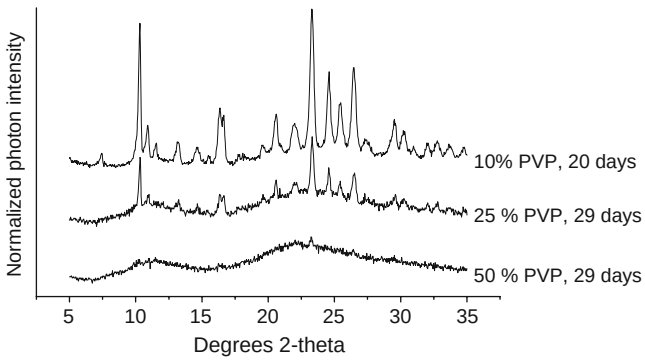

Fig. 1. X-ray diffractograms of amorphous solid dispersion samples containing (from *top* to *bottom*) 10%, 25%, and 50% PVP following storage at room temperature and 75% RH for 20, 29, and 29 days respectively.

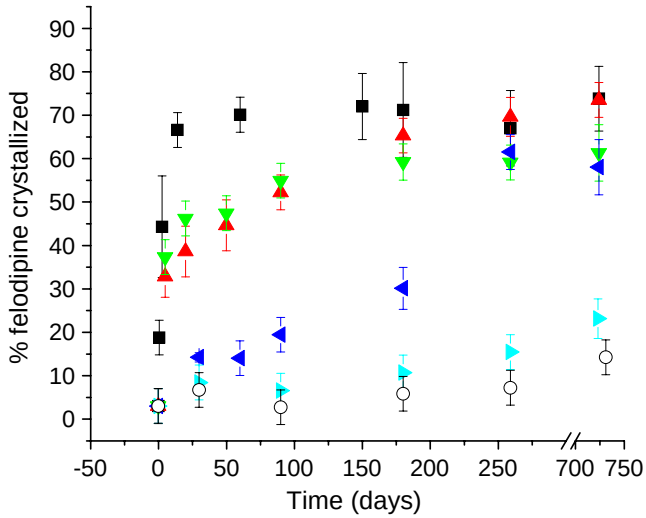

Fig. 2. Percentage of amorphous felodipine that has crystallized from solid dispersions containing 10% PVP following storage at room temperature and (○) 0, (▶) 33, (◀) 66, (▼) 75, (▲) 86, and (■) 93% RH. *Error bars* represent standard deviation of triplicate samples or, for instances where the standard deviations of the three crystallinity values were smaller than the RMSEP of the chemometric prediction models, the RMSEP values were used.

Interestingly, even after storage at 86% and 93% RH for extended periods (724 days for samples containing 10% PVP and 494 days for samples containing 25% and 50% PVP), some of the drug remained in the amorphous form. The amount of drug that crystallized from the solid dispersion samples appeared to have reached a plateau at approximately 70% for samples containing 10% PVP, 80% for samples containing 25% PVP, and 75% for samples containing 50%

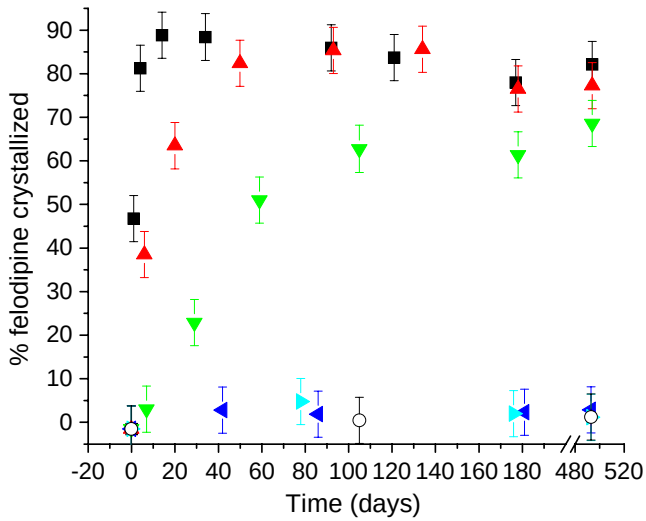

Fig. 3. Percentage of amorphous felodipine that has crystallized from solid dispersions containing 25% PVP following storage at room temperature and (○) 0, (▶) 33, (◀) 52, (▼) 75, (▲) 86, and (■) 93% RH. *Error bars* represent standard deviation of triplicate samples or, for instances where the standard deviations of the three crystallinity values were smaller than the RMSEP of the chemometric prediction models, the RMSEP values were used.

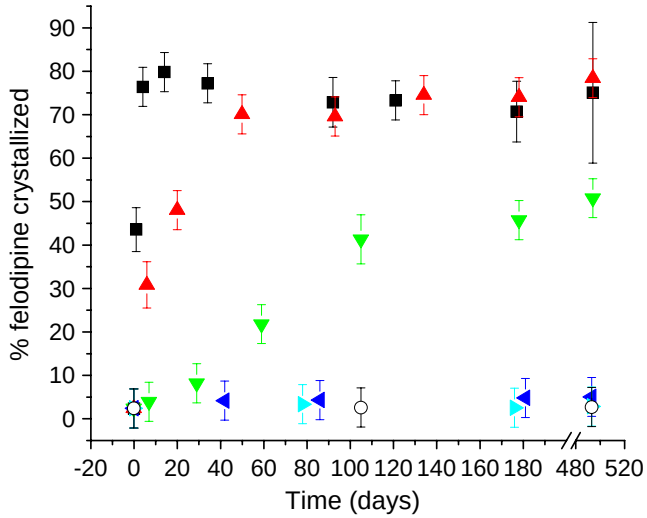

Fig. 4. Percentage of amorphous felodipine that has crystallized from solid dispersions containing 50% PVP following storage at room temperature and (○) 0, (▶) 33, (◀) 52, (▼) 75, (▲) 86, and (■) 93% RH. *Error bars* represent standard deviation of triplicate samples or, for instances where the standard deviations of the three crystallinity values were smaller than the RMSEP of the chemometric prediction models, the RMSEP values were used.

PVP (see Table I). No statistically significant difference was found between these plateau values.

Felodipine Crystallization from HPMCAS-Containing Amorphous Solid Dispersions

Samples containing 10% HPMCAS were found to undergo partial crystallization to a mixture of two different crystalline phases of felodipine; therefore, no quantification was performed on these samples (see Fig. 5). The second crystalline phase was identified as the Form II modification of felodipine as reported by Rollinger and Burger (30). The percentage of felodipine that crystallized as a function of time from the 25% and 50% HPMCAS-containing amorphous solid dispersion samples stored at 0%, 33%, 52%, 75%, 86%, and 93% RH is shown in Figs. 6 and 7.

For samples stored at 0% and 33% RH, the extent of crystallization of the drug was low even after extended periods of time (around 10%), and no statistically significant difference could be observed between dispersions containing 25% and 50% polymer. At higher RHs, crystallization from samples containing 25% HPMCAS commenced after a short storage time. In contrast, crystallization from samples containing 50% HPMCAS appeared to exhibit an induction period: samples analyzed after 100 days storage at 52% RH, 75 days storage at 75% RH, 120 days storage at 86% RH, and 35 days storage at 93% RH showed negligible amounts of crystalline drug present (see Fig. 7). However, after long time periods, no statistically significant difference was found between the extent of crystallization for samples containing either 25% or 50% HPMCAS at a given storage RH. Interestingly, statistical analysis also showed that, for a given polymer concentration, RH had no significant effect on the extent of crystallization for the HPMCAS dispersions. This can be seen clearly from Fig. 7 which shows the insensitivity of the crystallization rate to RH for dispersions containing 50% HPMCAS.

When the crystallization rates of felodipine from HPMCAS-containing dispersions are compared to PVP-containing dispersions, the following observations can be made: at low storage RHs (0%, 33% and 52% RH), no statistically significant difference was found in the stabilizing ability of the two polymers at a given concentration level. At high storage RHs (75%, 86% and 93% RH), HPMCAS was clearly a better stabilizer of the amorphous form of felodipine than PVP, with crystallization proceeding at a much slower rate. Furthermore, while crystallization from PVP-containing dispersions stored at high RHs achieved a steady-state plateau value within a few days, crystallization from HPMCAS-containing dispersions stored at 86% and 93% RH still showed indications of increases in crystallinity after ~490 days.

DISCUSSION

Crystallization is the process by which crystalline structures, identifiable by their anisotropy and the presence of long-range three-dimensional order, are formed (31). Typically, this process occurs either from a supersaturated solution or from an undercooled melt. If occurring from an undercooled melt, crystallization can also be described as the process by which a supercooled liquid (or a glass) undergoes a first-order phase transition to form the thermodynamically more stable crystalline phase. This process is affected by different thermodynamic, kinetic, as well as other molecular factors (32–34). Thermodynamically, crystallization of an

Table I. Percentage of Felodipine that has Crystallized from the Amorphous Solid Dispersion Samples at the Last Time-Point Analyzed

	10% PVP	25% PVP	50% PVP	25% HPMAS	50% HPMAS
0% RH time (days)	14.2 (0.1) 724	1.2 (0.4) 493	2.7 (1.1) 493	8.6 (0.3) 487	9.3 (0.3) 487
33% RH time (days)	23.1 (4.55) 724	1.1 (0.1) 493	2.8 (0.3) 493	9.1 (0.3) 488	10.7 (0.9) 488
52% RH time (days)		2.8 (0.3) 493	5.0 (0.9) 493	9.7 (0.7) 489	9.7 (0.4) 489
66% RH time (days)	58.0 (6.4) 724				
75% RH time (days)	61.3 (6.5) 724	68.6 (1.6) 494	50.8 (1.4) 494	13.9 (0.5) 490	10.6 (1.9) 490
86% RH time (days)	73.5 (2.2) 724	77.2 (0.9) 494	78.4 (3.3) 494	16.4 (0.6) 490	9.2 (0.7) 490
93% RH time (days)	73.8 (7.5) 724	82.1 (1.4) 494	75.1 (16.2) 494	27.7 (2.8) 491	16.6 (5.7) 491

Results reported as Average (Standard Deviation) % crystallinity of felodipine, with the storage time in days indicated on right. $n=3$. Note that if standard deviations between the samples were smaller than RMSEP of the method, then the RMSEP was used to analyze difference between variables.

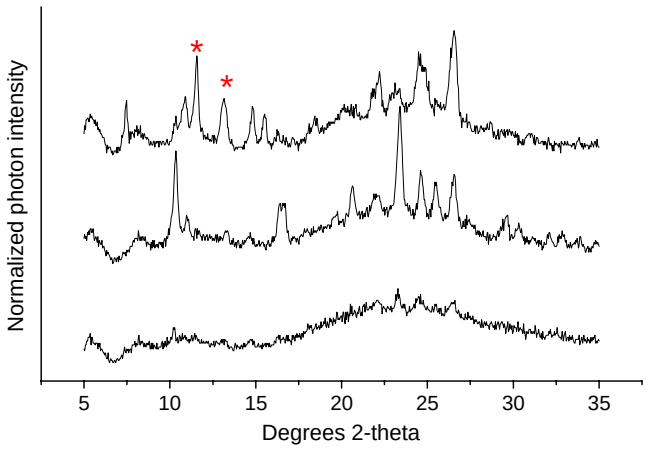

Fig. 5. X-ray diffractograms of amorphous solid dispersions containing (from *top* to *bottom*) 10%, 25%, and 50% HPMCAS following storage at room temperature and 93% RH for 491 days. Peaks identified by * are characteristic of Form II of felodipine as published in reference (30).

amorphous material is affected by the driving force for crystallization (ΔG_c), which can also be thought of as "degree of undercooling." For pure amorphous drug, this value can be calculated as the difference in the enthalpy and the entropy of the amorphous and crystalline forms of the material (35,36), or approximated using the well-known Hoffman equation (35,37). When a second component, such as a polymer, is mixed at the molecular level with the amorphous material, ΔG_c for the crystallizable component of the mixture is not easily quantifiable. One way to try and determine this value is by calculating the additional free energy change of the system upon mixing (ΔG_{mix}) with the polymer, for example as done by Marsac *et al.* using data obtained from melting point

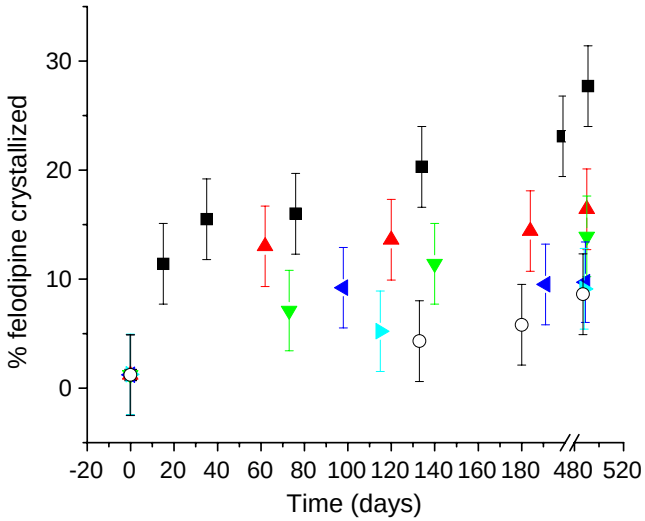

Fig. 6. Percentage of amorphous felodipine that has crystallized from solid dispersions containing 25% HPMCAS following storage at room temperature and (○) 0, (▶) 33, (◀) 52, (▼) 75, (▲) 86, and (■) 93% RH. *Error bars* represent standard deviation of triplicate samples or, for instances where the standard deviations of the three crystallinity values were smaller than the RMSEP of the chemometric prediction models, the RMSEP values were used.

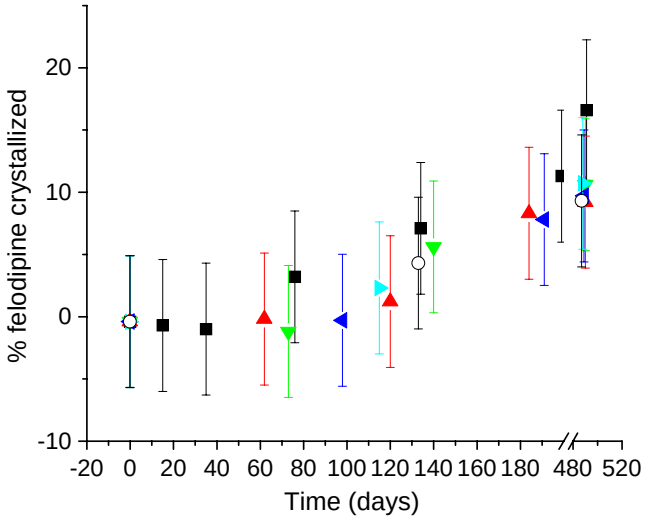

Fig. 7. Percentage of amorphous felodipine that has crystallized from solid dispersions containing 50% HPMCAS following storage at room temperature and (○) 0, (▶) 33, (◀) 52, (▼) 75, (▲) 86, and (■) 93% RH. *Error bars* represent standard deviation of triplicate samples or, for instances where the standard deviations of the three crystallinity values were smaller than the RMSEP of the chemometric prediction models, the RMSEP values were used.

depression experiments (38). In the presence of a third component, such as the case when water is sorbed by a molecular level solid dispersion comprised of a drug and a polymer, ΔG_c will be further affected. However, determining a reasonable estimate is extremely difficult, since contributing factors will include the relative amounts of drug, water, and polymer, as well as the drug–water, drug–polymer, and polymer–water interactions, which are liable to change in the presence of the other components (24).

From a kinetic perspective, intimately mixing a large molecule, such as a polymer, with an amorphous drug has been shown to reduce the overall molecular mobility in the system, for example as indicated by an increase in the T_g of the mixed system. Since crystallization of an amorphous material has been shown to highly depend on molecular mobility, reducing the mobility can be expected to reduce the crystallization rate of the drug, as shown in literature (5,39). Aside from these two factors, other factors have also been shown to impact crystallization from the amorphous phase, including molecular motif recognition (40,41) and drug–polymer specific interactions (10,17).

Phenomenologically, the process of crystallization is commonly described using two sequential sub-processes: nucleation and crystal growth (42–44). Nucleation is a process by which nuclei, seeds, or embryos that can act as centers of crystallization develop (43), and depends on the kinetic and thermodynamic factors mentioned above, as well as other factors, such as interfacial surface energy. Once nucleation has occurred, crystal growth (which is also affected by thermodynamic and kinetic factors, for example as shown by Andronis and Zografi with indomethacin (45)) can proceed. To properly examine the effects of moisture on the crystallization behavior of a drug from an amorphous solid dispersion system, it is helpful to consider all the factors mentioned above.

Felodipine Crystallization from PVP-Containing Amorphous Solid Dispersions

It is apparent from Figs. 2, 3 and 4 that felodipine crystallization rates from PVP dispersions are extremely sensitive to RH. At low storage RH, PVP was an extremely effective crystallization inhibitor whereby the crystallization tendency decreased with increasing polymer content. For example, when stored at 0% RH, less than 15% of the drug had crystallized from samples containing 10% PVP after ~730 days, while complete crystallization of pure amorphous felodipine under the same storage condition was achieved in less than 12 days. In addition, no crystallization (within the error of the measurement) was observed in samples containing 25% and 50% PVP after 490 days storage at the same RH. A similar trend was observed for samples stored at 33% and 52% RH. Clearly, when the moisture content of the samples is limited, formation of a solid dispersion with PVP resulted in a system with excellent physical stability over pharmaceutically relevant time periods.

When felodipine-PVP solid dispersions were stored at 75% RH or above, crystallization of the drug proceeded rapidly and a large fraction of the drug crystallized. For samples stored at 93% RH, Figs. 2, 3 and 4 show that crystallization was rapid, with the maximum extent of crystallization being observed after twenty days; hereafter, no additional crystallization was observed, even though not all of the drug had crystallized. To analyze the trend further, the incremental mass of felodipine that crystallized from samples stored at this condition was calculated and plotted in Fig. 8. The results show that under this storage condition, the amount of felodipine crystallizing per unit time from samples containing different levels of PVP is comparable. In other words, the absolute rates of felodipine crystallization from amorphous solid dispersions containing 10%, 25%, and 50% PVP are independent of the amount of polymer added when stored at 93% RH. This trend is clearly different than results obtained for samples stored at 33% RH, where the drug crystallization rate for samples containing 50% PVP is significantly lower than for samples containing 10% PVP.

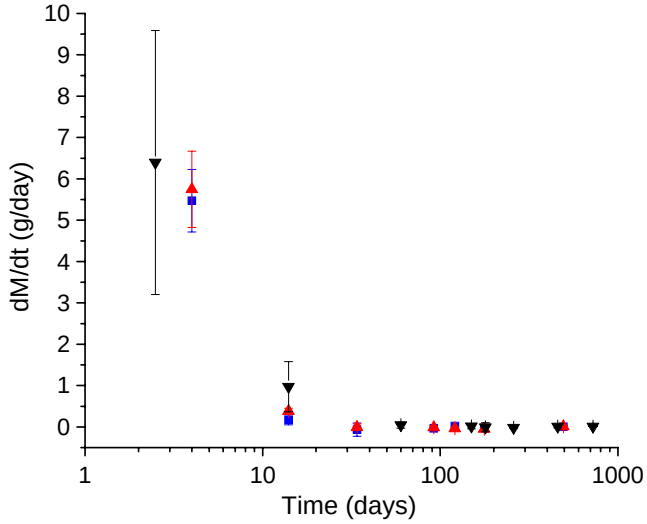

Fig. 8. Incremental mass of felodipine crystallizing from amorphous solid dispersion samples containing (▼) 10, (▲) 25, and (■) 50% PVP when stored at 93% RH.

To understand the effects of storage at high RH on PVP-containing dispersions, it is necessary to consider an interesting phenomenon reported for this drug–polymer system, namely that exposure of the samples to relative humidities of around 75% RH and above resulted in the formation of drug-rich and polymer-rich amorphous phases (16,33,46). In the event of moisture-induced amorphous–amorphous phase separation, it would be expected that the physical stabilization of the amorphous phase of the drug through the addition of polymer would be significantly reduced, if not altogether eliminated in the most extreme case (where all the drug and polymer molecules are completely phase separated). Furthermore, the overall crystallization rate would be expected to be independent of the amount of polymer in the dispersion, since the final concentrations will be dependent on the extent of moisture-induced drug–polymer immiscibility. This is exactly what was observed in this study, supporting the supposition that the rapid crystallization at high relative humidities can be explained in part by the phenomenon of moisture-induced amorphous–amorphous phase separation, in addition to the enhanced molecular mobility resulting from the sorbed moisture. Interestingly, the kinetics of crystallization for the phase-separated dispersions up to the plateau value was comparable to pure amorphous felodipine stored at 93% RH, which completely crystallized in less than 12 days. Additional support is also provided by a study of the linear growth rates of felodipine crystals from thin films containing 2.5%, 5%, and 10% PVP which were found to be comparable to each other following storage at 93% RH (24).

Felodipine Crystallization from HPMCAS-Containing Amorphous Solid Dispersions

Overall, the extent of felodipine crystallization from HPMCAS dispersions was quite low, reaching a maximum of about 30% for a dispersion containing 25% polymer after storage at 93% RH for approximately 500 days. At low RHs (0% and 33% RH), crystallization from samples containing 25% and 50% HPMCAS was minimal, whereby less than 10% of the drug had crystallized after 500 days in each system. Furthermore, the crystallization rate of felodipine from HPMCAS-containing dispersions was clearly much less sensitive to changes in storage RH as compared to PVP-containing dispersions. Similar results have been observed in studies of the nucleation rate of felodipine in the presence of HPMCAS, where a relatively minor effect of RH on nucleation rate was reported when the polymer was present at a concentration of 25%.

When the HPMCAS dispersions were stored at 52% RH and above, the dispersions containing 50% HPMCAS seemed to display a lag time before crystallization was detected; lag times are commonly associated with the process of nucleation and growth until the crystalline particles can be detected using the method chosen (47). However, once the felodipine crystallization profile from sample containing 50% HPMCAS diverged from 0, the rate of crystallization was comparable to the 25% dispersion, as estimated by comparing the slopes of the percentage crystallization as a function of time (see Figs. 6 and 7). This was especially obvious for samples stored at 93% RH. Assuming the growth of felodipine crystals above and below the detectable levels are governed by the same factors,

this trend suggests that for samples containing 50% polymer and stored at high RH, felodipine crystal nucleation was delayed. But once the process of nucleation occurred, the crystallization rate is governed by the same factors as for the dispersion containing 25% HPMCAS. It can thus be speculated that the growth rates are similar at 25% and 50% polymer concentrations.

It is also of interest to compare crystallization rates of felodipine from HPMCAS-containing solid dispersions to those from PVP-containing solid dispersions. At low storage RH (52% RH or below) felodipine crystallization from PVP-containing solid dispersions was in general comparable to HPMCAS-containing solid dispersions. Similar results have been reported for the nucleation rates of felodipine in the presence of these two polymers, where little differentiation in effects was observed for dispersions containing either polymer at 0% or 33% RH (16). When the storage RH was increased to 75% RH or above, felodipine crystallization from PVP-containing solid dispersions clearly occurred much faster than crystallization from comparable HPMCAS-containing solid dispersions. These observations can be explained by the increased hygroscopicity of the PVP dispersions relative to the HPMCAS dispersions (24), and the susceptibility of the PVP systems to undergo moisture-induced drug–polymer immiscibility as previously explained.

Further speculation can also be made on the origin of the felodipine crystallization plateaus that were reached in each case and especially apparent for PVP-containing systems stored at 75% RH and above. The "abrupt" nature by which these plateaus were attained seemed to suggest that these plateaus are in fact thermodynamic in nature, namely that felodipine has reached its "solubility limit" in the remaining amorphous phase mixture of felodipine, PVP, and water. However, close examination of the actual values of the plateaus suggests differently. For example, if we consider the concentration of felodipine that remained uncrystallized from samples containing 50% PVP after extended storage at 93% RH to be 20% of the original amount present, then the remaining amorphous phase would contain approximately 0.1 g felodipine for every 0.86 g PVP-water mixture (0.5 g PVP and 0.36 g water) (24). Such large amounts of moisture have been shown to result in at least one order of magnitude decrease in the solubility of felodipine in the methylpyrrolidone system (18). Assuming similar effects in PVP, then the solubility of felodipine in PVP-water mixture would be reduced from around 0.25 g felodipine for every g "solvent" (dry PVP in this instance) (38) to no more than 0.025 g felodipine for every 1-g PVP-water mixture, smaller than values observed at the plateau. Thus, retardation of further felodipine crystallization possibly represents the amount of drug in polymer-rich phase which has not crystallized due to kinetic limitations.

CONCLUSIONS

PVP and HPMCAS were found to be effective crystallization inhibitors of felodipine when the solid dispersions were protected from moisture. When the storage RH was increased to 75% RH or above, felodipine crystallization from PVP-containing solid dispersions proceeded much faster than for comparable HPMCAS-containing solid dispersions. This trend can be attributed to the higher amounts of moisture sorbed by PVP-containing solid dispersions, which has been shown to cause moisture-induced drug–polymer immiscibility, in addition to reducing the T_g of the systems. For PVP-containing solid dispersion samples stored at 75% RH and above, crystallization of the model drug felodipine seemed to approach a kinetic plateau, whereby a fraction of the drug still remained amorphous even after storage for 500 days or more. Results obtained in this study highlight the importance of considering the effects of storage conditions on the miscibility of amorphous solid dispersions when interpreting drug crystallization data.

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