Physical Properties of Solid Molecular Dispersions of Indomethacin with Poly(vinylpyrrolidone) and Poly(vinylpyrrolidone-co-vinyl-acetate) in Relation to Indomethacin Crystallization

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Received April 30, 1999; accepted July 24, 1999

Purpose. To measure solid-state features of amorphous molecular dispersions of indomethacin and various molecular weight grades of poly(vinylpyrrolidone), PVP, and poly(vinylpyrrolidone-co-vinylacetate), PVP/VA, in relation to isothermal crystallization of indomethacin at 30°C.

Methods. The glass transition temperatures (Tg) of molecular dispersions were measured using differential scanning calorimetry (DSC). FT-IR spectroscopy was used to investigate possible differences in interactions between indomethacin and polymer in the various dispersions. The enthalpy relaxation of 5%w/w and 30%w/w polymer dispersions was determined following various aging times. Quantitative isothermal crystallization studies were carried out with pure indomethacin and 5%w/w polymers in drug as physical mixtures and molecular dispersions.

Results. All coprecipitated mixtures exhibited a single glass transition temperature. All polymers interacted with indomethacin in the solid state through hydrogen bonding and in the process eliminated the hydrogen bonding associated with the carboxylic acid dimers of indomethacin. Molecular mobility at 16.5°C below Tg was reduced relative to indomethacin alone, at the 5%w/w and 30%w/w polymer level. No crystallization of indomethacin at 30°C was observed in any of the 5%w/w polymer molecular dispersions over a period of 20 weeks. Indomethacin alone and in physical mixtures with various polymers completely crystallized to the γ form at this level within 2 weeks.

Conclusions. The major basis for crystal inhibition of indomethacin at 30°C at the 5%w/w polymer level in molecular dispersions is not related to polymer molecular weight and to the glass transition temperature, and is more likely related to the ability to hydrogen bond with indomethacin and to inhibit the formation of carboxylic acid dimers that are required for nucleation and growth to the γ crystal form of indomethacin.

KEY WORDS: indomethacin; molecular dispersion; polymer; crystallization; molecular mobility; glass transition.

INTRODUCTION

It is well recognized that crystalline drugs exhibiting very poor water solubility often have inadequate bioavailability when administered in solid dosage forms. Converting such a material to the high-energy amorphous state offers a strategy for improving dissolution rates and hence bioavailability (1,2). Such amorphous states, however, are metastable relative to the crystalline state and under certain conditions of temperature and relative humidity during storage and use they can spontaneously crystallize (3–5). From a pharmaceutical perspective, therefore, it is necessary to add excipients that might be able to retard any tendencies for such instability over meaningful timescales.

Co-lyophilization or co-precipitation of a drug with a second component having a higher glass transition temperature, Tg, to form a miscible molecular dispersion has been suggested as a way to meet this objective (6,7). The basic premise is that the molecular dispersion will have a Tg greater than that of the drug alone, and hence that the molecular mobility of the drug will be reduced, therefore reducing tendencies for crystallization. In particular, polymeric excipients with high Tg values would appear to provide the basis for accomplishing these objectives; and, indeed, there have been a number of reports of enhanced physical stability of amorphous drugs using polymers such as poly(vinylpyrrolidone), PVP (8,9).

In this laboratory we have carried out a series of studies using indomethacin and PVP90 as a model system. Having characterized the amorphous properties of indomethacin (5,10,11) and PVP90 (12,13) individually, we have examined the glass transition temperature, intermolecular hydrogen bonding and inhibition of crystallization of indomethacin as function of PVP90 concentration (14,15). We have shown significant inhibition of crystallization at low levels of PVP90, where the Tg values of the mixtures were very close to that of indomethacin alone due to nonidealities of mixing. Using FTIR spectroscopy we were able to observe significant hydrogen bonding between indomethacin and PVP90 and the elimination of FTIR spectral peaks associated with the dimerization of indomethacin (15). A possible relationship of such hydrogen bonding to crystallization inhibition by PVP was suggested (15).

Amorphous indomethacin presents an interesting challenge with regard to crystallization because it can form one of two polymorphs depending on the storage temperature relative to its Tg of 42°C; the more thermodynamically stable γ form crystallizes well below Tg and the less stable α form preferentially crystallizes above Tg (10). Whereas many amorphous systems tend to exhibit optimal conditions for nucleation and crystal growth above Tg, where molecular mobility is greater, the γ form of indomethacin exhibits an optimal rate of both nucleation and growth near its Tg of 42°C (16). Thus, it is this crystal form that must be inhibited during storage at or below Tg to maintain the amorphous form of indomethacin. In this study we have focused our attention on storage at 30°C because we are interested in the crystallization behavior of a drug like indomethacin when it is stored under room temperature conditions. It has been shown that storage of amorphous indomethacin at temperatures about 40–50°C below Tg, near refrigerator temperatures, can and does prevent crystallization over very long time periods (10). For most solid dosage forms, such as capsules or tablets, however, such low temperature storage is not practical, and room temperature storage is more desirable. We also have focused our attention on using low levels of polymer so that we can produce the smallest total weight (small

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0724-8741/99/1100-1722$16.00/0

capsule or tablet size) needed to provide the necessary dose of drug, while still maintaining long term stability.

MATERIALS AND METHODS

Materials

Indomethacin 1-(p-chlorobenzoyl)-5-methoxy-2-methlyl-indole-3-acetic acid, was obtained in its γ crystal form from Sigma Chemical Co. Poly(vinylpyrrolidone) (PVPK90, K30, 17PF, 12PF) and Poly(vinylpyrrolidone-co-vinylacetate) (PVP/VA64) were obtained from the BASF corporation. The weight-average molecular weight of each PVP was reported by the supplier to be 1,000,000 ~ 1,500,000, 44,000 ~ 54,000, 7,000 ~ 11,000 and 2,000 ~ 3,000 respectively (17). PVP/VA64 is a random copolymer containing vinyl pyrrolidone and vinyl acetate at a molar ratio of 60:40 with a reported molecular weight range of 45,000 ~ 70,000 (17). PVP and PVP/VA were dried at 105°C for 12 hours under vacuum before use.

Methods

Preparation of Molecular Dispersions

Molecular dispersions were prepared using a solvent evaporation technique, wherein 2 g of the appropriate ratios of the two components were dissolved in 20 ml of anhydrous methanol at 65°C. The solvent was removed under vacuum at 50°C using a rotary evaporator. Any residual solvent was removed by drying under vacuum at room temperature for 24 hours. Amorphous indomethacin was prepared by quench-cooling of the melt of the γ crystal form. The melt was held at 165°C for 5 min and then quench-cooled by immersion into liquid nitrogen (5). The samples were ground gently in a mortar, passed through a 60 mesh sieve, and stored at −20°C over phosphorous pentoxide.

X-ray Powder Diffraction

A scanning X-ray powder diffractometer (PadV, Scintag Inc., Santa Clara, CA) controlled by a computer (Model #B10610, Tektronix Inc., Wilsonville, OR) was used to quantify the presence of any crystalline indomethacin in the various samples. The radiation used was generated by a copper Kα filter, with a wavelength of 1.5418Å at 35 kV and 40 mA. Samples were scanned over a range of 2θ values from 5° to 50° at a scan rate of 2.5°/min.

Density Determination

The densities of the various samples used in this study were determined by helium pycnometry (Quantachrome Corp.) at ambient temperature. The densities of the PVP90, PVP30, PVP17, PVP12 and PVP/VA were determined to be 1.21, 1.20, 1.16, 1.17 and 1.18 gcm^{-3}, respectively. The density of amorphous indomethacin was previously determined to be 1.31 gcm^{-3} (10).

Differential Scanning Calorimetry

DSC measurements were performed using a Seiko SSC5200 DSC (Seiko Instruments, Horsham, PA) fitted with an automated liquid nitrogen cooling accessory. Samples (7–15 mg) were carefully weighed out into aluminum pans that allow removal of any residual water with a pinhole in the lid. Dry nitrogen was used as the purge gas and liquid nitrogen as the coolant. Unless otherwise noted, heating and cooling rates of 10°C/min were used. Temperatures and enthalpy values were calibrated with pure indium and gallium. Glass transition temperatures (Tg) were determined by first heating the samples to at least 20°C above Tg to erase the previous thermal history of the samples and then cooling them to 100°C below Tg at a cooling rate of 40°C/min. The samples were subsequently heated a second time to 220°C during which the onset Tg and the change in heat capacity at Tg (ΔCp) were determined. Enthalpy relaxation for pure amorphous indomethacin and the various molecular dispersions containing 5%w/w and 30%w/w polymers was determined by first heating the samples to at least 20°C above Tg and then cooling to 100°C below Tg to form a glass with a standardized thermal history. The samples were heated to 16.5°C below Tg and held isothermally from 0 to 16 hours. The samples were subsequently cooled to −40°C and then reheated through Tg to 220°C. The pronounced endothermic recovery peak reflecting enthalpy relaxation was analyzed. The area of the endotherm (ΔH) was determined by constructing a tangent to the curve in the region above Tg and extrapolating to lower temperatures as reported previously (18,19). The ΔH of pure indomethacin was corrected for dilution with polymer to allow comparison with that of the dispersions with polymer.

IR Spectroscopy

IR absorbance spectra were measured by the KBr disk method using a Mattson Galaxy 5020FTIR spectrometer equipped with a DTGS detector. 64 scans were collected for each sample at a resolution of 2 cm^{-1} over the wave number region 4000 ~ 400 cm^{-1}.

Isothermal Crystallization Studies

Mixtures of indomethacin containing 5%w/w of the various PVP samples and PVP/VA, as physical mixtures and molecular dispersions, and amorphous indomethacin itself were used to estimate the extent of any crystallization from the amorphous state. Samples (250 mg) were placed in sealed glass vials and stored in desiccators containing P_2O_5 at a constant temperature below Tg for up to 20 weeks. The presence of either α or γ crystals as a possible crystalline form was monitored by removing vials at appropriate time intervals, mixing with 20%w/w of LiF and measuring the X-ray peak height ratios. The ratios of peak height at 2θ = 8.5° for the α form and 11.6° for the γ form to that of LiF at 2θ = 38.7° were used for the determination of the crystalline indomethacin fraction based on calibration curves as previously reported (3,4,14).

RESULTS AND DISCUSSION

Glass Transition Temperatures

The onset Tg values and ΔCp values at Tg for indomethacin, PVP and PVP/VA used in this study are given in Table I, where it can be seen that the Tg values of PVP increase as the molecular weight of the sample increases, consistent with the expected molecular weight dependence of Tg (20). The Tg

Table I. Glass Transition Temperature, Tg, and Change in Heat Capacity at Tg, ΔCp, for Single Components Measured using DSC with a Heating Rate of 10°C/min

Material	Onset Tg (°C)	ΔCp(Tg) (J/g K)
indomethacin	42	0.55
PVP90	172	0.30
PVP30	156	0.26
PVP17	136	0.33
PVP12	99	0.34
PVP/VA	102	0.39

Note: The standard deviations in the measurement of Tg and ΔCp are within ± 1°C, 0.02 J/g, respectively.

value of PVP/VA is lower than that of PVP30, both having about the same molecular weight, and very similar to that of PVP12. Figure 1 shows plots of the onset Tg values versus the weight fraction of PVP and PVP/VA for the various dispersions. The amorphous nature of all samples was verified by X-ray powder diffraction analysis. A single Tg between the Tg values of the pure components is observed over the entire composition range, indicating a single miscible amorphous phase for all dispersions. At the lower concentration range of PVP and PVP/VA (5–30%w/w), the Tg values of all dispersions are not significantly different for a particular weight %w/w of polymer as given in Table II.

The extent to which these dispersions might exhibit deviations from ideal mixing was evaluated by comparison of the experimental Tg values with those predicted using Eq. 1.

$$Tg = \frac{w_1 Tg_1 + K w_2 Tg_2}{w_1 + K w_2} \quad (1)$$

where w_1 and w_2 are the weight-fractions of each component, and Tg_1 and Tg_2 are the corresponding Tg values of each component. Using free volume theory, the constant K can be estimated with a knowledge of the density (ρ_1, ρ_2) of both components using the Simha-Boyer rule (21). In this form equation 1 is the Gordon-Taylor equation (22), and

$$K \approx \frac{\rho_1 Tg_1}{\rho_2 Tg_2} \quad (2)$$

Using a thermodynamic model, equation (1) is known as the Couchman-Karasz equation, where K now is defined as in Eq. 3 (23).

$$K = \frac{\Delta Cp_2}{\Delta Cp_1} \quad (3)$$

where ΔCp is the change in heat capacity at Tg.

The lines in Fig. 1 show the values of Tg that would be predicted from Eq. 1 using both the free volume and thermodynamic models. As has been shown before (24), the two theoretical models generally produce small but, in some cases, significant differences in predicted values. In all of the molecular dispersions evaluated in this study the experimental values of Tg fall well within reasonable agreement with either predicted values, indicating fairly ideal mixing. However, in the case of PVP90, up to about 20%w/w PVP, there appears to be no significant change in Tg, a clear indication of non-ideal mixing in this range of concentration for the highest molecular weight form of PVP (10).

FTIR Studies

Figure 2 shows the IR spectra of the carbonyl region of the various dispersions at different polymer concentrations for only PVP90, PVP12 and PVP/VA, since the spectra for PVP17 and PVP30 were identical to other PVP samples. In this figure we focus on three major regions associated with: 1) the dimerization of the carboxylic acid groups of indomethacin at 1710 cm^{-1}; 2) the non-hydrogen bonded carbonyl group of PVP at 1680 cm^{-1} (and vinyl acetate in the case of PVP/VA at 1745 cm^{-1}; and 3) the hydrogen bonding between polymer and indomethacin at 1726 cm^{-1}, as described in great detail earlier (15). The patterns observed with PVP90 are in excellent agreement with our earlier study using this polymer and, as observed earlier also, no changes in spectra for indomethacin are observed when amorphous indomethacin and polymers are physically mixed, rather than being formed as coprecipitates (15).

Up to the 5%w/w polymer level, in all cases, we could detect no significant changes in spectra relative to that of pure amorphous indomethacin. However, above this composition the absorbance at 1710 cm^{-1}, assigned to the asymmetric stretch of the carboxylic acid in a dimer structure, significantly decreases in intensity until somewhere between 20%w/w and 30%w/w polymer it reaches a minimum value. At this point absorbance at 1726 cm^{-1}, attributed to the hydrogen bonding between the indomethacin carboxyl and the PVP carbonyl group (15), becomes significant. It is important to note that such changes are essentially the same for all PVP samples and PVP/VA. The PVP free carbonyl dominates the spectra as the concentration of polymer increases beyond 30%w/w, as does the vinyl acetate peak at 1745 cm^{-1} for PVP/VA.

Enthalpy Relaxation Studies

To gain some measure of the effects of low polymer concentration on the molecular mobility of indomethacin when formed as molecular dispersions, structural relaxation for the 5%w/w and 30%w/w polymer systems below Tg was assessed by comparison of the rates of enthalpy change required to approach a supercooled liquid from the glassy state (18,19,25). In previous studies with pure indomethacin, PVP90, and sucrose, this approach was used to estimate the relaxation time (τ) as a function of temperature below Tg (18). Recent studies with sucrose-polymer molecular dispersions showed effects of polymers on molecular mobility, relative to sucrose alone, but no effects in physical mixtures (19).

The dispersions containing 5%w/w polymer were selected for evaluation, since the Tg values were essentially the same for all polymers used and for pure amorphous indomethacin. The dispersions containing 30%w/w polymer were also selected to evaluate the effect of the polymer concentration on the molecular mobility of indomethacin, since hydrogen bonding associated with carboxylic acid dimers was completely eliminated at this polymer level as indicated above and because all systems exhibited a higher Tg than that of indomethacin alone. Samples stored for 16 hours at 16.5°C below Tg showed no crystallization, but did exhibit a distinctly increasing enthalpy relaxation with time, reflecting greater structural relaxation of the glass towards the equilibrium supercooled liquid state.

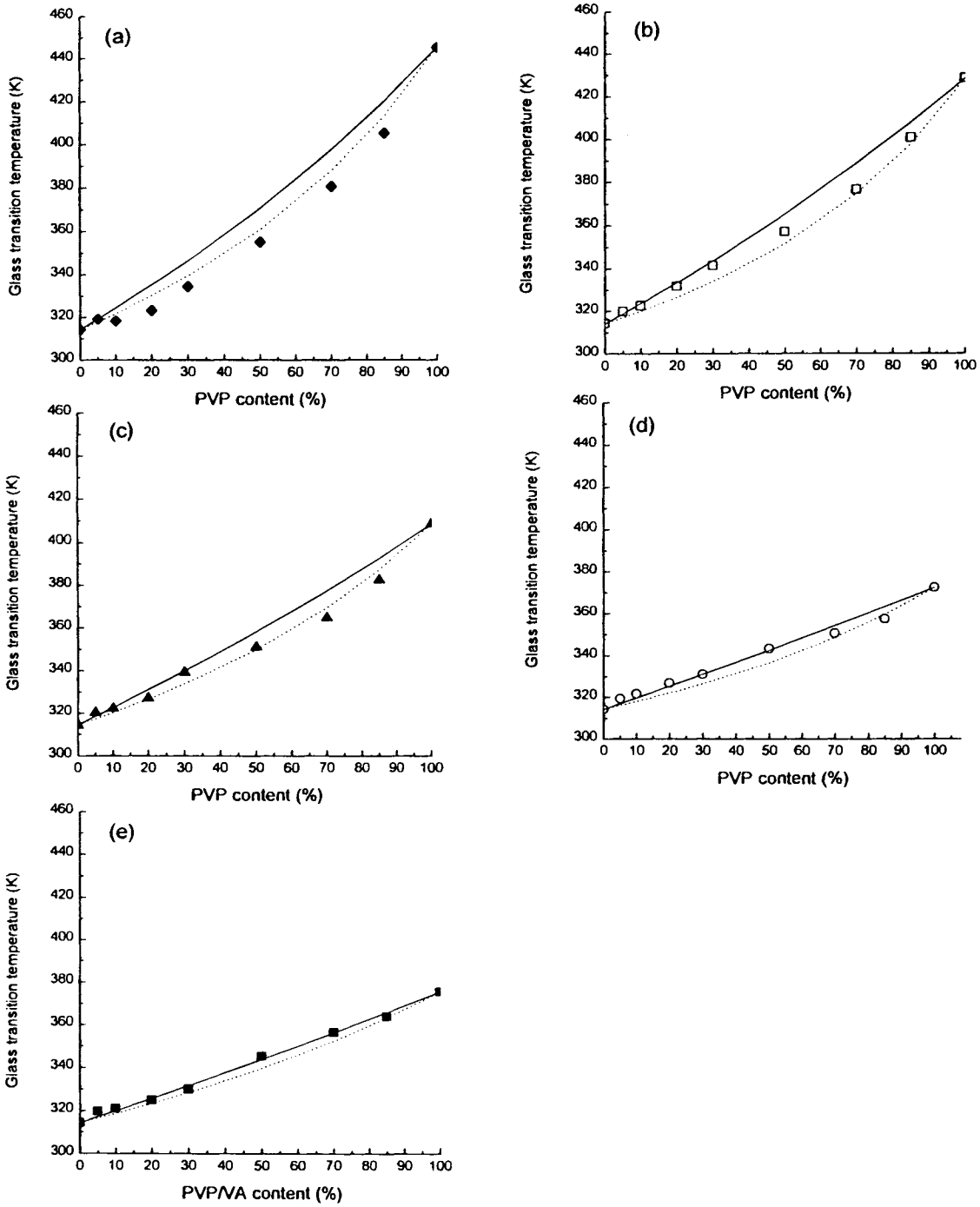

Fig. 1. Tg values of molecular dispersions of indomethacin with (a) PVP90, (b) PVP30, (c) PVP17, (d) PVP12, and (e) PVP/VA as a function of composition. The symbols represent the measured onset Tg values at a heating rate of 10°C min^{-1}. The solid lines represent the prediction of the Gordon-Taylor equation, and the dotted lines represent the prediction of the Couchman-Karasz equation. (eq.1, 2, 3 in text).

To compare the relative effects of the different molecular weights of PVP and of PVP/VA on the mobility of the dispersions, the extent of relaxation of the dispersions was calculated with respect to the total enthalpy change that was required for the glass to relax to a supercooled liquid. First the maximum enthalpy recovery for the dispersions (ΔH_∞) was calculated from the following Eq. 4 (26), where ΔH_∞ is assumed to be constant from the storage temperature to Tg.

$$\Delta H_\infty = (Tg - T) \cdot \Delta Cp \quad (4)$$

where Tg is the glass transition temperature, T is the experiment temperature, and ΔCp is the change in heat capacity at Tg. Equation 4 for estimating ΔH_∞ was validated using the 5%w/w dispersions and measuring ΔH after an extensive period of storage, i.e., 2,880 hours at 16.5°C below Tg. Values of ΔH after 2880 hours ranging from 7.2 to 7.4 J/g were obtained for

Table II. Glass Transition Temperature, Tg, for Molecular Dispersions of Indomethacin Containing 5%w/w and 30%w/w Polymers

Polymer	5%w/w dispersion(°C)	30%w/w dispersion(°C)
PVP90	47	61
PVP30	47	68
PVP17	46	66
PVP12	46	59
PVP/VA	46	57

Note: The Tg for pure indomethacin is 42°C.

all PVP and PVP/VA samples, while the ΔH_∞ values estimated from eq. 4 for these samples ranged from 7.1 to 7.6 J/g.

From this maximum enthalpy recovery a measure of the extent to which a material relaxes, $\varphi(t)$, under any given time (t) was calculated using equation 5 (25)

$$\varphi(t) = 1 - (\Delta H/\Delta H_\infty), \quad (5)$$

the greater value of $\varphi(t)$, the less the extent of relaxation.

To estimate the overall average relaxation time, τ, we use the KWW equation (18,25,28).

$$\varphi(t) = \exp(-(t/\tau)^\beta) \quad (6)$$

where τ is the mean relaxation constant and β is a relaxation time distribution parameter with an expected value of between 0 and 1. Typical relaxation processes in disordered systems are non-exponential, thus β generally is less than one. An iterative non-linear regression analysis procedure based on the Marquart-Levenberg algorithm was used to find the best fit to the data. The initial parameters provided were τ = 100s and β = 0.5 for all samples. Figure 3 shows the extent of relaxation of the dispersions containing 5%w/w and 30%w/w polymer, respectively, in terms of $\varphi(t)$ versus time. Here we may note that whereas indomethacin alone exhibits a value of $\varphi(t)$ after 16 hours of about 0.3, 5% and 30% polymer compositions produce significantly less change. In the case of the 5% samples, the value is in the range of 0.4 to 0.5; while at the 30% level, the changes with molecular weight of PVP, for example, range from 0.5 to 0.8. Thus, at least with the higher molecular weight PVP samples, at 30% polymer where Tg is higher, there is a significant reduction in the extent of relaxation (higher $\varphi(\tau)$) relative to lower molecular weight samples; much less differences are noted with the 5% samples where Tg values are relatively unchanged. Values of τ and β are listed in Table III where we can see that at the 5%w/w polymer level each sample produces roughly double the average relaxation time, τ, of indomethacin alone, with no significant differences in β, reflective of the distribution of relaxation times. However, there do not appear to be any systematic differences between the various molecular weight grades of PVP or PVP/VA. At the 30% w/w polymer level the values of τ appear to be consistently larger than those of the corresponding 5% polymer mixtures, while the β terms again, are relatively unchanged. Given the larger standard deviations for τ at the 30% level, it is difficult to determine whether τ values for the various polymer samples are significantly different.

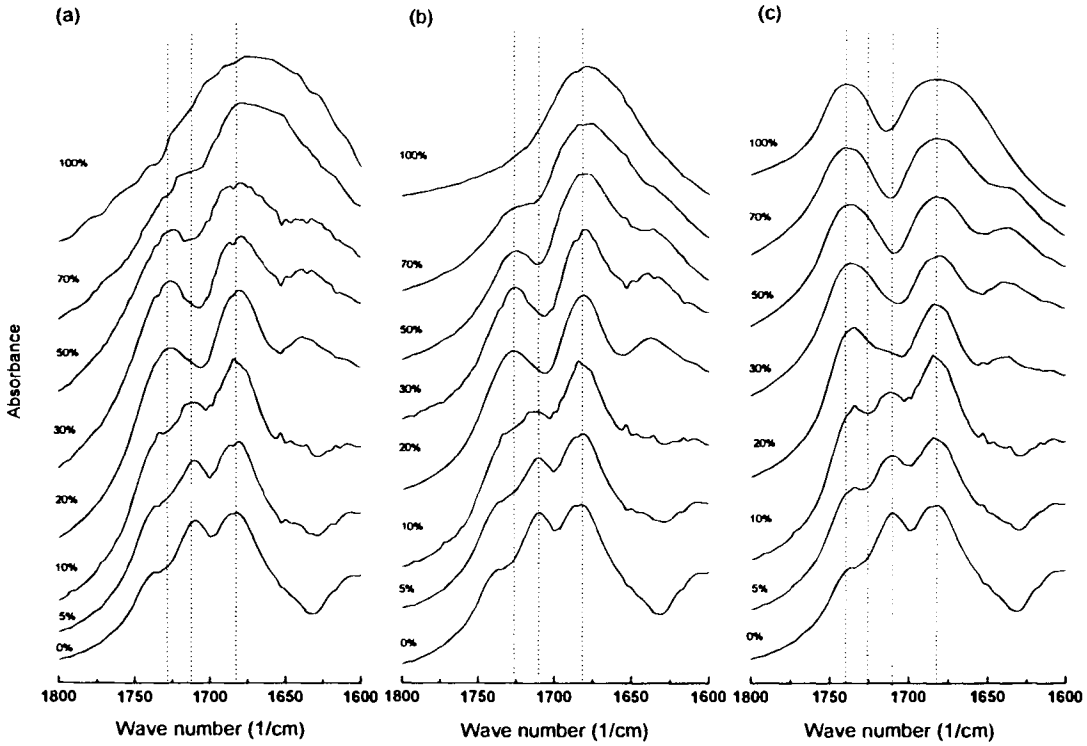

Fig. 2. IR spectra of the carbonyl stretching region of molecular dispersions of indomethacin with (a) PVP90, (b) PVP12, and (c) PVP/VA. The percentages refer to the amount of PVP90, PVP12, and PVP/VA, respectively. Vertical lines depict wave numbers monitored with different systems (see text)

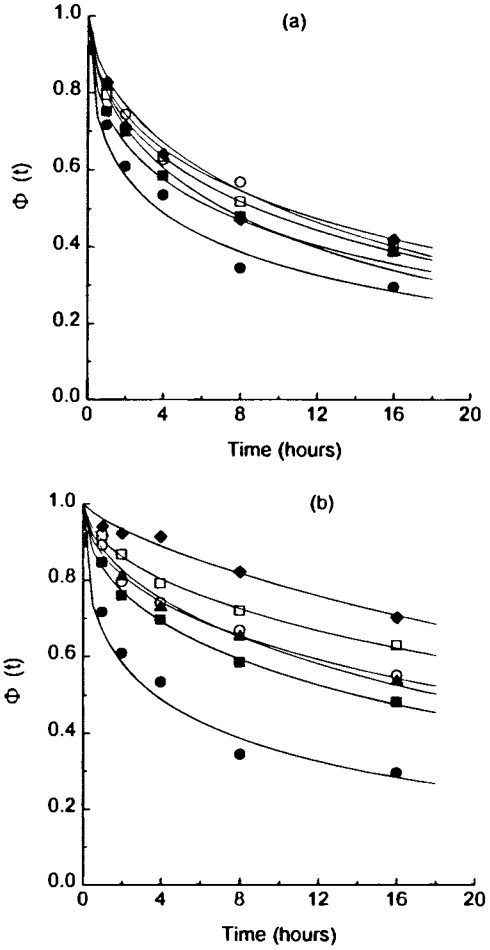

Fig. 3. Proportion of glass that has relaxed with aging time for molecular dispersions of indomethacin containing (a) 5%w/w polymers, (b) 30%w/w polymers. Key:(♦) PVP90; (□) PVP30; (▲) PVP17; (○) PVP12; (□) PVP/VA; (●) Indomethacin alone. The lines represent non linear fits to the Kohlrausch-Williams-Watta equation (eq. 6 in text).

Crystallization Studies

Previously, Yoshioka *et al.* reported that a molecular dispersion of 5%w/w PVP90 and indomethacin stored at 30°C exhibited no crystallization after 20 days of storage (14). In this study all samples evaluated for possible crystallization were stored for 20 weeks (140 days) at 30°C to allow more time for any crystallization. Such studies were carried out with pure amorphous indomethacin, the physical mixture and the molecular dispersion. Figure 4 shows the results for pure indomethacin and the 5%w/w PVP90 mixture, as representative of all results at the 5%w/w polymer level. Whereas pure indomethacin and the physical mixture are completely crystallized to the γ polymorphic form within 14 days, the molecular dispersion remains uncrystallized for the entire 20-week period. This is also true for the other 5%w/w molecular dispersions. Thus, over this time period all polymer samples at a 5%w/w level are equally effective inhibitors of crystallization.

Table III. The Parameters of the Kohlrausch-Williams-Watts Equation Calculated by Nonlinear Regression Analysis for Molecular Dispersions of Indomethacin Containing 5%w/w and 30%w/w Polymer

	5%w/w dispersion		30%w/w dispersion	
Polymer	τ (days)	β	τ (days)	β
PVP90	17.9 ± 4.3	0.52 ± 0.09	62.5 ± 21.0	0.78 ± 0.14
PVP30	18.8 ± 3.2	0.59 ± 0.06	60.6 ± 16.9	0.56 ± 0.07
PVP17	13.9 ± 2.2	0.55 ± 0.07	34.1 ± 7.1	0.59 ± 0.07
PVP12	21.3 ± 3.5	0.51 ± 0.06	41.5 ± 15.2	0.52 ± 0.10
PVP/VA	14.9 ± 3.3	0.45 ± 0.07	28.8 ± 10.0	0.52 ± 0.10

Note: The τ and β values for pure indomethacin are 9.1 ± 1.7 days, 0.48 ± 0.08, respectively.

CONCLUSIONS

From the results of the crystallization studies reported above, we can reach two fundamental conclusions. First, these studies reveal that molecular dispersions of PVP and PVP/VA, made with indomethacin by coprecipitation, are all capable of inhibiting crystallization at 30°C over a period of at least 20 weeks, at levels of polymer as low as 5%w/w, whereas indomethacin alone and in 5%w/w physical mixtures, exhibits complete crystallization within 14 days. A second important observation is that up to 20 weeks storage at 30°C there appear to be no differences in the ability of PVP, ranging in molecular weight from about 10^3 to 10^6 $gmole^{-1}$ and in Tg values from 99°C to 172°C, to inhibit crystallization at a 5%w/w polymer level. Also, there appears to be no difference when about 40% of the vinylpyrrolidone monomers are replaced by vinyl acetate groups, as in PVP/VA. Thus, a minimum number of monomer units available to the indomethacin molecule appears to be a critical factor, as opposed to some property more reflective of molecular size of the polymer chain, or as in the case of PVP/VA, any differences in the hydrogen bonding capability of the vinyl pyrrolidone versus vinyl acetate carbonyl groups (24).

Since the Tg values of all dispersions at the 5%w/w polymer level are essentially the same as that of indomethacin alone, any antiplasticizing effects of polymers at the 5% level, based directly on mobility associated with the glass transition temperature, would not appear to be significant. From the enthalpy

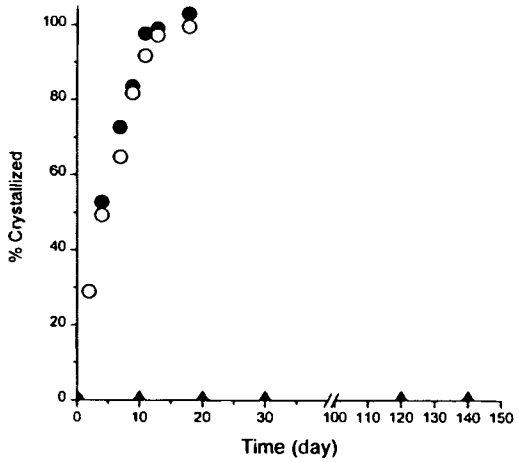

Fig. 4. Isothermal crystallization of amorphous indomethacin stored at 30°C as a function of time. Key(▲) Molecular dispersion containing 5%w/w PVP90; (○) Physical mixture with 5%w/w PVP90; (●) Indomethacin alone.

relaxation data in Table III, we can see that the 5%w/w polymer samples produce relaxation times, τ, at about 30°C (Tg − T = 16.5°C) that are somewhat longer than that for the pure indomethacin. However, we believe that they may not be long enough to totally account for the extensive increase in stability of indomethacin with this level of polymer.

The most compelling evidence for identifying possible factors giving rise to such efficient inhibition of crystallization would appear to come from the FTIR studies shown in Fig. 2. Here, with all polymer samples, we see a distinct loss of the peak associated with the carboxylic acid dimerization of amorphous indomethacin over the range of 5–30%w/w polymer, and the development of a new peak related to the formation of the polymer-indomethacin hydrogen bond (15). This ability to inhibit dimerization would seem to be important since such dimerization is required in the formation of the γ crystal nucleus, as shown from its crystal structure (29). It is interesting to note in this regard that the dimer peak is completely eliminated by all polymer samples, presumably due to indomethacin-polymer hydrogen bonding, in the range of 20–30%w/w, where we have shown previously that the molar ratio of indomethacin to monomer unit of the polymer is close to 1:1, or close to enough monomer units, if accessible, to interact with most of the indomethacin molecules present (15). Since changes in IR spectra at very low levels of polymer, $\leq$ 5% could not be detected in these systems, it will be important to probe these very dilute systems with more sensitive techniques to ascertain more definitely whether or not such hydrogen bonding at these low polymer levels actually is the critical factor in the inhibition of indomethacin crystallization.

ACKNOWLEDGMENTS

The authors wish to thank the sponsors of the Purdue/Wisconsin Joint Program on Molecular Mobility and Solid-State Properties for financial support of this project. We are grateful to Dr. James Dumesic of the Chemical Engineering Department, University of Madison-Wisconsin for access to the FTIR instrument. Takahiro Matsumoto expresses his appreciation to Daiichi Pharmaceutical Company for granting him a one-year leave of absence to pursue these studies.

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