Physical Stability of Amorphous Acetanilide Derivatives Improved by Polymer Excipients

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Crystallization rates of drug-polymer solid dispersions prepared with acetaminophen (ACA) and *p*-aminoacetanilide (AAA) as model drugs, and polyvinylpyrrolidone and polyacrylic acid (PAA) as model polymers were measured in order to further examine the significance of drug–polymer interactions. The crystallization of AAA and ACA was inhibited by mixing those polymers. The most effective inhibition was observed with solid dispersions of AAA and PAA. The combination of AAA and PAA showed a markedly longer enthalpy relaxation time relative to drug alone as well as a higher T_g than predicted by the Gordon–Taylor equation, indicating the existence of a strong interaction between the two components. These observations suggest that crystallization is effectively inhibited by combinations of drug and polymer that show a strong intermolecular interaction due to proton transfer between acidic and basic functional groups.

Key words crystallization rate; solid dispersion; drug–polymer interaction; enthalpy relaxation; glass transition temperature

Preparation of amorphous forms of poorly water-soluble pharmaceuticals is one of the most effective methods to improve their solubility. However, amorphous solids are physically unstable, and crystallization during storage presents a problem. It is known that crystallization can be inhibited by increasing the glass transition temperature (T_g) of the solid dispersion by addition of a polymer excipient with a high T_g. Decreases in crystallization rates with increasing T_g have been demonstrated for several systems.[1—3] Nevertheless, stabilizing effects that could not be explained only by an increase in T_g have been reported. The crystallizations of amorphous sucrose[4] and indomethacin[5] were effectively inhibited in solid dispersions with a small amount of polymer (<10%) that exhibited no significant increase in T_g. In our previous report concerning the crystallization of amorphous acetaminophen (ACA) in solid dispersions with 10% polyacrylic acid (PAA) or polyvinylpyrrolidone (PVP), the crystallization rate in the temperature range 45—60 °C was slower in ACA–PAA dispersions than in ACA–PVP dispersions with a similar T_g.[6] These results indicate that other factors in addition to T_g can influence the crystallization rate. Drug–polymer interactions such as hydrogen bonding may decrease crystallization rates, as indicated by infrared[2,5,7] and Fourier transform Raman[8,9] spectroscopy and nuclear magnetic resonance relaxation[10] measurements. In solid dispersions with PVP, the carbonyl group is believed to participate in the interaction.[2,5,7—10] The participation of carboxyl group of PAA in salt forming with basic drugs have also been reported.[11,12]

The purpose of this study was to further examine the significance of interactions to the physical stability of solid dispersions. The isothermal crystallization behavior was investigated using various solid dispersions prepared with ACA and *p*-aminoacetanilide (AAA) as model drugs. They have acetanilide moiety in common and an opposite polar group at the para position: hydroxyl group (ACA) and amino group (AAA). For polymers, PAA with a carboxyl group and PVP with a carbonyl group were selected. PVP only acts as proton acceptor, while PAA acts as both a proton donor and an acceptor. Besides the crystallization rate, the enthalpy relaxation time and the T_g were measured as indicators of drug–polymer interaction. The role of salt forming in stabilizing amorphous solids was compared with that of hydrogen bonding.

Experimental

Materials ACA, AAA and PVP (average molecular weight (M_w) of 360000) were obtained from Sigma Chemical Co. PAA (M_w 5000) was obtained from Wako Pure Chemical Industries Ltd.

Preparation of Amorphous Drugs and Drug–Polymer Solid Dispersions Amorphous ACA and AAA were prepared by melt quenching in a cell of a differential scanning calorimeter (DSC2920, TA Instruments) with a dry nitrogen gas purge at 20 ml/min. Crystalline drug (2—3 mg) was put in an aluminum pan and sealed with a pierced lid. The pan was heated to 182 °C at a heating rate of 20 °C/min, kept at that temperature for 3 min, and cooled to −80 °C for ACA and −90 °C for AAA at a cooling rate of 40 °C/min by pouring liquid nitrogen into the cooling jacket surrounding the cell. And then it was reheated to room temperature at a heating rate of 20 °C/min. The temperatures of −80 °C and −90 °C corresponded to the temperature 100 °C below the T_g for ACA and AAA, respectively.

Drug–polymer solid dispersions and polymer-alone samples were prepared by freeze-drying. Aqueous solutions of an acetanilide derivative and a polymer at the desired mixing ratio were frozen in polypropylene vessels by immersion in liquid nitrogen for 10 min and were then dried at a vacuum level of <5 Pa for 24 h in a lyophilizer (Freezvac 1CFS, Tozai Tsusho Co.). The shelf temperature was −40 °C for the first hour, 20 °C for the subsequent 19 h, and 35 °C for the rest of the period to complete the dehydration. The obtained mixtures or polymer cakes (2—3 mg) were put in an aluminum pan and sealed with a pierced lid. The pan was heated to approximately 20 °C above the T_g at a heating rate of 20 °C/min, then cooled to approximately 100 °C below the T_g at a cooling rate of 40 °C/min and reheated to room temperature at a heating rate of 20 °C/min, in order to give the same thermal history and to remove residual water from samples. No endothermic peak resulting from evaporation of water was observed in the second heating run. Since mixtures containing more than 50% ACA or AAA crystallized during the freeze-drying or during heating in the DSC cell, samples were heated to more than 10 °C above the end of melting endothermic event, kept at that temperature for 3 min, and rapidly cooled to approximately 100 °C below the T_g. And then it was reheated to room temperature at a heating rate of 20 °C/min.

Measurement of Isothermal Crystallization Rate The isothermal crystallization rate was measured with pure drugs and solid dispersions containing 2—10% polymer. The samples were stored at a constant temperature in desiccators containing P_2O_5. After various periods of time, change in heat capacity (ΔC_p) at T_g was measured by DSC with a heating rate of 20 °C/min. The ratio of amorphous form remaining at time t, $x(t)$, was calculated according to Eq. 1:

$$x(t)=\Delta C_{pt}/\Delta C_{p0} \quad (1)$$

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where ΔC_{pt} and ΔC_{p0} are the changes in ΔC_p at time t and initially, respectively. The decrease in $x(t)$ as a function of storage time was analyzed according to the Avrami equation (Eq. 2) with a n value of 3, to calculate the time required for 10% of the amorphous solid to crystallize (t_{90}):

$$x(t)=\exp(-kt^n) \quad (2)$$

where k is the crystallization rate constant and n is the Avrami index related to the nucleation mechanism and the dimensionality of the growth process.

Measurement of Enthalpy Relaxation The samples were stored at a constant temperature (10—35 °C below the T_g). Storage was performed in desiccators containing P_2O_5 putting in water baths or air baths for temperatures under 90 °C, and was performed in the DSC cell for temperatures above 90 °C.

After various periods of time, the samples were cooled to approximately 100 °C below the T_g and heated (20 °C/min) through their T_g to measure endothermic recovery by DSC. The fraction of glass relaxed at time t, $\phi(t)$, was calculated by Eq. 3:

$$\phi(t)=\Delta H_t/\Delta H_\infty \quad (3)$$

where ΔH_t is the enthalpy recovery at time t and ΔH_∞ is the maximum enthalpy recovery calculated from T, T_g and ΔC_p according to Eq. 4:

$$\Delta H_\infty=\Delta C_p(T_g-T) \quad (4)$$

The T_g and ΔC_p values observed for the sample before storage were used to calculate the ΔH_∞ value. The enthalpy relaxation time (τ) was calculated according to the Kohlrausch–Williams–Watts (KWW) equation (Eq. 5):

$$1-\phi(t)=\exp[(-t/\tau)^\beta] \quad (5)$$

where β is a parameter representing distribution of the relaxation time. No crystallization was observed during the enthalpy relaxation measurements.

Measurement of T_g and Prediction of T_g from the Gordon–Taylor Equation T_g measurements of amorphous drugs and drug–polymer solid dispersions were performed by DSC with a dry nitrogen gas purge at 20 ml/min. Indium was used to calibrate the cell constant and the temperature of the instrument. Samples were heated at a rate of 20 °C/min and the values of ΔC_p and T_g at the inflection point were obtained.

The T_g values of the amorphous solid dispersions were predicted with the Gordon–Taylor equation, which assumes that the two components are ideally mixed[13]:

$$T_{g12}=(w_1T_{g1}+Kw_2T_{g2})/(w_1+Kw_2) \quad (6)$$

where w_1 and w_2 are the mass fractions of each component and T_{g1} and T_{g2} are the glass transition temperatures of each component. The constant K is related to the free volume of the two components and can be calculated by the Simha–Boyer rule:

$$K=T_{g1}\rho_1/T_{g2}\rho_2 \quad (7)$$

where ρ_1 and ρ_2 are the densities of each component. Density values were measured by helium pycnometry (AccuPyc 1330, Shimadzu Co.) at ambient temperature. Amorphous ACA and AAA were prepared by melting the crystalline form in Teflon vessels at 180 °C for 10 min followed by quench cooling by immersion into liquid nitrogen. Amorphous polymers were freeze-dried samples. Table 1 shows the T_g and density values of the drugs and polymers in the amorphous state.

Table 1. T_g and Density Values of Drugs and Polymers

Sample	T_g (°C)	Density (g/cm^3)
ACA	25.1±0.6	1.23±0.003
AAA	9.5±0.4	1.19±0.001
PAA	117.6±0.5	1.40±0.002
PVP	181.6±0.5	1.20±0.000

Values are mean±S.D. (n>3).

Table 2. T_g (°C) Values of Amorphous Drugs and Solid Dispersions

Polymer content (%)	ACA		AAA	
	PAA	PVP	PAA	PVP
0	25.1±0.6		9.5±0.4	
2	26.2±0.4	25.6±0.2	12.9±0.5	13.0±0.1
5	26.8±0.6	—	15.3±0.3	14.1±0.2
10	29.3±0.4	27.8±0.3	19.7±0.7	16.4±0.3

Values are mean±S.D. (n>3).

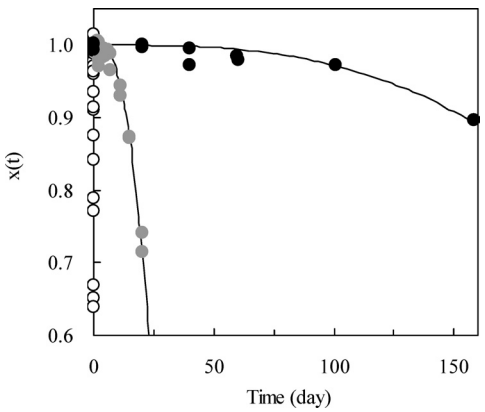

Fig. 1. Ratio of Amorphous form Remaining in AAA and AAA–PAA Solid Dispersions at 15 °C

○: drug alone, ●: 2%PAA, ●: 5%PAA. Solid lines denote the fitting to the Avrami equation.

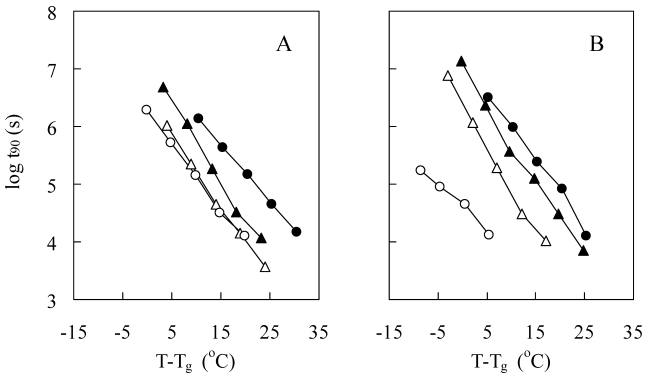

Fig. 2. Effect of PAA on the t_{90} for Crystallization of ACA (A) and AAA (B) at Various Storage Temperatures

○: without PAA, △: 2%PAA, ▲: 5%PAA, ●: 10%PAA.

Results

Isothermal Crystallization of Drug–Polymer Solid Dispersions A small amount of polymer somewhat increased the T_g of amorphous ACA and AAA (Table 2). Figure 1 shows typical time profiles of AAA crystallization in amorphous AAA and amorphous AAA–PAA solid dispersions at 15 °C as measured by the decrease in ΔC_p. Increasing amounts of PAA progressively retarded the crystallization. The t_{90} were calculated by fitting the data showing $x(t)$>0.6. Figures 2A and B show the effect of PAA on the t_{90} for crystallization of ACA and AAA in the solid dispersions at various storage temperatures (T). Compared at the same ($T-T_g$), the t_{90} increased with increasing amounts of PAA in both ACA–PAA and AAA–PAA solid dispersions. Especially for AAA, 2% PAA increased the t_{90} by more than one order of magnitude relative to that of pure AAA. Figure 3 shows the effect of polymer species on the t_{90}. Figure 3A also shows the previously reported results for 10% polyacrylic acid with M_w

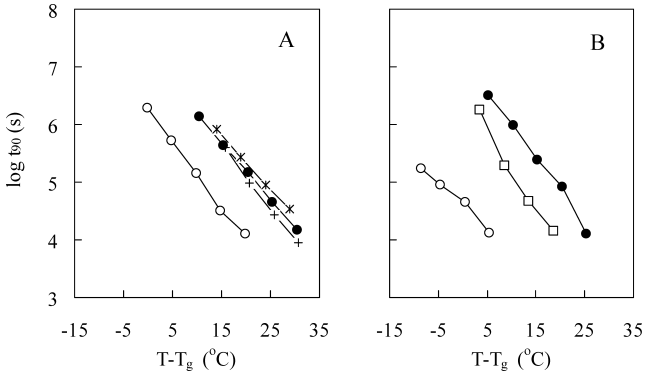

Fig. 3. Effect of Polymers on the t_{90} for Crystallization of ACA (A) and AAA (B) at Various Storage Temperatures

(A) ○: ACA, ●: ACA-PAA, ∗: ACA with polyacrylic acid (M_w of 25000)*, +: ACA with polyvinylpyrrolidone (M_w of 40000)*. (B) ○: AAA, ●: AAA–PAA, □: AAA–PVP. The mixing ratio of drug–polymer solid dispersions was 90 : 10. * The data were taken from ref. 6.

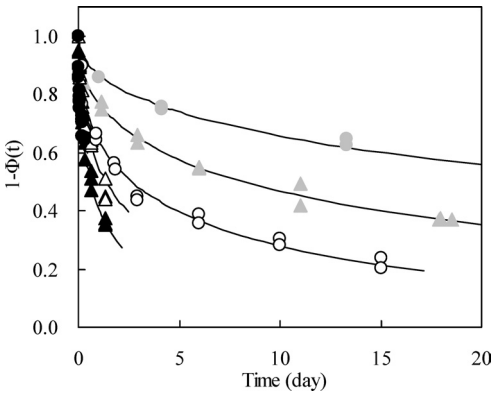

Fig. 4. Enthalpy Relaxation Behavior of Amorphous Samples

▲: ACA at 5 °C, ▲: ACA–PAA (70 : 30) at 25 °C, △: ACA–PVP (90 : 10) at 10 °C. ●: AAA at −10 °C, ●: AAA–PAA (70 : 30) at 30 °C, ○: AAA–PVP (90 : 10) at −3 °C. The lines denote the fitting to the KWW equation.

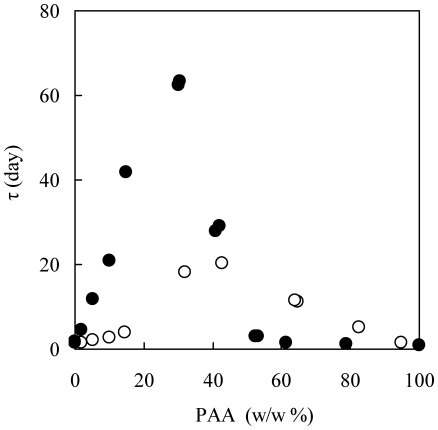

Fig. 5. Relationship between PAA Content and τ of ACA–PAA (○) and AAA–PAA (●)

Samples were stored at 20 °C below the T_g.

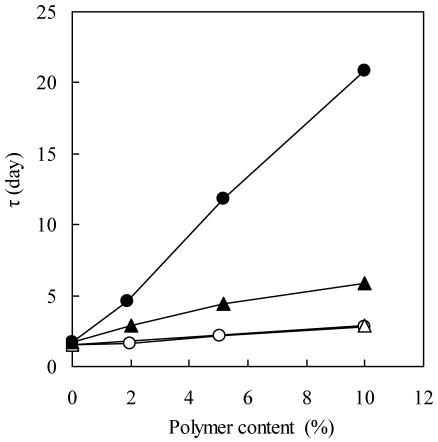

Fig. 6. Changes in τ of Solid Dispersions with Increasing Polymer Content

○: ACA–PAA, △: ACA–PVP, ●: AAA–PAA, ▲: AAA–PVP. Samples were stored at 20 °C below the T_g.

of 25000 and for 10% polyvinylpyrrolidone with M_w of 40000 (T_g: 31.3±0.5, 30.3±0.3 °C, respectively).[6] The inhibition effect of 10% polymer on the ACA crystallization rate was nearly the same irrespective of polymer species and the M_w. On the contrary for AAA, the t_{90} varied with polymers: PAA>PVP.

Enthalpy Relaxation of Amorphous Drug–Polymer Solid Dispersions Figure 4 shows typical profiles of the enthalpy relaxation behavior of drugs and drug–polymer solid dispersions at 20 °C below their T_g. All the enthalpy relaxation behaviors observed in this study could be analyzed according to the KWW equation with β between 0.46 and 0.48. Figure 5 shows the relationship between PAA content and τ of drug–PAA solid dispersions stored at 20 °C below their T_g. Maximum τ values were shown around 30—40% PAA, where the ratio of the number of drug molecules to the number of repeating unit (–CH(COOH)–CH_2–) in PAA chains was approximately 1 : 1. The maximum τ value of the AAA–PAA solid dispersions was approximately three times longer than that of the ACA–PAA dispersions.

Figure 6 illustrates the effect of small amount of polymer on τ. The τ of pure drug was similar for both ACA and AAA, and the increase in τ with PAA content was more marked in the AAA–PAA dispersions than in the ACA–PAA dispersions. The difference in τ-extending effect between PAA and PVP was not significant for ACA, however, it was apparent for AAA: PAA>PVP.

***T_g* of the Drug–Polymer Solid Dispersions** A single T_g was observed for the ACA–polymer and AAA–polymer solid dispersions over the entire composition range. The T_g values obtained are plotted in Fig. 7. The lines in the figures represent predictions from the Gordon–Taylor equation. The AAA–PAA solid dispersions showed apparent positive deviation from the predicted values, whereas the T_g values of the ACA–PAA dispersions were in reasonable agreement with the predictions. The positive deviation was similar to those reported for the loperamide–PAA dispersions due to salt formation.[12] The T_g values of the drug–PVP dispersions tended to be lower than the prediction, as reported for sugar–PVP systems due to the overall loss in the number and strength of hydrogen bonds.[9]

Discussion

A single T_g was observed for all solid dispersions prepared with mixing the model drugs ACA or AAA, and the model polymers PAA or PVP, indicating a complete miscibility of

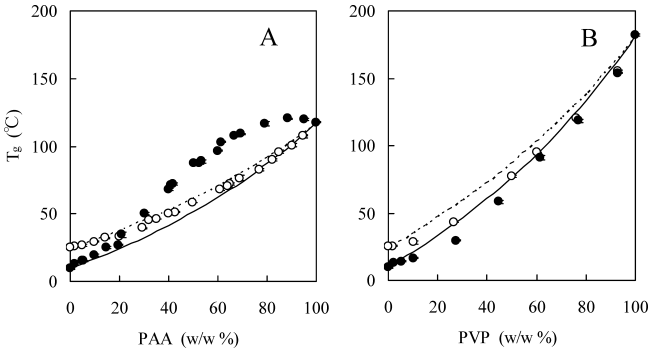

Fig. 7. T_g of Drug–PAA (A) and Drug–PVP (B) Solid Dispersions as a Function of Polymer Content

○: ACA, ●: AAA. The dotted and solid lines represent the prediction by the Gordon–Taylor equation for ACA and AAA, respectively. Each point represents the mean±S.D. ($n>3$).

the drug and polymer within the sensitivity limit of the DSC method. Thus, changes in matrix mobility may explain the retarded crystallization of ACA and AAA in the presence of PAA or PVP. The T_g of the solid dispersions increased with increasing polymer content. The increase in T_g caused by PAA was larger than that by PVP (Table 2). However, changes in matrix mobility can not completely explain the retarded crystallization, because the t_{90} values plotted against $(T-T_g)$ does not overlap each other (Fig. 2). Although the stabilizing effect of PAA for ACA crystallization was similar to that of PVP (Fig. 3A), PAA stabilized AAA to a greater extent than PVP (Fig. 3B). In addition, positive deviation in the T_g was observed for AAA–PAA dispersions (Fig. 7). This finding suggests that proton transfer occurred between AAA and PAA, as reported for basic drugs with PAA loperamide–PAA dispersions,[12] and resulted in the greater decrease in the crystallization rate of AAA. The interaction between the salt-forming components appeared to stabilize the amorphous state more effectively than the interaction through hydrogen bonding.

The stronger interaction between AAA and PAA was might also be confirmed by the enthalpy relaxation measurements. The AAA–PAA solid dispersions exhibited longer τ values than other dispersions in the range of 2—10% polymers (Fig. 6). This indicates that the molecular mobility of the AAA–PAA dispersion was reduced more intensely than others due to stronger interaction.

Conclusion

The crystallization of amorphous acetanilide derivatives was inhibited by mixing polymers having high T_g. The most effective inhibition was observed with solid dispersions of AAA and PAA. The combination of AAA and PAA showed a markedly longer τ relative to drug alone as well as a higher T_g than predicted by the Gordon–Taylor equation, indicating the existence of a strong interaction between the two components. These observations suggest that crystallization is effectively inhibited by combinations of drug and polymer that show a strong intermolecular interaction due to proton transfer between acidic and basic functional groups.

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