Effect of Molecular Weight, Temperature, and Additives on the Moisture Sorption Properties of Polyethylene Glycol

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Effects of the Molecular Weight and Concentration of Polymer Additives, and Temperature on the Melt Crystallization Kinetics of a Small Drug Molecule

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ABSTRACT: The purpose of the present study was to investigate the effect of molecular weight (MW) and concentration of a polymeric additive, poly(vinyl pyrrolidone) (PVP), on the crystal growth rate of a small molecule drug, felodipine. PVP samples with three different molecular weights ($2-3 \times 10^3$ g/mol for PVP K-12, $4-5 \times 10^4$ g/mol for PVP K-29/32, and $1-1.5 \times 10^6$ g/mol for PVP K-90) were used to study the effect of molecular weight. Optical microscopy was used to measure the growth rates at various temperatures in the range of 70−110 °C. While PVP was found to reduce the crystal growth rate at all temperatures, the inhibitory effect was much greater at lower temperatures. The inhibiting effect of PVP on the crystal growth rate of felodipine increased as a function of polymer molecular weight. The effect of polymer concentration on the crystal growth rate was investigated with varying concentrations of PVP K-29/32 (0.5−4.5 wt %), and a log linear relationship between crystal growth rate and concentration was observed. The calorimetric glass transition temperatures (T_g) of the solid dispersions were not significantly different from the T_g of pure felodipine. IR spectroscopy results indicate that among the PVP polymers of three different MWs, there is no difference in their hydrogen-bonding interactions with felodipine molecules. We present discussions of these experimental results with reference to established thermodynamic theories of crystallization kinetics and mass transfer models.

Introduction

The introduction of high throughput screening methods in the drug discovery process has resulted in many new drug candidates that are hydrophobic. This drug hydrophobicity leads to lower solubility and dissolution, potentially resulting in low bioavailability of orally administered drugs.[1,2] It is well recognized that the amorphous form of a solid drug can improve the dissolution rate.[3,4] However, the amorphous solid form of a drug normally has a tendency to convert to the more stable crystalline form over pharmaceutically relevant time scales thereby negating the desired effect of an increased dissolution rate of the amorphous formulation.

Molecular dispersion in a suitable carrier, typically a polymeric material, has been demonstrated to be a useful strategy to prevent, or at least delay, crystallization of the drug.[5−7] A number of explanations have been proposed to explain the effects of polymers on the stabilization of amorphous solids against crystallization.[8−13] Recently, several reports in the pharmaceutical literature have shown that certain polymers are capable of inhibiting the crystallization process of amorphous drugs even at small concentrations of polymer (i.e., < 10% by weight).[14−17] The exact mechanism by which a polymer inhibits the crystallization of the amorphous drug at such low polymer concentrations as of yet remains unexplained. Several explanations have been proposed, including the possible accumulation of the polymers at the interface between the crystallized domain and the amorphous matrix,[14] a local antiplasticization effect of the polymer,[15] a decrease in molecular mobility due to the addition of the polymer,[17] and specific interactions (such as hydrogen bonding) between the drug molecule and the polymer segment.[18] Improved understanding as to exactly how some polymers so effectively suppress the crystallization of amorphous drugs will benefit future efforts to design and develop better polymer materials for inhibition of drug crystallization. The present study seeks to contribute to this need.

In this work, felodipine, an antihypertensive drug, was chosen as the model hydrophobic compound, and poly(vinyl pyrrolidone) (PVP) was used as the polymeric inhibitor. Specifically, our study investigated the effects of both the molecular weight and concentration of PVP on the rate of the growth of felodipine crystals from the melt under various temperature conditions. Felodipine crystals grow relatively slowly as compared to other amorphous drug compounds such as nifedipine or indomethacin,[16,19] which allowed us to examine their crystallization behavior in an experimentally convenient range of temperature (i.e., 70−110 °C). The effect of the molecular weight (MW) of the polymer on the kinetics of the crystal growth was studied using PVP polymers with three different MWs ($\bar{M}_w$ = 2500, 45 000, and 1 250 000 g/mol); hereafter, these polymers will be denoted, respectively, as PVP K-12, PVP K-29/32, and PVP K-90. The rates of the crystal growth of felodipine in the presence of PVP were measured under various combinations of temperatures and PVP MWs and concentrations. We found that (i) the crystal growth rate of felodipine is dramatically affected by a decrease in temperature both in the absence and in the presence of PVP

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additives; (ii) increasing the MW of the PVP polymer increases the effectiveness of inhibition by PVP; (iii) the effect of the polymer is greater at higher polymer concentrations; (iv) based on detailed analysis of the data, the inhibitory effect of PVP on the crystal growth of felodipine is most likely kinetic in origin.

Materials and Methods

Felodipine (form I polymorph) was a generous gift from Astra-Zeneca, Södertälje, Sweden, and poly(vinyl pyrrolidone) (PVP) K-29/32 was purchased from Sigma-Aldrich Co, St. Louis, MO. PVP K-12 and PVP K-90 were supplied by BASF Corp. The weight-average molecular weights (provided by the suppliers) are $4-5 \times 10^4$ g/mol for PVP K-29/32, $2-3 \times 10^3$ g/mol for K-12, and $1-1.5 \times 10^6$ g/mol for K-90. The PVP powder was dried under a vacuum for 2 days prior to use to minimize the amount of moisture in the polymer. Dichloromethane and ethanol were obtained from Mallinckrodt Baker Inc., Paris, KY, and Aaper Alcohol and Chemical Co., Shelbyville, KY, respectively.

A two-step process was used to prepare a PVP dispersion in felodipine for measurements of the rate of the crystal growth. A 10% PVP (K-12, K-29/32 or K-90) dispersion in felodipine was prepared by rotary evaporation from a PVP/felodipine solution in a 1:1 (by weight) mixture of ethanol and dichloromethane. Afterward, the sample was further dried in a vacuum oven for 48 h to remove any residual solvent. The 10% PVP dispersion in felodipine was diluted by mechanically blending with an appropriate amount of additional pure crystalline felodipine in a cryogenic mill (6750 freezer mill, Spex Sampleprep, Metuchen, New Jersey) to yield a PVP-in-felodipine mixture at a lower concentration. This same procedure was used to prepare PVP/felodipine mixtures at different PVP concentrations (i.e., 0.5%, 0.75%, 1.5%, 3%, and 4.5% w/w). Rotary evaporation of samples containing < 5 wt % polymer would result in partial crystallization of felodipine and potentially nonhomogenous mixtures.

A two-stage isothermal technique was used to prepare samples for the growth rate measurements. About 2−4 mg of the PVP/felodipine mixture was melted on a precleaned microscopic cover glass to form an optically transparent amorphous film which was covered with another cover glass. The sample was rapidly quenched to a temperature of −5 °C (which is 50 °C below the T_g of felodipine). Care was taken to keep the relative humidity (RH) below 15% during sample preparation. The samples thus obtained were confirmed to be amorphous by the absence of birefringence using polarization light microscopy (Nikon Eclipse E600 POL microscope, Nikon Corp Tokyo, Japan). These samples were stored over P_2O_5 (0% RH) inside desiccators placed in an oven maintained at 40 °C. The rate of the growth of the crystal nuclei initially formed at 40 °C was subsequently monitored at various designated temperatures in the range of 70−110 °C. The temperature was maintained using a hot stage (Linkam THMS 600, Surrey, Great Britain). The hot stage was calibrated for temperature using the melting points of naphthalene and adipic acid (Mettler Thermometric Standards, Mettler Instrument Corporation, Princeton, NJ). The progress of the crystal growth was recorded by time-lapse photography at regular time intervals. Regardless of the crystallization conditions (i.e., temperature, PVP molecular weight, and concentration), the resultant felodipine crystals formed between the two glass slides were found to have an almost identical thickness ($5.5 \pm 2\,\mu$m). Therefore, among the crystals grown under the different conditions, the growth rates can be compared by comparing the rates of increase in the diameter of the crystal. At all conditions studied, the measured diameters of crystallites were found to increase linearly as a function of time, and therefore the slope of the diameter vs time relationship was taken to be the growth rate.

The steady shear viscosities of pure felodipine and PVP/felodipine dispersions were measured using an Anton Paar MCR Series 301 rheometer (Anton Paar, Ashland, VA, USA). These measurements were conducted using a 25-mm diameter parallel plate geometry with a 1-mm gap size between the plates. The temperature was controlled using Peltier plates inside a heating hood, which produces a gradient-free temperature field. Each sample was loaded onto the lower plate in a solid powder form at ambient temperature. The sample was then melted by heating at a rate of 10 °C/min to a temperature 5 °C above the melting temperature of felodipine and holding the sample at that temperature for a few minutes to ensure complete melting of the powder. The upper plate was then lowered, and excess material was trimmed along the border of the plates. A preshear of 10 s^{-1} was applied for 5 min at this temperature to remove sample history. Afterward, the temperature was lowered to a designated temperature, and the sample was equilibrated at the test temperature for a sufficient length of time. A shear deformation was applied at a rate of 1 s^{-1} under the constant temperature condition, and the shear viscosity value was recorded when a steady-state reading was obtained. For some samples, the viscosities were measured at five different temperatures: 110, 105, 100, 95, and 90 °C. At a polymer concentration of 3% by weight, the shear-rate dependences of the viscosities were examined for the three different polymers as presented in Figure S1 (Supporting Information).

Thermal analysis was conducted on the PVP/felodipine samples using a TA Q2000 differential scanning calorimetry (DSC) instrument equipped with a refrigeration cooling accessory (TA Instruments, New Castle, DE, USA) in order to determine the glass transition and melting temperatures of the PVP/felodipine systems. Using the standard mode of operation, the instrument was calibrated for temperature using benzophenone (Sigma-Aldrich Inc., St. Louis MO, USA) and indium (Perkin-Elmer Corporation, Norwalk, CT, USA). Indium was also used to calibrate the enthalpic response. Nitrogen served as the purge gas (at a flow rate of 50 mL/min), and the weights of the reference and sample pans were matched to within 0.01 mg. 2−5 mg of the sample was loaded into an aluminum T zero sample pan with a pinhole (TA Instruments, New Castle, DE, USA) and sealed. The glass transition temperature (T_g) was determined by heating the sample at a ramp rate of 10 °C/min, and the onset temperature was taken to be the glass transition temperature. To erase the thermal history, the sample was heated to 20 °C above the T_g of the sample, and the sample was cooled to 50 °C below the T_g at a rate of 10 °C/min; the actual T_g measurement was made during the second heating temperature cycle. Melting point (T_m) depression measurements on pure felodipine and felodipine in the presence of 3% PVP K-12 were made by heating the samples at 1 °C/min to beyond the melting point. PVP K-12 was intimately mixed with pure crystalline felodipine using a cryogenic mill. The extrapolated offset of the bulk melting endotherm was taken as the offset of melting. For PVP/felodipine blends containing the K-29/32 or K-90 polymer, the melting temperature of felodipine was not measured, because the T_g's of the polymers are higher than the drug's melting point.

Infrared (IR) spectroscopy measurements were conducted using a Bio-Rad FTS 6000 (Bio-Rad, Cambridge, MA) to determine the existence and extent of the hydrogen bonds formed between felodipine and PVP of different molecular weights. The IR samples were prepared by using a spin coating method. Feldodipine and the polymer (PVP K-12, K 29/32, or K90) were dissolved in a 1:1 (by weight) mixture of ethanol and dichoromethane, and deposited onto a ZnS window by spin coating (500−2000 rpm) using a KW-4A spin coater (Chemat Technology Inc., Northridge, CA). Residual solvent was removed by placing the sample at 90 °C for several minutes before the IR spectra were recorded. To minimize contact with moisture in the air, the sample compartment of the instrument was purged with nitrogen gas throughout the duration of the experiment. A total of 128 scans were collected for each sample in transmission mode over the wavenumber range of 4000−400 cm^{-1}. A PVP concentration of 20% by weight was chosen to ensure sufficient sensitivity in terms of detecting drug−polymer interactions.

Raman microscopy measurements were performed using a Renishaw Ramascope Raman Microscope system (Renishaw Plc., New Mills, Gloucestershire, UK) attached to a Leica microscope equipped with a 783-nm diode-laser source. Spectra were acquired using a 30−60-s exposure time over a wavenumber range of 2000−200 cm^{-1}, a 50× objective lens, and a laser power of about 21 mW.

X-ray diffraction data were obtained under Cu-Kα radiation using a Shimadzu XRD-6000 powder diffractometer (Shimadzu Scientific Instruments, Columbia, MD) operating at 40 kV and 30 mV. The pure felodipine, 0.5% PVP/felodipine, and 3% PVP/feodipine samples were allowed to completely crystallize on microscope cover glasses. Afterward, the top cover glass was removed, and the bottom cover glass was placed on an aluminum sample holder. For each

Table 1. Thermal Properties of Felodipine, the PVP Polymers, and the PVP/Felodipine Dispersions[a]

material	T_g (°C)	T_m (°C)
felodipine	43.3	141.5
0.5 wt % PVP K-29/32/felodipine	43.6	
1.5 wt % PVP K-29/32/felodipine	43.4	
3.0 wt % PVP K-29/32/felodipine	43.5	
4.5 wt % PVP K-29/32/felodipine	43.6	
3.0 wt % PVP K-12/felodipine	44.1	140.7
3.0 wt % PVP K-90/felodipine	44.0	
PVP K-12	102.9	
PVP K-29/32	163.9	
PVP K-90	174.9	

[a] Standard deviations were within ±1°C.

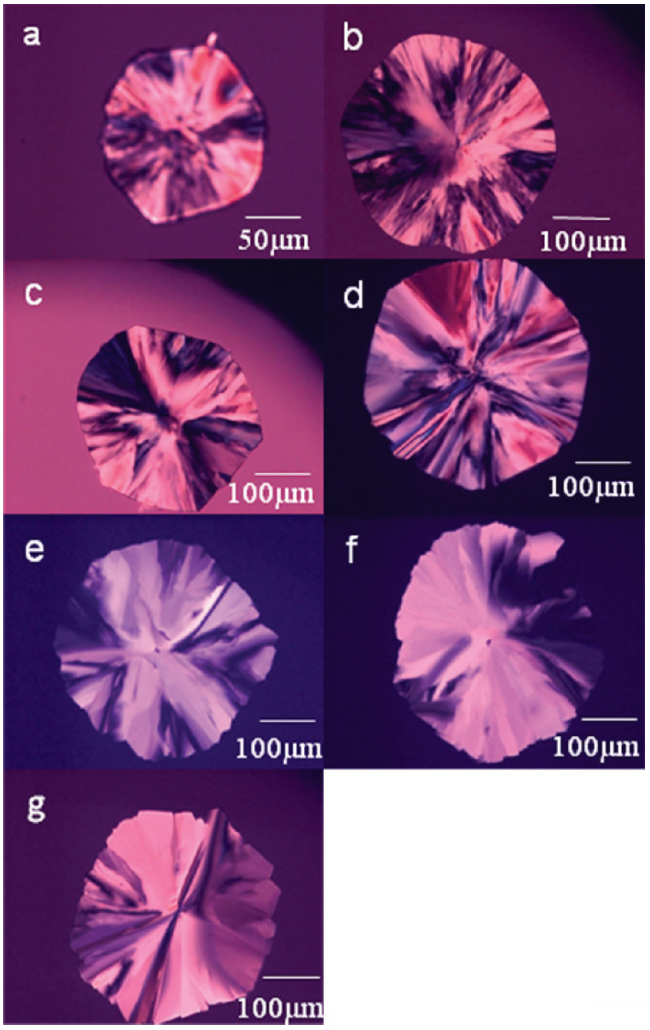

Figure 1. Representative polarizing optical microscopy images of pure felodipine crystals grown at (a) 70, (b) 80, (c) 90, (d) 95, (e) 100, (f) 105, and (g) 110 °C.

sample, the X-ray measurements were conducted in a scan range of 5−35° angle (2θ) at a scan rate of 4°/min with a step size of 0.04°.

Results

The glass transition temperatures (T_g's) of pure felodipine, the PVP polymers, and the PVP/felodipine dispersions are presented in Table 1; note in this paper, we use the term, (solid) dispersion, to denote a molecularly mixed, single-phase homogeneous mixture between the drug and polymer compounds, following the common usage of this term in the pharmaceutical literature.[20] There was no detectable difference between the glass transition temperature of pure felodipine and that of felodipine in the presence of PVP for the PVP concentrations studied, as has been observed previously for other polymer/drug dispersions.[15,16] Raman microscopy was used to determine the phases of the felodipine crystals grown under various combinations of molecular weights (MWs) and concentrations of PVP, and temperatures. In all cases, the crystals grown in the bulk region of the sample were observed to be the metastable form II polymorph regardless of the crystallization temperature, the PVP MW, or the polymer concentration; the form II crystals could be identified, for instance, using the peak at 1648 cm^{-1} (which corresponds to the stretching vibration of the C=C bond) and the peak at 1503 cm^{-1} (which corresponds to the aliphatic bending vibrations).[21] In the absence of the polymer, some nucleation and growth of crystals of form I were observed near the edges of the cover glass, but these sites were excluded in the measurement of the growth rate. Representative Raman spectra obtained from the form I and form II crystals of felodipine are shown in Figure S2, Supporting Information. Melting point differences measured using a hot stage were consistent with the observed crystal polymorphs; the form II crystal showed a lower melting temperature than the form I polymorph. Therefore, all growth rate data reported herein are for the metastable form II polymorph of felodipine.

Effect of PVP Molecular Weight on the Rate of the Crystal Growth. Figure 1 presents representative optical microscopy images (under polarized light) of the pure felodipine crystals grown at seven different temperatures between 70 and 110 °C. The shapes of the crystals grown at the various temperatures are all spherulitic, and at relatively low temperatures (< 100 °C) the crystallization appears to produce faceted, laterally straight interfaces between the crystallized domain and the amorphous matrix, whereas the interface line becomes more zigzag shaped at higher temperature. At a given temperature, the presence of PVP does not give rise to any significant change in the macroscopic morphology of the crystals regardless of the molecular weight of PVP. See Figure 2, for example, for cross-polarization images of the felodipine crystals grown in the presence of PVP (3% by weight) at various PVP molecular weights at 90 °C. Felodipine crystals grown in the presence of the PVP polymers under other temperature conditions did not exhibit any considerable difference in their macroscopic shape from the ones displayed in Figure 2. Figure 3 presents the values for the diameters of the felodipine crystals measured in the absence of PVP as functions of time at four different temperatures of 90, 95, 100, and 105 °C. Each set of data were fit to a linear equation, and the slope of the linear regression line was taken as the linear rate of the crystal growth. The values of the growth rates of the pure felodipine crystals thus evaluated for the above four plus three other temperatures are summarized in a plot shown in Figure 4. In the case of pure felodipine, the growth rate appears to peak at around 105 ± 5 °C, and it decreases dramatically with decreasing temperature; the growth rate decreased by approximately 2 orders of magnitude as the temperature was lowered from 110 to 70 °C.

In general, the addition of even a small amount of PVP (e.g., 3 wt %) substantially reduced the growth rate of the felodipine crystal (Figure 4). The detailed shape of the growth rate vs temperature curve was also affected by the addition of the polymers; the inhibiting effect of the polymer

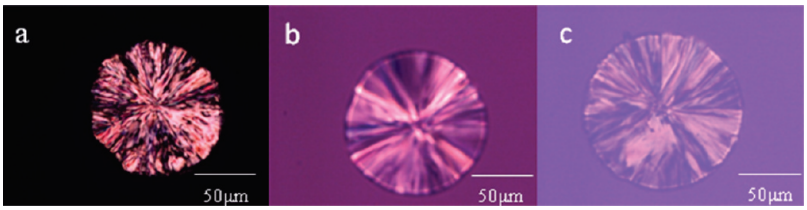

Figure 2. Representative polarizing optical microscopy images of the felodipine crystals formed in the (a) 3 wt % PVP K-12/felodipine, (b) 3 wt % K-29/32/felodipine, and (c) 3 wt % K-90/felodipine mixtures at 90 °C.

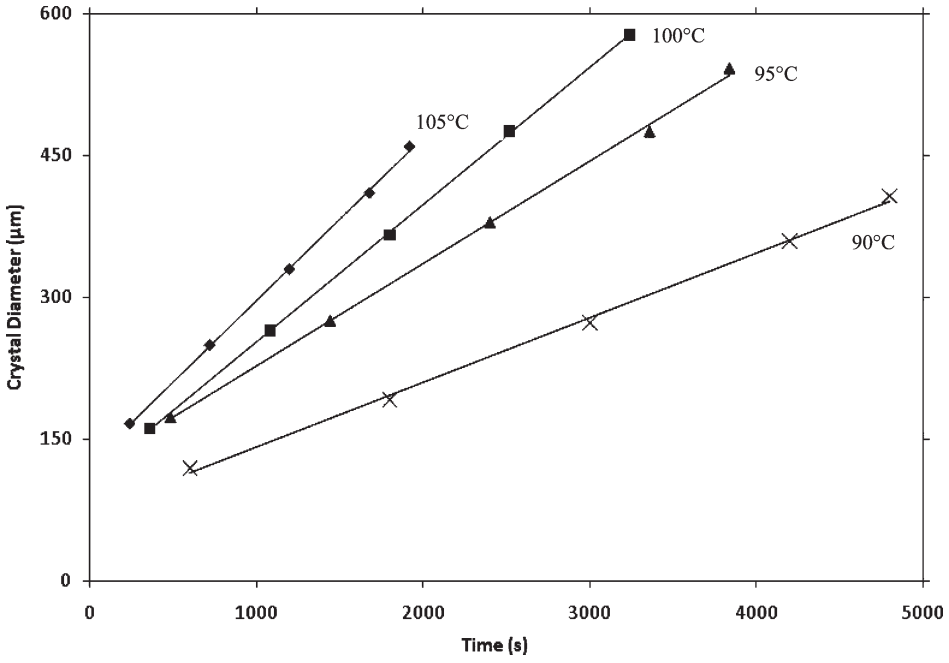

Figure 3. Diameters of the pure felodipine crystals measured as functions of time at four different temperatures. The data were fit to linear equations, and the slopes of the fit lines were taken as the rates of the crystal growth for the different temperatures.

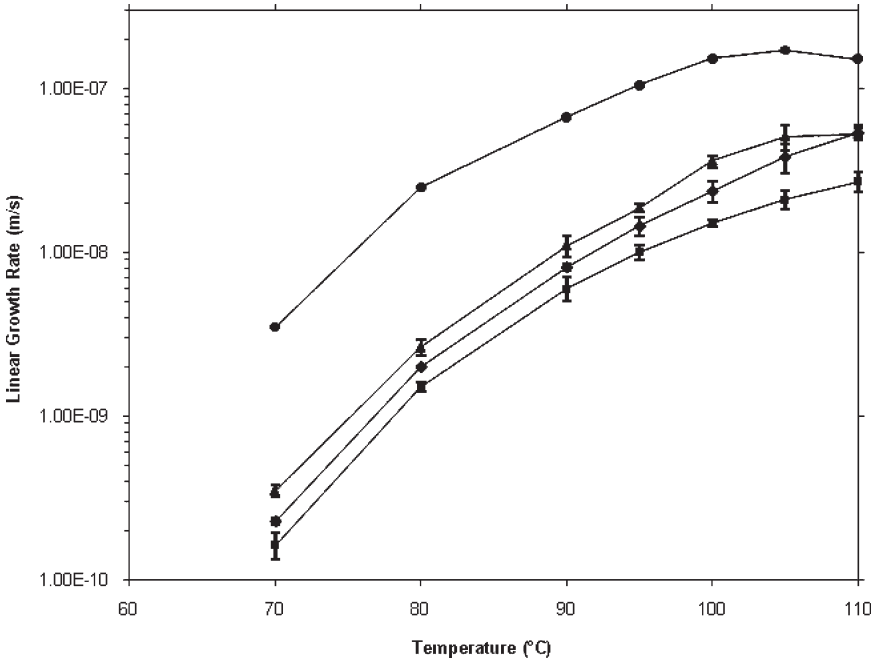

Figure 4. Linear growth rates of the felodipine crystals grown in (●) a pure felodipine melt, (▲) a 3 wt % PVP K-12/felodipine mixture, (◆) a 3 wt % PVP K-29/32/felodipine mixture, and (■) a 3 wt % PVP K-90/felodipine mixture under various temperature conditions.

appears to be smaller at high temperatures. For instance, at 110 °C the addition of 3 wt % PVP K-12 or PVP K-29/32 caused a decrease in the growth rate of the felodipine crystal by a factor of 3, whereas at 70 °C the same concentration

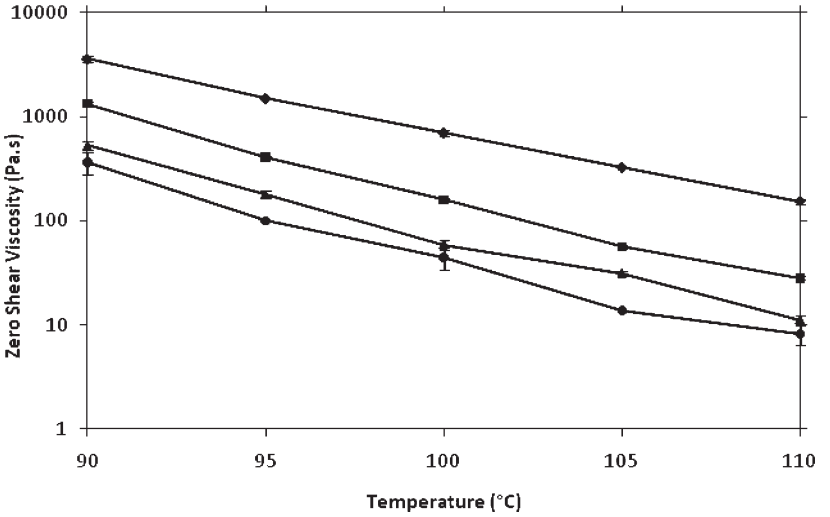

Figure 5. Zero-shear (or near zero-shear) viscosities of (●) pure felodipine, (▲) a 3 wt % PVP K-12/felodipine mixture, (■) a 3 wt % PVP K-29/32/felodipine mixture, and (◆) a 3 wt % PVP K-90/felodipine mixture, all in the supercooled amorphous state, under various temperature conditions.

caused a 11-times (in the PVP K-12 case) or 15-times (in the PVP K-29/32 case) reduction in the crystal growth rate. Also, as can be seen from the figure, the effect of PVP was in general molecular weight dependent. The highest molecular weight PVP (PVP K-90) was found to be most effective in suppressing the crystallization of amorphous felodipine at a given PVP concentration. For example, at 110 °C, the crystal growth rate was 6-fold reduced by the addition of 3 wt % PVP K-90, and at 70 °C, the rate reduction was 21-fold.

One might question whether the observed PVP molecular weight dependence of the felodipine crystallization kinetics is due to the dependence of the hydrogen bond interaction between felodipine and PVP on the PVP molecular weight. In order to examine this point, we conducted IR spectroscopy measurements on the PVP K-12/felodipine, PVP K-29/32/felodipine, and PVP K-90/felodipine dispersions, all containing the same amount of PVP (i.e., 20% by weight), at 25 °C. The NH group on the felodipine molecule is a hydrogen bond donor, and the peak position is sensitive to the strength of the hydrogen bond formed.[22] Therefore, the NH peak can be used as an indicator to detect the formation of a hydrogen bond between the drug and the polymer. In the case of pure amorphous felodipine, the NH group can hydrogen-bond with the carbonyl group present in other felodipine molecules, resulting in a NH stretching peak at 3341 cm^{-1} (Figure S3, Supporting Information). In the presence of PVP this peak undergoes a shift to a lower wavenumber (3337 cm^{-1}) along with a broadening of the peak shape at 20 wt % PVP. These changes indicate stronger and/or more numerous interactions between the drug and polymer molecules than between the same two drug molecules. However, as shown also in the figure, the extent of the NH peak shift and broadening showed no dependence on the molecular weight of the polymer, indicating that the felodipine−PVP interaction does not depend on the molecular weight of PVP in the range of PVP molecular weights studied.

In order to evaluate the impact of the polymers on the dynamic properties of the polymer−drug dispersions, which, in turn, is expected to influence the kinetics of the felodipine crystallization, the zero-shear (or near zero-shear) viscosities of the 3 wt % PVP K-12/felodipine, PVP K-29/32/felodipine, and PVP K-90/felodipine dispersions in the supercooled liquid region were measured as a function of temperature in a temperature range of 110−90 °C. In this range of temperature, the absence of the crystallites in the sample during the time scale of the viscosity measurement was confirmed by optical inspection. Under these temperature conditions, the nucleation process typically takes approximately 4 h,[21] and the viscosity measurements were normally completed within 20 min after the temperature has been adjusted to a measurement temperature; therefore, the Krieger-Dougherty-type contribution of the crystallized particles to the bulk viscosity is expected to be negligible.[23] At lower temperatures (i.e., < 90 °C), the same experimental protocol resulted in non-negligible levels of crystallization during the time period of the viscosity measurement; thus, the data are not included in the figure. All measurements were conducted in the low-shear limit (i.e., at a shear rate of 1 s^{-1}); at this shear condition, the 3% PVP K-12/felodipine was confirmed to be Newtonian, whereas the shear viscosity (η) of the 3% PVP K-29/32 and the 3% PVP K-90/felodipine dispersions showed a slight dependence on the shear rate ($\dot{\gamma}$) with a scaling exponent of $\alpha = 0.28$ (i.e., $\eta \sim \dot{\gamma}^{\alpha}$) for the PVP K-90 system. The resultant zero-shear viscosity data under the various temperature and PVP molecular weight conditions are presented in Figure 5. As shown in the figure, the (zero-shear) viscosities of the amorphous PVP/felodipine mixtures are strongly dependent upon the molecular weight of the PVP additive; at the given polymer concentration (i.e., 3 wt %), PVP K-12 caused only a slight change in the viscosity relative to that of pure felodipine, while the next higher molecular weight polymer, K-29/32, increased the viscosity by a factor of 3−4, and the K-90 polymer by 10−20-fold. The observed increasing trend of the viscosity with polymer molecular weight is well understood within the conventional picture of polymer solution dynamics; due to the coil-like nature of the polymer chains, at a given mass concentration, the (pervasive) volume under the dynamic influence of the chains is an increasing function of polymer molecular weight, and the effect of the molecular weight is expected to be strong because of the favorable interaction between the polymer and drug molecules which causes the chains to swell beyond their Gaussian size.[24]

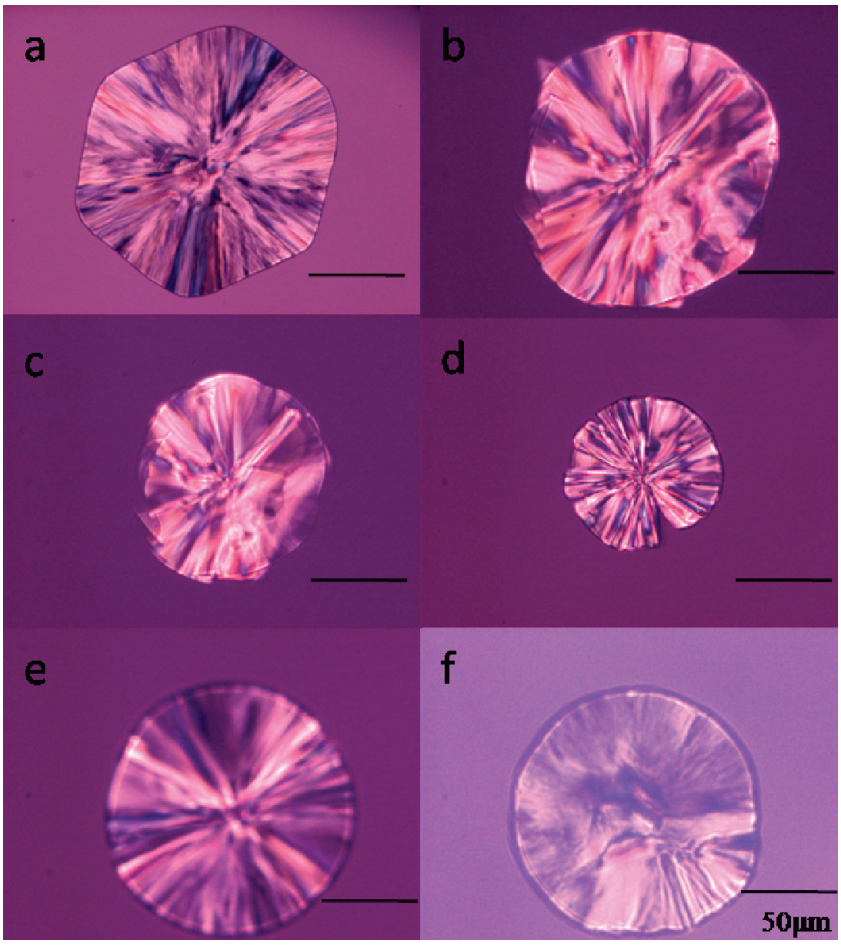

Figure 6. Representative polarizing images of the felodipine crystals grown at 80 °C in the presence of added PVP K-29/32 at various PVP concentrations, that is, at (a) 0, (b) 0.5, (c) 0.75, (d) 1.5, (e) 3 and (f) 4.5 wt %. Scale bars represent 50 μm.

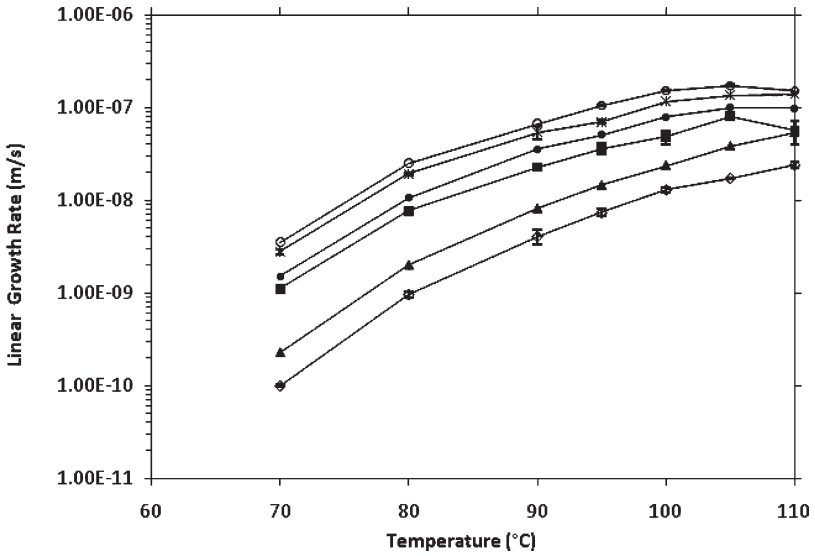

Figure 7. Linear growth rates of the felodipine crystals grown in PVP K-29/32/felodipine mixtures under various concentrations of the PVP polymer (i.e., (○) zero, (x with vertical line through it) 0.5, (●) 0.75, (■) 1.5, (▲) 3.0, and (◊) 4.5 wt %) as functions of temperature.

Effect of PVP Concentration on the Rate of the Crystal Growth. Figure 6 presents representative polarizing optical microscopy images of the felodipine crystals grown at 80 °C in the presence of added PVP K-29/32 at various PVP concentrations (i.e., at zero, 0.5, 0.75, 1.5, 3.0, and 4.5 wt %). At other temperatures (e.g., 70 and 90−110 °C), the macroscopic morphological features of the felodipine crystals grown under the same set of conditions (images not shown) were not any different from those shown in Figure 6; a felodipine crystal grows into a two-dimensional spherulitic

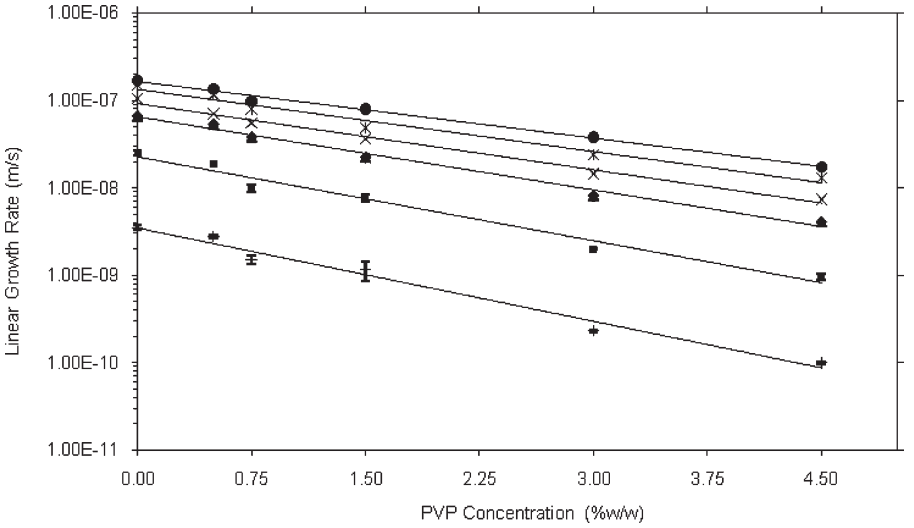

Figure 8. Linear growth rates of the felodipine crystals grown in PVP K-29/32/felodipine mixtures under various temperature conditions (i.e., (●) 105, (x with vertical line through it) 100, (×) 95, (◆) 90, (■) 80, and (+) 70 °C) as functions of PVP concentration. The straight lines represent linear regressions to the data.

(i.e., disk-like) structure having a smooth and distinct interface with the surrounding melt.

In order to determine whether the unit cell lattice structure of the felodipine crystal is influenced by the existence/concentration of PVP, X-ray diffraction measurements were conducted on the crystals formed at 110 °C in samples of pure felodipine and 0.5 and 3 wt % PVP K-29/32/felodipine mixtures. The results are presented in Figure S4, Supporting Information. As shown in the figure, we detected no discernible difference between the diffraction patterns of the felodipine crystals grown under the three different PVP concentrations, which suggests that, regardless of the presence and concentration of PVP, the PVP polymer does not co-crystallize with felodipine, and the crystal domain is composed solely of felodipine.

The effect of PVP concentration on the growth rate of the felodipine crystal has been evaluated using PVP K-29/32/felodipine dispersions at various temperatures between 70 and 110 °C. As shown in Figure 7, the concentration of PVP has a significant impact on the crystallization kinetics of felodipine. At a given temperature, the crystallization process becomes more retarded with higher polymer concentration. Also it was observed that the concentration dependence of the inhibiting effect of PVP is increased monotonically as temperature is lowered. For instance, at 110 °C as the PVP K-29/32 concentration was increased from zero to 1.5 to 4.5 wt %, the crystal growth rate was reduced by factors of 2 and 6, respectively, relative to the no-PVP condition, whereas at 70 °C the same, 1.5 and 4.5 wt % concentrations of PVP K-29/32 caused inhibition of the crystallization by 3-fold and 35-fold, respectively. Interestingly, we found that at all the temperatures studied, the logarithm of the growth rate of the felodipine crystal shows a linear dependence on the concentration of added PVP (Figure 8). Further, it was also observed that the slope of the log−linear relationship between the crystal growth rate and the polymer concentration is a linearly increasing function of temperature (Figure 9). As displayed in Figures 8 and 9, we found that correlations between the crystal growth rate of felodipine and PVP concentration and between the growth rate and temperature are rather strong. A general empirical equation for predicting

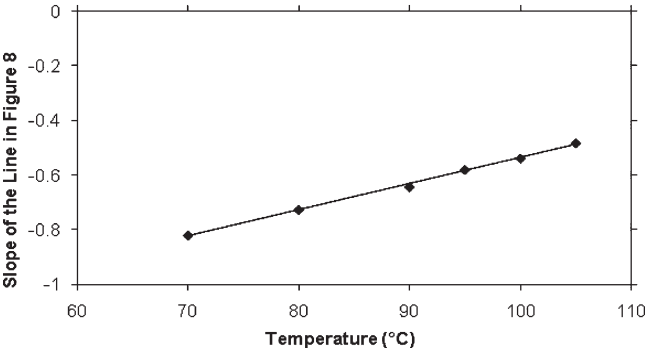

Figure 9. The slopes of the linear relationships for the change in the logarithm of the growth rate as a function of the PVP concentration (shown in Figure 8) at the various temperatures.

the growth rate (GR) of felodipine in the presence of PVP at any temperature T (°C) and concentration, x, of the polymer is given by

$$\ln(\mathrm{GR})_{(T,x)} = \ln(\mathrm{GR}_0)_T + (aT + b)x \qquad (1)$$

where GR_0 represents the growth rate of felodipine in the absence of any polymer, and a and b are constants where $aT + b$ represents the equation of the line shown in Figure 9 with values of $a = 0.0096$ and $b = -1.494$ for the PVP−felodipine system. These results suggest that the crystal growth rate of the drug at a given amount of polymer additive might be reasonably estimated for conditions more representative of actual pharmaceutical processes, for example, spray drying, by using data measured at more experimentally convenient conditions (i.e., at high temperatures at which the growth rates are faster, and thus the measurements can be conducted more rapidly). However, one needs to be careful when attempting to infer the crystallization behavior of a drug at temperatures below or close to the T_g of the drug from data obtained at $T \gg T_g$, because the crystallization kinetics are known to become drastically different near or below the T_g of the material.[25,26] Similarly, the temperature extrapolation cannot exceed the temperature of maximum growth.

Discussion

In an effort to obtain an understanding of the experimental observations, theoretical considerations have been investigated as follows. The rate of growth of a crystal face is expected to be proportional to the product of the inverse of the viscosity of the medium, and the Boltzmann factor representing the probability that the crystallization process overcomes the activation barrier for two-dimensional nucleation:

$$v = \frac{k}{\eta}\exp\left(-\frac{\Delta G^*}{k_B T}\right) \quad (2)$$

Here, v is the crystal growth rate (in units of length/time), k is a constant, η is the viscosity of the melt from which the crystal is formed, ΔG^* is the free energy barrier to nucleation of a new crystal monolayer, k_B is the Boltzmann constant, and T denotes the temperature.[27] For crystallization of small, nonpolymeric molecules (such as felodipine), it is not difficult to show that the activation free energy can be estimated (approximately) by

$$\Delta G^* = -\frac{\pi b \gamma^2}{\Delta G_v} \quad (3)$$

where b is the size of the crystallizing molecule, γ is the free energy per area of the interface between the crystal phase and the melt medium, and ΔG_v is the free energy change of crystallization per unit volume of a crystal of infinite size, which is a negative quantity. At the crystal's equilibrium melting temperature (T_m), the thermodynamic driving force for crystallization is infinitesimal, that is, ΔG_v ($= \Delta H_v - T_m \Delta S_v$) $= 0$, which gives $\Delta S_v = \Delta H_v / T_m$; note ΔH_v and ΔS_v are, respectively, the enthalpy and entropy of crystallization. Therefore, for a given degree of supercooling, ΔT ($\equiv T_m - T$), the bulk crystallization free energy can be written as

$$\Delta G_v = -\frac{\Delta H_v \Delta T}{T_m} \quad (4)$$

Combining all the above equations, we obtained

$$v = \frac{k}{\eta}\exp\left(\frac{\pi b \gamma^2 T_m}{k_B T \Delta H_v \Delta T}\right) \quad (5)$$

Within this theory, it is now visible that, for instance, a decrease of crystallization temperature will have competing effects on the overall rate of crystal growth; as T is lowered below T_m, the mobility of the crystallizing molecules will be reduced (i.e., η will be increased), which will tend to reduce v; on the other hand, with decreasing T, the thermodynamic driving force for crystallization ($\sim\Delta T$) will be increased, and consequently the secondary nucleation sites on the crystal surface will be more readily and frequently formed, which will contribute toward an increase in v. As shown in Figure 7, in the felodipine/PVP mixtures, the overall rate of crystal growth decreases with higher supercooling over the temperature range probed (T = 70−110 °C; ΔT = 71.4−31.4 °C), indicating that in this supercooling region, the transport term is dominant over the thermodynamic term, and the crystal growth is a diffusion-limited process; these results are consistent with the behavior reported previously for crystalline polymers and small organic molecules under high supercooling conditions.[28,29]

To better understand the inhibitory effect of PVP on the crystallization kinetics in the context of eq 5, the data for felodipine and PVP K-12/felodipine dispersions, shown in Figure 4, have been rescaled with respect to viscosity (Figure 10). Because the PVP K-90 and PVP K-29-32/felodipine dispersions showed non-Newtonian behavior (Figure S1, Supporting Information), data for these systems have been omitted. It can be seen that the slope of the fit is significantly lower for the PVP/felodipine dispersion than it is for the pure felodipine system, which suggests that the thermodynamic driving force increases with addition of PVP; the slope is proportional to the quantity $\gamma^2/\Delta H_v$ (see eq 5). If this holds true, then addition of PVP should increase the viscosity-corrected growth rate of felodipine. However, Figure 10 shows the opposite effect. This observation, therefore, suggests that viscosity cannot be used as a precise measure of the mobility of the felodipine molecules.

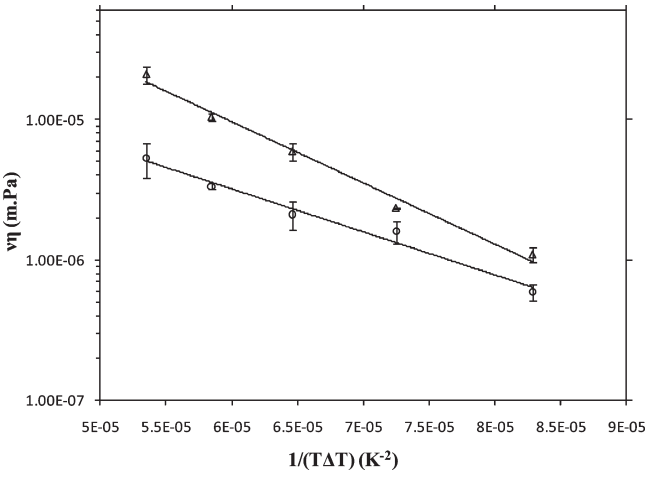

Figure 10. LN ($\nu\eta$) vs $1/(T\Delta T)$ for pure felodipine (Δ) and a 3 wt % PVP K-12/felodipine dispersion (○). The straight lines represent linear regression to the data.

It is of interest to evaluate if the observed decrease in crystal growth can be explained by a reduced thermodynamic driving force for crystallization. The presence of a miscible additive would be expected to decrease the thermodynamic driving force for crystallization by reducing the chemical potential of the crystallizable component in the liquid phase.[30] A reduced chemical potential would render ΔH_v (and therefore ΔG_v) to be less negative, and evidence of this phenomenon would likely be manifested as a depression in the melting temperature of the crystalline component in the presence of the polymer. As summarized in Table 1 and also as has been reported in a previous publication,[30] no such trend has been observed; instead, the melting temperature of felodipine was found to be unaffected by the presence of 3 wt % PVP. This thus would leave the effect of the polymer on the interfacial free energy of the crystal−melt interface (γ) as the remaining thermodynamic cause of the polymer inhibitory effect. However, the adsorption of the polymer to the surface of the crystal does not fit within this picture, because such behavior would lead to the opposite effect (i.e., γ would be decreased rather than increased).[31] On the basis of this analysis, it is unlikely that the observed effect of PVP on the crystal growth rate can be ascribed to the polymer having a substantial influence on the thermodynamic driving force, suggesting that the effect is perhaps of purely kinetic origin.

As shown in Figure 4, the crystal growth rate is impacted by the molecular weight of the PVP additive; the higher the polymer molecular weight is, the greater the suppression of the crystal growth. Interestingly, the impact of polymer MW

on the crystal growth rate is not nearly as large as the impact of simply adding the polymer. In other words, the incremental gain in the inhibitory effect of the polymer by increasing the molecular weight of the polymer is small. However, this trend is opposite to the observed changes in viscosity (Figure 5). Addition of PVP K-12 resulted in only a small increase in viscosity relative to the viscosity of pure felodipine compared to the 10−20 fold increase observed for PVP K-90. Therefore, there is no simple correlation between the increasing extent of inhibition with polymer MW and the magnitude of the corresponding viscosity change, again suggesting that viscosity is of limited value as a measure of the mobility of felodipine molecules. We also found that the hydrogen bonding interaction between felodipine and PVP is independent of the PVP molecular weight (Figure S3, Supporting Information), and thus differences in intermolecular interactions cannot explain the observed molecular weight effect.

It is also of interest to compare the trend in the effect of polymer MW on the crystal growth rate observed in this study with the literature. The effects of polymer molecular weight on the crystallization of the polymer itself and also on the crystallization of a second component that coexists in a polymer-containing system have been the subject of research by several groups of investigators.[11,18,32−35] In one-component polymeric systems, increasing the molecular weight of the polymer decreases the apparent tendency for the system to crystallize.[32,33] In small molecule−polymer mixtures however, the molecular weight of the added polymer (such as the PVP polymer used in our study) has been observed to have differing effects on the crystallization behavior of the other component. Several studies have shown that with increased molecular weight of the polymer additive, the crystallization tendency of the small molecule from the amorphous matrix decreases.[11,34,35] On the other hand, it has also been shown that, although a polymer such as PVP can effectively inhibit the crystallization of indomethacin, the molecular weight dependence of the inhibiting effect of the polymer was rather negligible.[18] We suspect one possible explanation for this varying behavior is that the molecular weight dependence of the polymer's crystallization-inhibition capability asymptotically disappears in the large molecular weight limit. Our results appear to hint at this possibility. For example, at 70 °C and a PVP concentration of 3 wt %, PVP K-29/32 ($M_w = 4-5 \times 10^4$ g/mol) is about 1.55 times more effective in slowing down the process of felodipine crystallization than PVP K-12 ($M_w = 2-3 \times 10^3$ g/mol), whereas the inhibiting effect of the highest molecular weight polymer, PVP K-90 ($M_w = 1-1.5 \times 10^6$), is only a factor of 1.4 different from that of the next highest molecular weight polymer, PVP K-29/32.

Concerning how/why polymer additives retard the kinetics of crystallization of a supercooled melt of a drug compound, it has been proposed that certain polymers can suppress the crystallization of a drug through antiplasticization of the system (i.e., by increasing the glass transition temperature and thereby reducing the mobility (assuming that mobility $\sim 1/\eta$) of the drug.[9,36] Other studies, however, have shown that a polymer can stabilize a drug melt even when the polymer does not affect the glass transition temperature of the drug or when addition of the polymer leads to a lowering of the glass transition temperature.[11,14,18] Our DSC results indicate that, in the PVP/felodipine samples studied in this work, the glass transition behavior of the system is largely unaffected by the presence and concentration of the PVP additives (Table 1), which suggests that the antiplasticization effect is not the cause of the crystallization-inhibiting effect. We speculate that the (main) cause of the decrease in the felodipine mobility with added PVP results from the formation of hydrogen bonding interactions between the two species. It has been suggested that this could result in coupling between the motions of the polymer and the drug molecules;[10] PVP is miscible with felodipine, and forms hydrogen bonds with felodipine over the entire range of PVP concentration and temperature up to the melting temperature of felodipine.[14,37] Furthermore, it has been shown that the extent of hydrogen bonding increases with increasing concentration.[14] The known dependence of hydrogen bonding strength on temperature[38−41] would also provide a potential explanation for the observation that the polymers are less effective growth rate inhibitors at higher temperatures (Figure 4). Indeed, for this particular system (PVP-felodipine), the hydrogen bonding strength has been shown to decrease with an increase in temperature.[37]

It is also worthy of note that at all conditions studied, the crystal size was found to grow linearly with time; that is, the growth rate is independent of time. This constancy of the crystallization rate indicates that over the measurement time scale (0−60 h), the growing crystal surface experiences a constant environment. This result may appear surprising, because it is not unreasonable to expect the polymer molecules to gradually accumulate at the crystal surface with the progress of the crystallization process, given that the diffusivity of the polymer is expected to be much smaller than the crystallization speed (as will be discussed in further detail below). Also, it is known in the literature that in a mixture of crystalline and noncrystalline polymers, the crystallization of the crystallizable component causes expulsion of a considerable fraction of the amorphous polymers from the crystalline phase.[42] Therefore, it is a compelling question; how a felodipine/PVP dispersion is able to maintain a constant composition near the growing crystal front throughout the growth process? To answer this question, we have conducted a theoretical analysis of the mass transfer process that is expected to take place, as explained below. The time-dependent concentration profile of the PVP molecules, $c(r,t)$, can be determined by solving the Fick's second law equation for nonsteady-state diffusion of the polymer in the crystallizing drug medium, that is,

$$\frac{\partial c(r,t)}{\partial t} = D_m \nabla c(r,t) \tag{6}$$

where D_m is the mutual diffusivity of the felodipine/PVP mixture. Using the similarity variable technique, Frank has shown that in cylindrical coordinates, the solution of this diffusion equation under the initial and boundary conditions, $c(r,0) = c_\infty$, and $c(\infty,t) = c_\infty$, is of the form[43]

$$c(r,t) = -\frac{1}{2}A(t)E_1\left(-\frac{r^2}{4D_m t}\right) + c_\infty \tag{7}$$

where $A(t)$ is a time-dependent constant characteristic of the boundary condition at the crystal surface, and $E_1(x)$ denotes the exponential integral function defined as

$$E_1(x) = \int_x^\infty \frac{e^{-t}}{t}\,dt \tag{8}$$

Using the mass conservation constraint

$$\int_{R(t)}^\infty 2\pi r[c(r,t) - c_\infty]\,dr = \varepsilon\pi R(t)^2 c_\infty \tag{9}$$

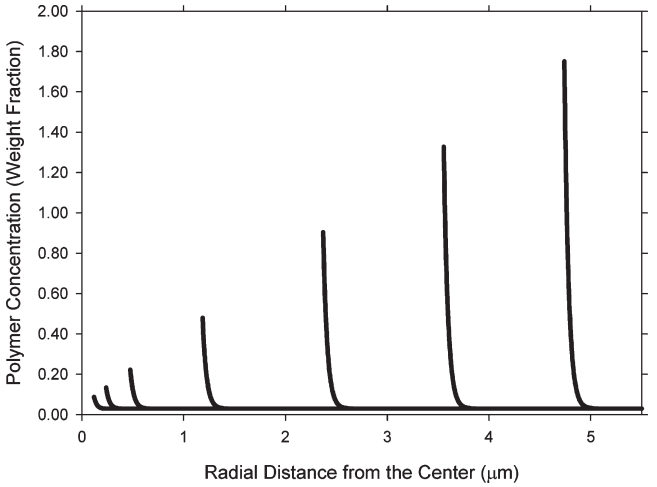

Figure 11. Predicted polymer concentration profiles at various time points (t = 5, 10, 20, 50, 100, 150, and 200 s). The parameter values used are c = 0.03 (weight fraction of PVP K-29/32 in the melt bulk); T = 100 °C; D_t (tracer diffusivity of PVP K-29/32) = 4.976×10^{-16} m/s^2; v (crystal growth rate) = 2.37×10^{-8} m/s. The polymer molecules are assumed to be completely expelled from the crystallized region (ε = 1).

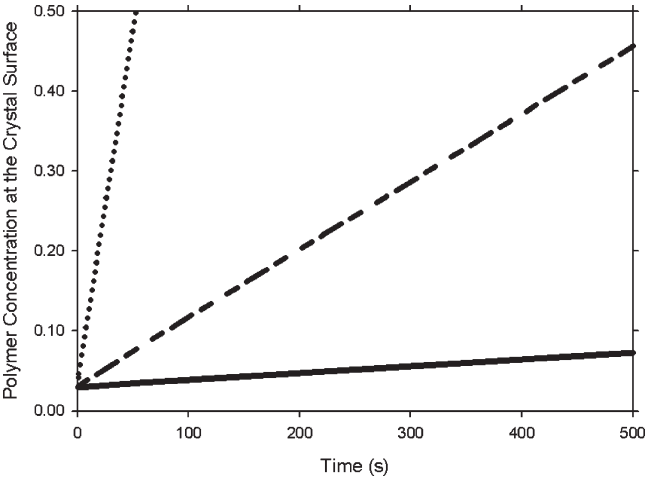

Figure 12. Model predictions of the concentrations (weight fractions) of the PVP polymers accumulating at the surface of the felodipine crystal as functions of time for three different cases: ε = 1 (dotted line), ε = 0.1 (broken line), and ε = 0.01 (solid line), where ε denotes the fraction of the PVP molecules expelled from the crystallized domain of felodipine. Other parameter values used are c = 0.03 (weight fraction of PVP K-29/32 in the melt bulk); T = 100 °C; D_t (tracer diffusivity of PVP K-29/32) = 4.976×10^{-16} m/s^2; v (crystal growth rate) = 2.37×10^{-8} m/s.

where $R(t)$ is the position of the crystal surface ($R(t) = vt$), and ε is the fraction of the polymers that have been expelled from the crystalline phase, and assuming negligible volume change on crystallization, we have estimated $A(t)$ to be

$$A(t) = \frac{\varepsilon R(t)^2 c_\infty}{-\int_{R(t)}^{\infty} rE_1\left(-\frac{r^2}{4D_m t}\right) dr} \quad (10)$$

Note that in our experimental system, the rate of crystal growth (v) has been measured to be time-invariant, and thus $R(t)$ is a linear function of time. In evaluating the values of $c(r, t)$, we used an approximation that the mutual diffusivity (D_m) is equal to the tracer diffusivity of the polymer at infinite dilution (D_t). This equality becomes exact in the $c \rightarrow 0$ limit. If the polymers accumulate significantly at the crystal surface, this assumption becomes invalid. However, even in such a situation, the conclusion that can be drawn from this analysis will not be influenced by this limitation, as can be seen below. The D_t values of the polymer have been calculated using the Stokes−Einstein equation

$$D_t = \frac{k_B T}{6\pi\eta_s R_h} \quad (11)$$

where η_s is the viscosity of the solvent (pure felodipine), and R_h is the hydrodynamic radius of a PVP coil. According to Kirkwood and Riseman,[44] for a Gaussian chain, the hydrodynamic radius is related to the radius of gyration of the polymer (Rg) through the relation, $R_h = 0.665\, R_g$. Assuming, for simplicity, that the PVP polymers in felodipine are Gaussian chains, the R_g values can be estimated by the equation, $R_g = (C_n n l/6)^{1/2}$ where C_n is the molecular-weight-dependent characteristic ratio of the polymer, n is the number of the C−C bonds along the backbone of the chain, and l is the C−C bond length (= 1.5 Å). Assuming that the PVP polymers used are isotactic materials, the C_n values have been estimated using the simulation data available in the literature: C_n = 5 for PVP K-12 (DP_w (weight-average degree of polymerization) = 22), and C_n = 10 for PVP K-29/32 (DP_w = 360) and PVP K-90 (DP_w = 11260).[45] On the basis of all the above information, we have calculated the polymer distribution profiles, $c(r,t)$, under various T, c_∞, and DP_n conditions. Figure 11 displays sample results obtained for a felodipine/PVP K-29/32 mixture containing 3 wt % PVP (c_∞ = 0.03) at 100 °C assuming that the PVP molecules are completely expelled from the felodipine crystals (ε = 1). Note at this condition the crystal growth rate has been measured to be $v = 2.37 \times 10^{-8}$ m/s, whereas the tracer diffusivity of the polymer is estimated to be $D_t = 4.98 \times 10^{-16}$ m^2/s. Therefore, as shown in the figure, we expect a large accumulation of PVP molecules near the crystallization front, and the amount of surface-accumulated polymer will only increase over time, as the polymers are continually pushed out of the crystalline region. We tested whether releasing the assumption of complete expulsion of PVP from the felodipine crystals would lead to a more constant crystallization environment. As shown in Figure 12, even at ε = 0.01 (i.e., even when 99% of the polymers are incorporated into the crystalline phase), the concentration of PVP at the crystal surface, $c(R(t),t)$, remains to be considerably time-dependent. It should also be noted that an increase of the D_t value even by 2 orders of magnitude does not change the qualitative nature of the results, confirming that the use of D_t (instead of D_m) is an acceptable approximation for drawing a qualitative picture. Taken together, it seems reasonable to conclude that all the polymer chains are in fact encaged in the crystalline domain, thereby giving rise to a constant composition of materials at the crystallization front (i.e., $c(R(t),t) = c_\infty$) throughout the growth process. It should be recalled that the X-ray diffraction data show that the unit cell structure of the felodipine crystal is not influenced regardless of whether the crystal is formed in the presence or absence of PVP (Figure S4, Supporting Information). Therefore, we conclude that PVP does not co-crystallize with felodipine, but exists in separate domains within the crystalline phase without altering the felodipine crystal structure. It is an important question how, on the molecular level, the polymer molecules are distributed inside the crystalline matrix of felodipine, because such effects

will in turn determine, for instance, how fast the drug molecules dissolve in water from the crystalline state. This is a subject of our future research.

Conclusions

The rate of crystal growth in supercooled felodipine was found to be significantly influenced by temperature as well as the molecular weight and concentration of poly(vinyl pyrrolidone) (PVP) additives. The addition of PVP suppresses the crystallization of felodipine. This inhibiting effect of PVP decreases with increasing temperature, while it increases with increasing molecular weight or concentration of the polymer. The PVP segments form hydrogen bonds with the felodipine molecules. Detailed analysis of the data on the basis of a theoretical model of crystal growth favors the idea that the retardation of the crystal growth rate of felodipine under the influence of added PVP is due to reduced mobility of the felodipine molecules due to the formation of drug−polymer specific interactions; therefore, the effect of PVP is believed to be kinetic rather than thermodynamic. The X-ray data indicate that the PVP segments do not co-crystallize with felodipine. However, a diffusion model suggests that the PVP chains remain in the interior of the spherulite structure of crystallized felodipine without affecting the unit cell symmetry and dimensions of the felodipine crystal.

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Supporting Information Available: Shear rate dependence of viscosities for 3% PVP K-90/felodipine, 3% PVP K-29/32/felodipine, and 3% PVP K-12/felodipine mixtures measured at 100 °C (Figure S1). Raman spectra of the two different polymorphs of felodipine crystals, (form I) and (form II) (Figure S2). IR spectra of NH stretching region obtained from different 20 wt % PVP-felodipine mixtures and for pure felodipine alone at 25 °C all in the amorphous state (Figure S3). X-ray diffraction patterns from the crystals formed at 105 °C in samples of pure felodipine and 0.5 and 3 wt % PVP K-29/32/felodipine mixtures (Figure S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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