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Inhibition of albendazole crystallization in poly(vinylpyrrolidone) solid molecular dispersions

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The main aim of the study was to investigate the mechanisms of the stabilizing effect of poly(vinylpyrrolidone) (PVP) on amorphous albendazole (ABZ). Solid dispersions of ABZ with PVP polymers and with a copolymer containing poly(vinylacetate) (PVP/VA) were prepared using the solvent casting method. The effects of PVP molecular weight, composition and content on the crystallization of ABZ from the amorphous state were investigated using differential scanning calorimetry. Stability of the amorphous drug with respect to isothermal crystallization was studied at different polymer concentrations and storage temperatures. Solid dispersions were found to be X-ray amorphous and exhibited a single glass transition temperature (T_g). Onset of crystallization and extent of inhibition increased with concentration and molecular weight of the homopolymer. In spite of its having a higher molecular weight, replacement of about 40% of vinylpyrrolidone monomers with vinylacetate groups (as in the copolymer) resulted in reduced inhibition of crystallization. ABZ crystallized from the amorphous state in the absence of polymer even when stored below the T_g. The solvent casting method greatly reduced the requirement for polymer to achieve X-ray amorphous solid dispersions. Such dispersions exhibited a significant increase in induction time and reduction in the rate of crystallization at polymer concentrations as low as 5% and at temperatures as high as 70 °C. Factors other than mobility, such as drug-polymer hydrogen bonding' were also found to be involved in crystallization inhibition.

1. Introduction

Solid dispersion is a popular pharmaceutical technology designed to improve the solubility and dissolution rate of poorly soluble drugs. The term refers to a dispersion of one or more active ingredients in an inert and hydrophilic carrier or matrix to give a microcrystalline dispersion, an amorphous precipitate, a molecular dispersion (solid solution) or a combination of different systems (Chiou and Riegelman 1971; Leuner and Dressman 2000). In many cases, the amorphous form of the drug may have increased bioavailability compared with the crystal form because of its higher water solubility. If the solid dispersion is an amorphous solid solution, not only is the drug particle size decreased to molecular level, but drug molecules will also be in a higher energy form (Sertsou et al. 2002). It is likely that there will be a decrease in the enthalpy required to separate the drug molecules from each other, or from the carrier molecules' compared with the energy required within a crystalline structure. The free energy of mixing or solution, may decrease as a result (Martin 1993) according to eq. (1):

$$\Delta G_m = \Delta H_m - T\,\Delta S_m \qquad (1)$$

in which G_m, H_m, and S_m represent free energy, enthalpy, and entropy, of mixing or solution, respectively, and Δ indicates the difference in these system parameters before and after dissolution. All other factors being equal, the more negative ΔG_m is, the more readily dissolution occurs.

Although the use of solid dispersions has been reported frequently in the literature, very few marketed products rely on the solid dispersion strategy. The main reason for this discrepancy is the physical instability (aging effects) of these structures, which are often metastable. Crystal growth or conversion from the amorphous (metastable) to the crystalline state during storage inevitably results in decreased solubility and dissolution rate (Mooter et al. 1999). It is therefore of crucial importance to identify and understand the factors influencing crystallization from the amorphous state. Poly(vinylpyrrolidone) (PVP) has been found to have incredible inhibitory effects on the crystallization of drugs both in solution and in the solid state due to its antiplasticizing effect in which the glass transition temperature (T_g) of the system is increased and hence the mobility of the drug molecules is reduced (Sekikawa et al. 1978; Ziller and Rupprecht 1988; Ma et al. 1996). The effect of mobility on crystallization has been previously investigated in different systems (Roos and Karel 1991; Saleki-Gerhardt and Zografi 1994). An important conclusion from these studies is that the T_g dictates the conditions for optimal storage of an amorphous system. The present study deals with the amorphous phase stability of a poorly soluble model drug, ABZ.

Complete crystallization in 6 months from a sample of amorphous indomethacin even at 46 °C below the T_g, has been reported previously (Otsuka and Kaneniwa 1988; Yoshioka et al. 1994). Therefore, to prevent crystallization over a period of months and perhaps years, storage of amorphous materials at least 50–60 °C below the T_g is required. To accomplish this for amorphous ABZ, with T_g of 69.1 °C, would almost require refrigeration unless one could disperse the drug in an amorphous matrix (PVP) where the overall T_g was not less than 85 °C, when it could be stored at room temperature. If absorbed water acts as a plasticiser for such a system, such a dispersion would have to have a T_g, higher than 85 °C. In the present study, solid molecular dispersions of ABZ employing PVP polymers with T_g ranging from 99–172 °C were prepared and physicochemical factors affecting crystallization inhibition during preparation and storage investigated.

Systemic absorption of ABZ is warranted for the treatment of inoperable or disseminated cases of hydatidosis, other systemic helminthiases, AIDS related microsporida, and giardiasis (Wen et al. 1993; Lecuit et al. 1994; Misra et al. 1995; WHO 1996; Lopez-Garcia et al. 1997; Keramidas et al. 2004). ABZ belongs to type II (low aqueous solubility with high permeability) of the biopharmaceutical classification system, thus showing dissolution-rate-limited absorption (Amidon et al. 1995; Jung et al. 1998). The drug satisfies the structural criteria (rule 5) proposed by Lipinski et al (1997) in that it does not have: more than 5 hydrogen-bond donor moieties; molecular weight > 500; log $P > 5$; more than 10 hydrogen-bond acceptor moieties.

2 Investigations, results and discussion

2.1. Characterization of solid dispersions

Amorphous ABZ and all solid dispersions were X-ray amorphous and they were sensitive to moisture. Crystallization was observed in solid dispersions when the humidity was not controlled during solvent evaporation. This observation was more pronounced for low polymer contents. Recrystallization was also observed if the cast films were dried at 40 °C under vacuum without pregrinding and drying the films under vacuum at room temperature for 24 h. These results indicate that there is increased mobility due to the presence of solvents (water or methanol) in the films leading to the crystallization of the drug (Crowley and Zografi 2002). It is to be noted that casting a solution of crystalline ABZ alone renders the drug partially amorphous and the presence of polymer only stabilizes the amorphous form during such a process.

Residual solvent is one of the factors affecting the mobility of molecules dispersed in a polymeric system (Crowley and Zografi 2002). Residual solvent analysis was also performed to assure the safety of the products because of the fact that ABZ is used for a prolonged period over several weeks in the treatment of echinococcosis (Horton 1997). The weight percentage of residual solvent was determined to be less than 0.2% and the samples passed the residual solvent test recommended for methanol (class 2 solvent) (Dwivedi 2002).

Quantification of crystalline and amorphous phases in the solid dispersions was carried out using the assay value and DSC analysis following a modified form of the method of Sertsou et al (2002). A typical DSC thermogram for ABZ-PVP K-30 dispersions is shown in Fig. 1. Crystalline drug was quantified from melting endotherm energies, and amorphous drug, from recrystallization exotherm energies.

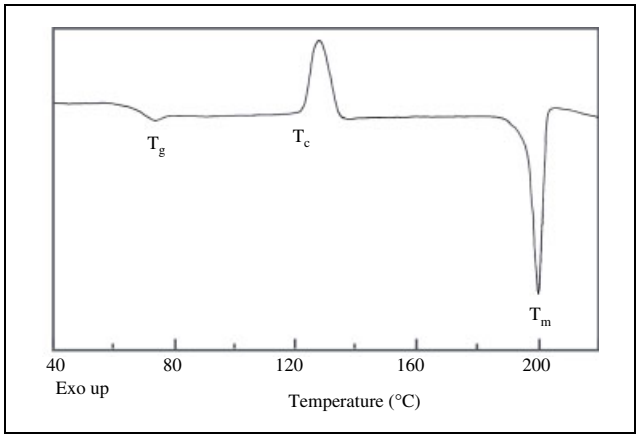

Fig. 1: Typical DSC trace of ABZ-PVP K-30 solid dispersions

The difference between the two gave the original amount of crystalline drug before heating in DSC.

The melting endotherms of crystalline drug in drug-polymer physical mixtures were measured to obtain a calibration curve of% w/w of crystalline drug in the polymer vs crystalline melting endotherm area. Recrystallization exotherms of physical mixtures of amorphous ABZ in polymer, and in crystalline ABZ were also measured and both sets of data were combined to give a composite calibration curve of recrystallization enthalpy vs amorphous drug content of physical mixtures. The estimated limit of detection (LOD) and limit of quantification (LOQ) of this technique for both amorphous and crystalline drug were found to be 2% and 6%.

2.2. Effect of polymer on glass transition temperature of solid dispersions

The effect of polymer content on the T_g of the solid dispersions was investigated by DSC. Polymers having an average molecular weight ranging from 2,500 to 50,000 were used. The T_g of these polymers ranged from 99 to 172 °C. Only one T_g was observed in the solid dispersions indicating that neither polymer nor amorphous drug occurred in appreciable amounts as a solitary phase. The dependence of the T_g values on polymer content is shown in Fig. 2. Dispersions showed a negligible change in T_g with 5% of any polymer. T_g values of solid dispersions, composed of PVP K-30 and PVP K-17, increased progressively with polymer content. The improvement was comparatively less with PVP K-12 and PVP/VA, particularly beyond 50% polymer content.

The T_g values of the solid dispersions were compared with the theoretical predictions of a modified form of the Gordon-Taylor equation (Sertsou et al. 2002; Gordon and Taylor 1952).

$$T_{g12} = (w_1 T_{g1} + K w_2 T_{g2})/(w_1 + K w_2) \qquad (2)$$

where T_g and w are the glass transition temperature and the weight fraction respectively of the components represented by subscripts, and

$$K \approx \varrho_1 T_{g1}/\varrho_2 T_{g2} \qquad (3)$$

in which ϱ is density. Density values for quench-cooled ABZ, precipitated PVP K-12, K-17, K-30 and PVP/VA determined by gas pycnometry were found to be 1.225, 1.261, 1.220, 1.225 and 1.233 g mL^{-1} respectively.

In all cases, the T_g values were higher than the predicted values suggesting the existence of a drug polymer interac-

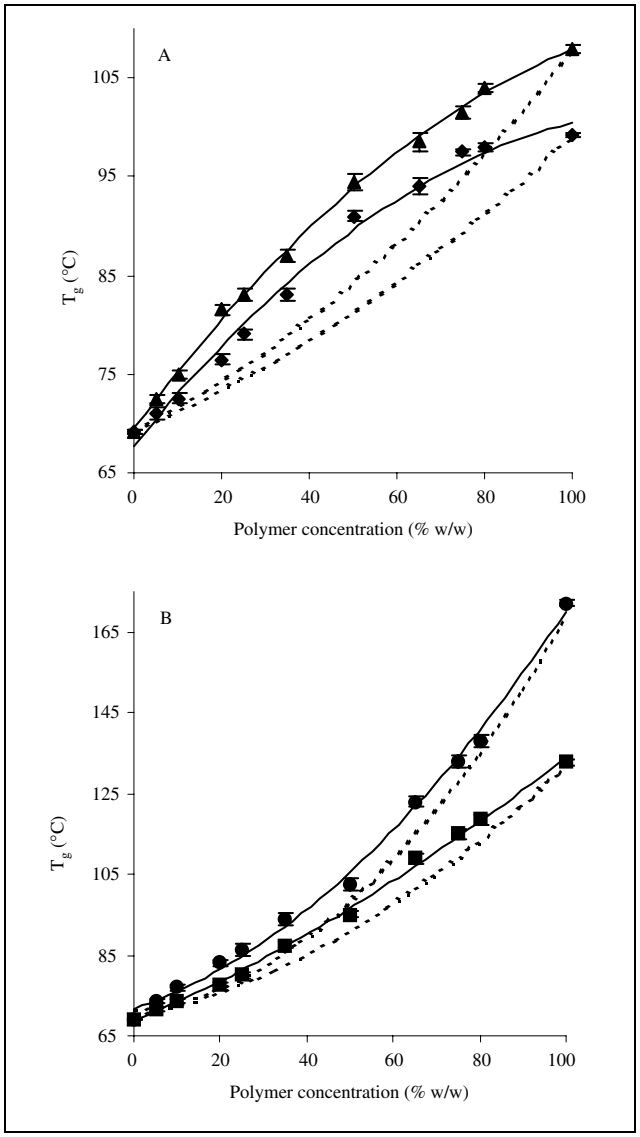

Fig. 2: Glass transition temperature (T_g) detected in solid dispersion, as a function of concentration of polymers. A, PVP K-12 (◆) and PVP/VA (▲); B, PVP K-17 (■) and K-30 (●). Dotted lines are fited to equations 2 and 3. Error bars indicate mean ± s.d.

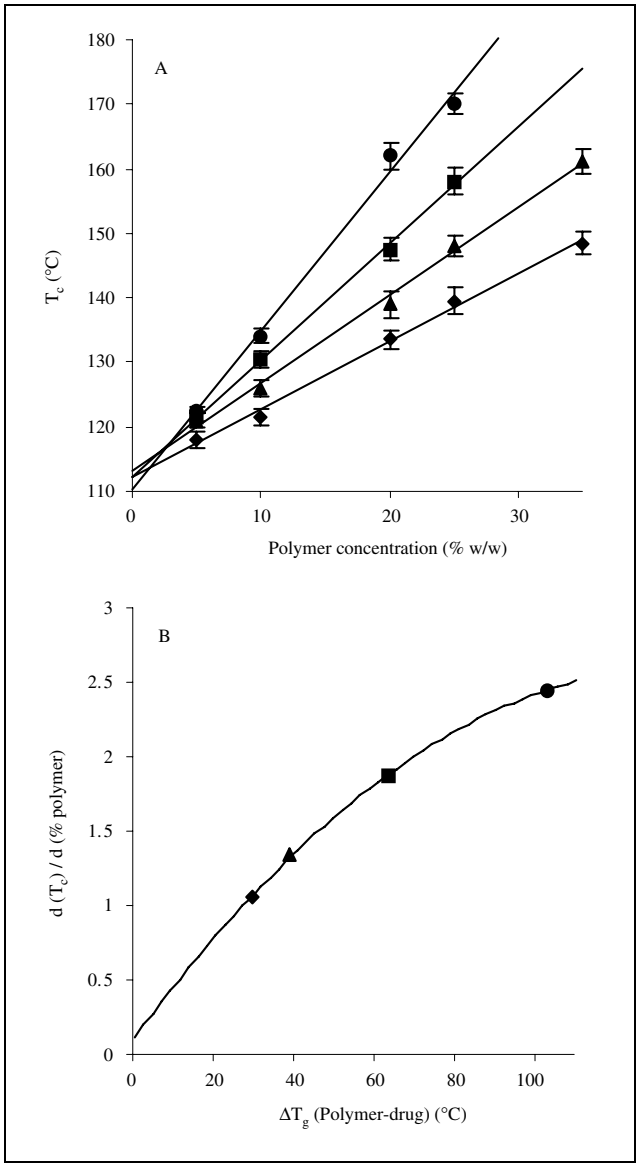

Fig. 3: Change in onset of crystallization (T_c). A, T_c versus polymer content; B, T_c versus polymer content as a function of the difference between the glass transition temperatures of the polymer and drug (ΔT_g) (PVP K-12 (◆), PVP/VA (▲), PVP K-17 (■) and K-30 (●)). Error bars indicate mean ± s.d.

tion. The deviation between the data and predicted values appears to be relatively less for both PVP K-17 and K-30 dispersions. The positive deviation from the Gordon-Taylor equation suggests that the drug polymer interactions are greater either in number or strength relative to the interactions between the individual components (like components) (Brekner et al. 1988; Schneider et al. 1997). This result is in contrast to other systems such as solid dispersions of indomethacin-PVP in which negative deviations have also been observed, due to dimerization of indomethacin (Taylor and Zografi 1997; Matsumoto and Zografi 1999).

2.3. Polymer effect on the onset and the extent of non-isothermal crystallization

Amorphous ABZ with a T_g of 69.1 °C crystallized at a T_c of 116.8 °C. The crystallized drug melted at 200 °C. The effect of polymer content on the onset temperature of crystallization (T_c) is shown in Fig. 3A. The dependence of the T_c values on the weight percentage of polymer is represented by a first order polynomial. The T_c value increased progressively with polymer content, indicating increased stability of the amorphous drug. The increase was significant with every 5% of polymer added except that PVP K-12, at 5% concentration could not produce a significant change. For instance, at 25% polymer content, the observed T_c values ranged from 139.5 °C to 171 °C. The magnitude of the increase in T_c was a function of the polymer and increased as follows: PVP K-12 < PVP/VA < PVP K-17 < PVP K-30. The rank order was also statistically significant with respect to the slope of the first order plot (Fig. 3A). The slopes of these lines as a function of the difference in the T_g values of the polymers and drug (ΔT_g) are described by a second order polynomial in Fig. 3B. From this trend, it is apparent that at a constant polymer content, the polymer with the highest T_g relative to the drug has the greatest effect on T_c. From the nonlinear tendency, it may be further understood that T_c is also influenced by factor(s) other than mobility of the system.

The extent of crystallization inhibition was evaluated from the change in the heat of crystallization (ΔH_c). These val-

Table 1: Extent of nonisothermal crystallization in solid dispersions

Polymer	ΔH_c (Jg^{-1}) for different concentrations of polymer					
	0%	5%	10%	25%	35%	50%
PVP K-12	−85.5(0.08)	−70.1(0.12)	−53.8(0.10)	−29.7(0.11)	−12.9(0.08)	−7.0**(0.05)
PVP K-17	−85.5(0.08)	−66.4(0.13)	−45.5(0.10)	−15.7(0.10)	***	*
PVP K-30	−85.5(0.08)	−60.8(0.12)	−37.2(0.08)	−13.0(0.06)	*	*
PVP/VA	−85.5(0.08)	−64.0(0.09)	−49.6(0.12)	−26.8(0.09)	−11.4(0.04)	*

* complete inhibition; ** complete inhibition with 65% polymer; *** small amount of crystallization observed by HSM. An absolute solid solution was achievable at 50–65% concentration of any polymer. Values are given as mean (n = 3) with s.d. in parentheses

ues are summarized in Table 1. The ΔH_c values decreased significantly with increasing polymer content. For instance, ΔH_c of the ABZ-PVP K-30 system decreased from −85.5 to −37.2 Jg^{-1} in the presence of 10% polymer and crystallization was completely inhibited at 35% of polymer. Similar trends were observed for other dispersions. Complete inhibition was confirmed by HSM. The percentage at which complete inhibition of the crystallization was observed, was inversely proportional to the molecular weight of the polymer. For instance, complete crystallization inhibition was observed at 35% PVP K-30, 50% PVP K-17 and 65% PVP K-12. At comparable weight fractions, polymers with higher molecular weight or higher T_g value appeared to be more effective in the inhibition of crystallization of the drug. The homopolymer was more effective in inhibiting crystallization than the copolymer for a comparable molecular weight of polymer. The increase in T_g continued with the concentration of polymer even beyond the level at which complete inhibition of crystallization was achieved' indicating the incorporation of the drug into amorphous solid solutions with the polymer.

2.4. Effect of polymer on induction time and rate of isothermal crystallization (storage study)

Induction times for the appearance of detectable ABZ crystals in samples aged at different storage temperatures (T) and with different polymer contents as determined by DSC, are given in Table 2. Monitoring for the appearance of crystalline ABZ in solid dispersions revealed no crystallization over a five-week period under the following storage temperatures: 20% polymer up to 50 °C; 10% polymer up to 40 °C and 5% at 30 °C. Amorphous ABZ alone exhibits an induction time at 30 °C of only 2.5 days (complete crystallization in 45–47 days), whereas the addition of just 5% polymer extends this induction time to at least one month. Even at 70 °C, no crystallization was observed over a 4–7 day period with 10% polymer content. This is in contrast to the relatively rapid crystallization of amorphous ABZ alone, with no induction period at above 40 °C. From these observations, it was found that solid dispersions can have a considerable effect on the induction times of isothermal crystallization at levels as low as 5–10% polymer or drug-polymer weight ratios of 19 : 1 to 9 : 1. PXRD pattern showed no evidence of polymorphism in samples aged at 70 °C.

From the data obtained at 70 °C, it was possible to gain some quantitative estimate of the rate of crystallization after the induction period by determining apparent first-order rate constants from log linear plots, as shown in Fig. 4, where,

$$\log\,(\%\ \text{amorphous}) = 2 - [k(t - t_i)/2.303] \qquad (4)$$

and where t is the total storage time and t_i is the induction time. Using the slope of the plot, the apparent rate constant, k was estimated and this differed significantly with the polymer concentration (Table 3). PVP K-12, PVP/VA, PVP K-17 and K-30 exhibited a statistically significant rank order, having a decreasing rate of crystallization. From this limited data, it is understood that for each 5% of polymer added the rate of crystallization of ABZ at 70 °C is reduced by a factor of 6.6, 6.0, 5.0 and 4.5 respectively with PVP K-30, PVP K-17, PVP/VA and PVP K-12. If this type of response were to continue to change in a similar manner, one might expect a more than 1897, 1296, 625 and 410 fold decrease in crystallization rate respectively with 20% of these polymers, compared to amorphous ABZ in the absence of any polymer.

Isothermal crystallization studies have also shown that T_c increased linearly with the polymer concentration. However, there is no assurance that the rate constants will continue to change by a constant factor with increasing polymer content. Study of stability at ambient temperature is also required to confirm the influence of concentration, T_g value and molecular weight of the polymer. Such a study has so far shown that ABZ with 50% of PVP K-30 or PVP K-17, is completely amorphous after 12 months of storage at 30 °C. At 25% polymer content, only the PVP K-30 dispersion remained completely amorphous at this storage temperature for 12 months and the relative degree of crystallinity found in the other systems was as follows: PVP K-17 < PVP/VA < PVP K-12.

At 0% polymer content and 40 °C ($T - T_g = -29.1$ °C), the sample remains completely amorphous only for 1.5 days. On the other hand, it is apparent that though 5% of any polymer produces almost no or very little change in T_g (Fig. 2), on storage at 50 °C ($T - T_g = -21$ to −24 °C) such dispersions show no detectable crystallization for 9–16 days (Table 2). Further, these systems, also

Table 2: Induction time (t_i) for isothermal crystallization of solid dispersions at various storage temperatures (T)

T (°C)	t_i (days) for PVP K-17 or K-30 concentrations				t_i (days) for PVP K-12 or PVP/VA concentrations		
	0%	5%	10%	20%	5%	10%	20%
30	2.5	>35	>35	>35	32.5 (2.5)	>35	>35
40	1.5	27.5 (2.5)	>35	>35	22.5 (2.5)	>35	>35
50	0	14.0 (2.0)	26.0 (2.0)	>35	11.5 (2.5)	23.0 (2.0)	>35
60	0	5.0 (1.0)	16.5 (1.5)	>35	4.0 (1.0)	3.5 (1.5)	30.0 (2.0)
70	0	0	6.5 (0.5)	21.0 (1.0)	0	4.5 (0.5)	17.0 (1.0)

Values are given as mean (n = 6) with s.d. in parentheses

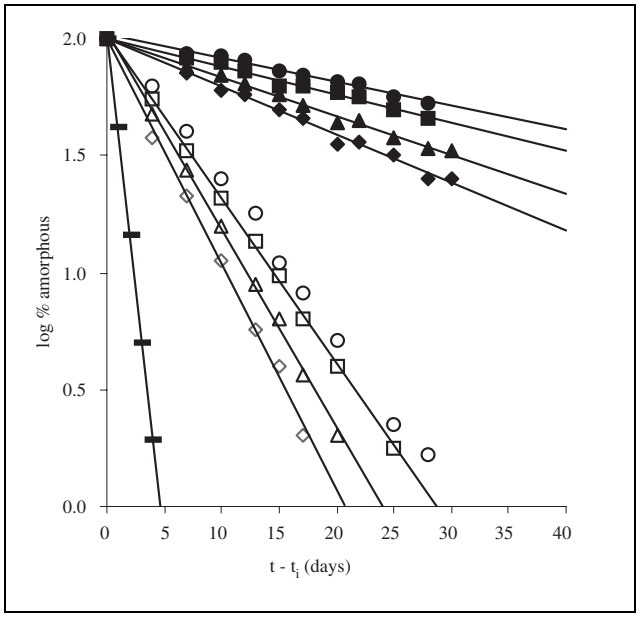

Fig. 4: Percent amorphous ABZ remaining after storage at 70 °C for various time periods (t) after an induction period (t_i) for solid dispersions with 0% (–), 5% (open symbols), and 10% polymer (closed symbols) (PVP K-12 (◆), PVP/VA (▲), PVP K-17 (■) and K-30 (●)). Each point is the mean of three determinations

show a manifold reduction in crystallization rate (Table 3). This is probably because additional factors other than mobility, such as drug-polymer interactions, also affect the crystallization process. Similar conclusions have been reached previously with the indomethacin-PVP system, which also showed an 8–66 fold decrease in crystallization rate relative to the amorphous drug for no increase in T_g at 5–10% PVP K-90 (Yoshioka et al. 1995). Though 10% PVP K-30 and 20% PVP K-12 dispersions produce a similar raise in T_g, the latter shows relatively better physical stability as seen in Table 2. Therefore, drug-polymer interaction may be greater in the PVP K-12 system than with PVP K-30.

2.5. Drug-polymer interaction

DSC study showed deviations in the observed T_g values from the predicted values suggesting the possibility of drug-polymer interactions. The specific interaction was investigated by FTIR spectroscopy using a potassium bromide (KBR) disc method. This method may result in changes in the spectrum depending on the disc thickness, which in turn is influenced by the weight of the sample, the mixing ratio of the polymer and the compression force applied. Alternatively, attenuated total reflection (ATR) spectroscopy may be used to obtain spectra of solids regardless of thickness (Silverstein et al. 1981). Since the comparison is between a solid dispersion and the corresponding physical mixture using discs made with similar compressive force, the spectral differences in the present study are indicative of drug polymer-interaction. Typical FTIR spectra for the ABZ-PVP K-12 solid dispersions and physical mixtures with increasing polymer content are shown in Fig. 5. The drug has a characteristic N–H stretch at 3325 cm^{-1}, whereas PVP has a cyclic amide C=O stretching band at 1660 cm^{-1} merged with N–H bending vibration of the drug (1525–1630 cm^{-1}). A single peak in drug and PVP spectra at 2940–2960 is due to C–H stretching. Physical mixtures show the superimposed spectra of the drug and PVP. In the solid dispersions, the N–H stretching band decreases in intensity compared with the physical mixtures. Reduction in the frequency of the cyclic amide band of PVP (by ~10 cm^{-1}) can be noticed at 10–65% PVP content. Broadening of the same band occurs at PVP concentrations above 35%. Such changes were almost the same for all PVP dispersions and PVP/VA. In addition to this, the carbonyl frequency shift for PVA (1730 cm^{-1}) was also observed with PVP/VA dispersions. Thus the drug interacted with both the cyclic amide group of PVP and the carbonyl group of the copolymer. PVP K-17 and K-30 dispersions did not show a significant change in the frequency of carbonyl stretching, but only a reduction in carbonyl transmittance intensity indicating that the higher the molecular weight, the weaker the interaction. As the number of terminal groups in PVP is in inverse proportion to the molecular weight, drug carrier interaction might be relatively high in PVP K-12 dispersions (Sekizaki et al. 1995).

In solid dispersions, the C=N stretching vibration (1290 cm^{-1}) of the polymer changes neither in intensity nor in frequency. Hydrogen bonding through the polymer

Table 3: First order rate constant (k) of isothermal crystallization in solid dispersions at 70 °C

Polymer weight	k × 10 (day^{-1})
0%	9.99 ± 0.64
5% PVP K-12	2.22 ± 0.01
10% PVP K-12	0.48 ± 0.04
5% PVP K-17	1.65 ± 0.06
10% PVP K-17	0.28 ± 0.01
5% PVP K-30	1.52 ± 0.05
10% PVP K-30	0.23 ± 0.02
5% PVP/VA	1.99 ± 0.06
10% PVP/VA	0.38 ± 0.04

Values are mean ± s.d. (n = 3)

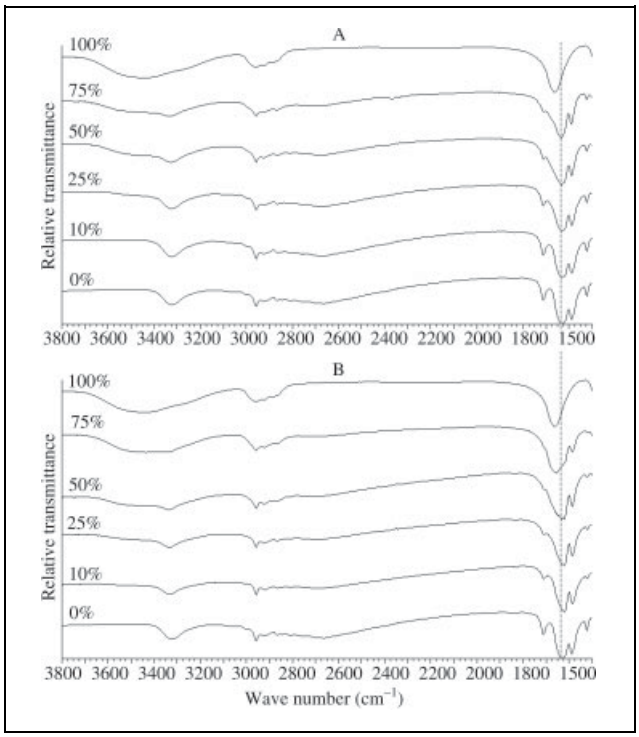

Fig. 5: FTIR spectra of drug-PVP physical mixtures (A) and solid dispersions (B), at different concentrations (%) of PVP K-12

nitrogen appears to be sterically unfavored (Taylor and Zografi 1999).

2.6. Mechanisms other than mobility of the system proposed for inhibition of crystallization

During the preparation of the solid dispersion, PVP might have accumulated at a higher concentration at the particle surface where it might be in a better position to inhibit nucleation and growth initiated at these areas (Hsu et al. 1995). It is also possible that the larger molecular size of PVP relative to ABZ, promotes a tendency to accumulate at the interface or to act as a very efficient steric barrier to nucleation and growth (Yoshioka et al. 1995). These factors must apply in the ABZ-PVP system due to the observation that polymers with high molecular weight appeared to be relatively more effective in inhibiting both isothermal and nonisothermal crystallization.

Another possible mechanism, which might inhibit drug crystallization, is drug-polymer complexation through hydrogen bonding as observed in DSC and FTIR studies.

The effects of polymer molecular weight, composition and content on the crystallization of ABZ in solid dispersions were investigated. The onset of crystallization increases with the concentration and molecular weight or ΔT_g of the polymer. Polymers with higher molecular weight are, also the most efficient crystallization inhibitors showing lower ΔH_c values in solid dispersions with comparable polymer content. In spite of having a higher molecular weight, replacement of about 40% of vinylpyrrolidone monomers with vinylacetate groups (as in PVP/VA) results in reduced inhibition of crystallization. The homopolymer is more effective in crystallization inhibition than the copolymer for a comparable molecular weight.

ABZ exhibits crystallization from the amorphous state even when stored below its T_g. The use of polymers significantly inhibits crystallization at levels as low as 5% and at temperatures as high as 70 °C. Though mobility of the system plays an important role in crystallization inhibition, dispersions also demonstrate a relatively lower tendency to crystallize than the amorphous drug for comparable values of $T - T_g$. Therefore, it is concluded that the inhibition of crystallization in the present systems also involves additional factors not related to the glass transition temperature and perhaps related to specific chemical and steric interactions, the latter being influenced by the molecular size of the interacting polymer (Yoshioka et al. 1995). Drug-polymer hydrogen bonding offers an explanation as to how the polymers are able to inhibit crystallization at levels of 5–10% where the antiplasticizing effect is minimal. Thus, the solvent casting method and PVP can be beneficially utilized to achieve high energy and stable solid dispersions for enhancing the bioavailability of ABZ.

Relative to the corresponding crystalline state, molecules in an amorphous phase are capable of absorbing large quantities of water vapor, which exerts a large T_g lowering effect on the amorphous dispersions (Crowley and Zografi 2002). Moreover, PVP is hygroscopic in nature. Hence, further investigations dealing with the effect of absorbed water on the mobility (T_g) of ABZ-PVP systems are being carried out in our laboratory.

3. Experimental

3.1. Materials

The following materials were used: ABZ (gift sample, Juggat Pharma, Bangalore, India), PVP K-12, K-17 and poly(vinyl pyrrolidone-co-vinyl-acetate) (PVP/VA-64) (gift samples from BASF India Ltd., Chennai, India), PVP K-30, anhydrous methanol and glacial acetic acid (SD Fine Chem, Mumbai, India). The average molecular weight of these polymers was reported by the supplier to be 2,000–3,000, 7,000–11,000, 44,000–54,000 and 45,000–70,000 respectively. PVP and PVP/VA were dried at 105 °C for 12 h under vacuum before use.

3.2. Preparation of amorphous ABZ

ABZ (5 g) contained in a stainless-steel beaker was heated in an oven under a stream of nitrogen gas and held at 210 °C for 5 min. It was then cooled by immersion into liquid nitrogen. The quench-cooled drug was removed from the beaker and ground gently with a mortar and pestle, passed through a 60 mesh sieve and stored at 0 °C over phosphorous pentoxide until immediately before use in experiments.

3.3. Preparation of solid molecular dispersions

Drug-polymer mixtures (5–100% w/w of polymer) were dissolved in anhydrous methanol, stirred overnight and cast on Teflon sheets. The solvent was allowed to evaporate in a partially open desiccator at room temperature for 3 days. The samples were then placed under vacuum for 2 days and the resulting films were gently ground into powder with a mortar and pestle for 1 min. The powder obtained was dried under vacuum at room temperature for 24 h and at 40 °C for 12 h. The samples were passed though a 60 mesh sieve and stored at 0 °C over phosphorous pentoxide until used.

3.4. Preparation of physical mixtures

Physical mixtures were prepared by mixing the components using a spatula and a glass mortar for 2 min. The samples were then dried at 40 °C under vacuum for 12 h. Dried physical mixtures were used immediately in the experiments.

3.5. Assay of ABZ

The drug content of the solid dispersions was determined spectrophotometrically (UV-1601PC, Shimadzu, Japan) by dissolving the sample in glacial acetic acid followed by sufficient dilution with distilled water to measure the absorbance at 291 nm.

3.6. X-ray analysis

Powder X-ray diffraction (PXRD) patterns were determined with an X-ray diffractometer (JDX 8030, Jeol, Japan), employing a Cu K_α radiation source and operating at 20 mA and 40 kV. Samples were scanned from 3 to 40° 2θ range at a scanning rate of 0.05° 2θ s^{-1}.

3.7. Density measurement

The density of amorphous (quench-cooled) ABZ and polymers precipitated from methanol were measured by helium pycnometry (Quantachrome Corp.) at ambient temperature. Measurements were made in triplicate on materials in powder form.

3.8. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out in hermetically sealed aluminum pans using a Shimadzu DSC 60 instrument (Shimadzu, Kyoto, Japan). Samples of 5–10 mg were scanned at a heating rate of 20 °C min^{-1} under a dry nitrogen gas purge of 40 mL min^{-1}. Such a scan (nonisothermal study) allowed an estimation of the glass transition temperature (T_g), onset of crystallization (T_c), heat of crystallization (ΔH_c), melting temperature (T_m), and the heat of fusion (ΔH_f) in a single run. The measurements were made in triplicate. TA 60WS (version 1.4) software (Shimadzu, Kyoto, Japan) was used to detect and analyze thermogram events.

3.9. Thermo-gravimetric analysis

Analysis of residual solvent in the solid dispersions was carried out by thermo-gravimetric analysis (TGA) using a Shimadzu DSC 60 instrument equipped with TA 60 (version 1.4) software (Shimadzu, Kyoto, Japan). Samples, of 10–15 mg, were heated in open aluminum pans at a rate of 10 °C min^{-1}, under a nitrogen purge of 40 mL min^{-1}, from room temperature to 110 °C. Subsequently, the samples were kept isothermally for 5 min at 110 °C. Weight loss occurring between ambient temperature and 110 °C was considered to be the weight of residual solvent. The samples were analyzed in triplicate.

3.10. Hot stage microscopy

The crystallization process at different temperatures was observed by hot stage microscopy (HSM) with a hot stage (FP 80, Mettler Instrument Corporation, Hightstown, NJ) under a suitable microscope (M3Z, Wild, Heerbrugg, Switzerland). Samples were heated at 10 °C min^{-1} under a nitrogen gas flow.

3.11. Isothermal crystallization studies

Samples of each solid dispersion and amorphous ABZ were placed into tightly sealed glass bottles and stored over phosphorous pentoxide at various temperatures ranging from room temperature to T_g of amorphous ABZ (isothermal aging). The time required for the appearance of any detectable crystallization (t_i) and the extent of crystallization over a 5-week period were determined by DSC analysis.

3.12. Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) spectra were obtained on a Perkin-Elmer FTIR infrared spectrophotometer (Spectrum one B 68718 with spectrum 5.1 software, Perkin-Elmer Instruments, USA) with a resolution of 2 cm^{-1} from 4000 to 400 cm^{-1}. Compressed discs were prepared by gently mixing the sample (2 mg) with dried KBr (200 mg).

3.13. Statistical analysis

Data are represented as mean $\pm$ s.d ($n = 3$). Two-way analysis of variance was performed to compare various formulations with respect to polymer used and concentration of the polymer. Differences between sets of data were accepted as significant at $P < 0.05$.

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