

Interaction between Water and Poly(vinylpyrrolidone) Containing Polyethylene Glycol

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Abstract □ Information on the interaction between water and polymers is indispensable for manufacturing solid dispersion of a drug by hot-melt extrusion because this interaction affects various properties of the water-polymer mixtures, such as their viscoelastic properties. In this study, poly(vinylpyrrolidone) K30 (PVP) containing 0%, 10%, and 20% poly(ethylene glycol) 400 (PEG) was used as model amorphous polymers. The interaction of water with these polymers was assessed by the evaluation of the glass transition temperature (T_g), the point on the isotherm corresponding to the weight of sorbed water required to form a complete monolayer on the solid surface (apparent W_m), and the maximal amount of nonfreezing water, which were measured by differential scanning calorimetry and water sorption isotherms. In all of the systems with a water content below a certain water fraction (0.1 for PVP, 0.12 for PVP-PEG 10%, and 0.16 for PVP-PEG 20%), the T_g values were successfully predicted using theoretical equations, whereas the experimental T_g values were higher than predicted for those with a water content above these water fraction levels. In addition, these values of water fraction are similar to the apparent W_m values determined using the Guggenheim-Anderson-DeBoer (GAB) equation (0.110, 0.117, and 0.147 weight fraction of water for PVP, PVP-PEG 10%, and PVP-PEG 20%, respectively). Nonfreezing water is detected above 0.47, 0.49, and 0.51 weight fraction of water for PVP, PVP-PEG 10%, and PVP-PEG 20%, respectively. Miscibility between water and PVP or PVP-PEG seems to change according to the water content in the system. All parameters increase with the concentration of PEG in the sample. This may be explained by the fact that PEG has a larger number of polymer repeating units, which may therefore interact with water more than PVP.

Introduction

Recently, a hot-melt extrusion technique has been applied to produce a polymer-based solid dispersion of a drug as a drug delivery system.^{1,2} Amorphous hydrophilic polymers are often used as a component of such solid dispersions for the modification of drug dissolution. During the hot-melt extrusion process, the drug is incorporated into a rubbery state of amorphous polymer mass.² Therefore, the glass transition temperature (T_g) of the amorphous polymer is one of the most important factors in the hot-melt extrusion process because the viscoelastic properties of the polymer, namely whether the polymer is rubbery or glassy at the manufacturing temperature, are affected by the T_g value.³ The T_g value of the polymer can be reduced to an appropriate temperature for the manufacturing process by adding a plasticizer such as poly(ethylene glycol) to the polymer. Moreover, it has been demonstrated that the

water in the polymer acts as a plasticizer to lower the T_g value of the polymer-water systems by increasing the molecular mobility and free volume.⁴⁻⁶ Amorphous polymer and plasticized polymer generally contain some amount of water, and water is sometimes added during the hot-melt extrusion process. As the water content affects the T_g value of the system, it is necessary to determine the interaction between water and polymers, in particular the effect of water content on the T_g value of the systems as basic information for the hot-melt extrusion process. However, although there have been some reports describing the relationship between the water content and the T_g value of polymer-water binary systems,^{7,8} there have been few reports on plasticized polymer-water ternary systems.⁶

In this study, three components, poly(vinylpyrrolidone) K30 (PVP) as a model amorphous polymer, poly(ethylene glycol) 400 (PEG) as a model plasticizer, and water, were chosen and the interaction of water with PVP containing 0%, 10% and 20% PEG was studied. The experimental T_g values of the systems containing various amounts of water were determined using differential scanning calorimetry (DSC) and were compared with those predicted by theoretical equations. The apparent W_m (the point on the isotherm corresponding to the weight of adsorbed water required to form a complete monolayer on the solid surface) was estimated by analyzing the water sorption isotherm of PVP and PVP-PEG. Furthermore, a maximal amount of nonfreezing water was calculated by DSC studies on aqueous PVP and PVP-PEG solutions.

Experimental Section

Materials—Poly(vinylpyrrolidone) K30 (viscosity average of molecular weight, 42 500), PVP (BASF) and poly(ethylene glycol) 400 (nominal molecular weight, 400), PEG (Colorcon) were used without further treatment. Aqueous solutions of PVP-PEG 0–40% were spray dried using a Mini Büchi 190 spray dryer (Büchi) to obtain homogeneous samples. The spray-dried samples were vacuum-dried at 70 °C for 48 h in an oven. After vacuum-drying, the samples were stored in closed glass bottles. The PEG concentrations are expressed as a percentage (w/w PVP). All other reagents employed were of analytical reagent grade.

Water Sorption Isotherm—Approximately 400 mg of spray dried PVP, PVP-PEG 10%, and PVP-PEG 20% mixtures were accurately weighed into glass bottles and stored at 20 °C in desiccators containing saturated inorganic salt solutions giving various equilibrium relative humidities (RH) (7–75% RH) until a constant weight was obtained (at least 5 weeks). The salts used (with their corresponding relative humidities at 20 °C) were lithium bromide (7% RH), lithium chloride (11% RH), potassium acetate (23% RH), magnesium chloride (33% RH), potassium carbonate (43% RH), magnesium nitrate (54% RH), sodium bromide (59% RH), and sodium chloride (75% RH). The water content of the samples was calculated using the initial water content and the change in weight induced by storing the samples under each relative humidity condition. The initial water content of the samples was determined by drying at 120 °C for 5 h.

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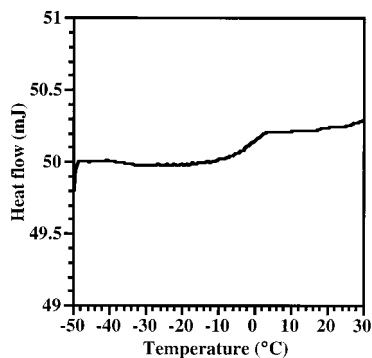


Figure 1—Typical DSC curve of a PVP–water system (glass transition).

Determination of T_g by DSC—Differential scanning calorimetry (DSC) measurements were performed using a Perkin-Elmer DSC 7 with a refrigerating system (Perkin-Elmer, Beaconsfield, UK). Samples (3–8 mg) stored under various RH were carefully transferred into aluminum pans in the desiccator, and the pans were hermetically sealed to prevent water loss during the DSC experiments. The samples were placed into the DSC under a nitrogen atmosphere and heated to 10–25 K above their T_g . The samples were subsequently cooled at 20 K/min to 273 or 223 K and then reheated. The first heating run exhibited an enthalpy relaxation endotherm at around the T_g value. Therefore, the T_g value of the samples was determined from the second heating cycle. Figure 1 illustrates a typical DSC curve of the second run for a sample of the PVP–water system (PVP stored under 75% RH). The T_g value was calculated by the half-extrapolated capacity method.⁹ No endothermic peak relating to the melting of PEG was found even in the DSC curves of the PVP–PEG 10% and PVP–PEG 20% mixtures.

For determination of the T_g value of samples containing no water, samples (4–7 mg) were stored over P_2O_5 in a sealed desiccator for more than 5 weeks and DSC studies were carried out in open aluminum pans. The samples were repeatedly heated to 10–25 K above their T_g and subsequently cooled to 273 K at 20 K/min under a dry nitrogen purge. As the samples exhibited negligible differences between the T_g value determined from the second heating cycle and that from the third heating cycle, the T_g value determined from the second heating cycle was considered as the T_g value of the sample containing no water. All experiments were performed at least twice.

Determination of Freezing Water by DSC—To determine the amount of freezing water in the systems, a Perkin-Elmer DSC 7 with a cooling accessory (Perkin-Elmer, Beaconsfield, UK) was also used. Samples (5–15 mg) of various concentrations of aqueous PVP solution containing 0%, 10%, and 20% PEG were transferred into hermetically sealed aluminum pans to prevent water loss during the experiments. Samples were placed into the DSC and cooled to 223 K to promote freezing of any unbound water. Then, they were heated at 10 K/min to 303 K under a nitrogen atmosphere. Figure 2 depicts some typical melting endotherms of PVP–water systems. In the DSC curves, a small baseline change (occasionally small peak) is found at around 243 K (–30 °C). It seems that the baseline changes are caused by heterogeneity in the system, and the changes may be attributed to the glass transition or recrystallization. However, as the changes are considerably small and are not sometimes reproducible, it is difficult to determine what causes them only from the conventional DSC studies. Therefore, in this study, only the enthalpy of fusion of ice corresponding to the amount of freezing water was determined. Determination by other methods such as a modulated temperature DSC is necessary to elucidate what causes the baseline changes. The experiments were performed at least three times.

Equation To Predict the Value of the T_g^{mix} of the Systems—An equation for the prediction of the value of the T_g of a ternary system was employed. This equation is an extension of the Gordon–Taylor equation,^{8,10} the equation for the prediction of the T_g value of a binary system. By assuming perfect volume additivity at the T_g and no specific interaction among the three systems, we can write

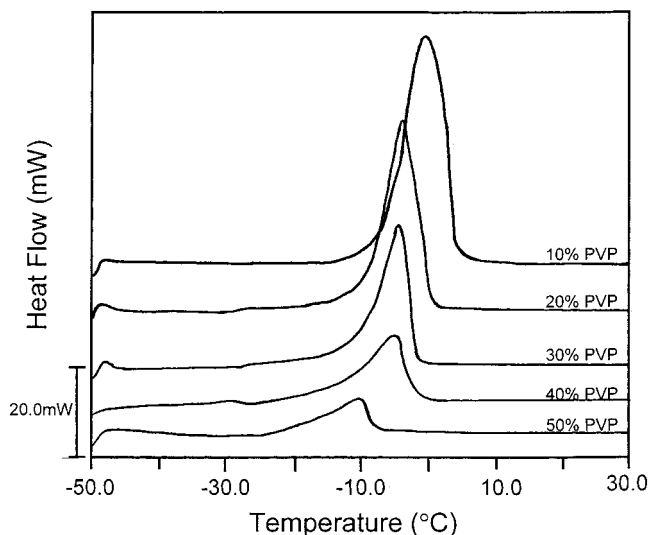


Figure 2—Typical DSC curves of PVP–water systems (melting peak).

$$T_g^{\text{mix}} = \Phi_1 T_{g1} + \Phi_2 T_{g2} + \Phi_3 T_{g3} \quad (1)$$

where F is the volume fraction of each component. As $\Phi = [(\Delta\alpha w)/\rho]$, where $\Delta\alpha$ is the change in thermal expansivity of T_g and $\Delta\alpha T_g \approx \text{constant}$,¹¹ it is possible to rewrite the equation as

$$T_g^{\text{mix}} = \frac{w_1 T_{g1} + K_2 w_2 T_{g2} + K_3 w_3 T_{g3}}{w_1 + K_2 w_2 + K_3 w_3} \quad (2)$$

where w_1 , w_2 , and w_3 are the weight fractions, and T_{g1} , T_{g2} , T_{g3} , and T_g^{mix} are the glass transition temperatures in Kelvin of components 1, 2, 3, and the mixture.¹² The constants K_2 and K_3 can be approximated as $K_2 = (\rho_1 T_{g1})/(\rho_2 T_{g2})$ and $K_3 = (\rho_1 T_{g1})/(\rho_3 T_{g3})$, where ρ is the density of the materials. This equation is the Gordon–Taylor equation when we consider $w_3 = 0$. The constants K_2 and K_3 were calculated from the value of the T_g of 135,¹³ 450, and 198 K¹³ (–138, 177, and –75 °C, respectively) for water, PVP, and PEG and the densities of 1.00, 1.25, and 1.12 g/cm³, respectively. The densities were measured using an air pycnometer (Air comparison pycnometer model 930, Beckman).

A similar equation, eq 3, can be readily derived for mixtures containing i components

$$T_g^{\text{mix}} = \frac{\sum K_i w_i T_{gi}}{\sum K_i w_i} \quad (3)$$

where $K_i = (\rho_1 T_{g1})/(\rho_i T_{gi})$.

X-ray Powder Diffraction—X-ray powder diffraction patterns were monitored by a diffractometer with $\text{Cu K}\alpha$ radiation and a nickel filter at 40 kV and 40 mA (RINT 2200V, RIGAKU). The samples of spray-dried PVP, PVP–PEG 10%, and PVP–PEG 20% stored over P_2O_5 in a sealed desiccator were transferred into a sample holder and scanned at 4°/min over a range of 2°–40°. All samples exhibited halo X-ray powder diffraction patterns and were considered to be amorphous.

Multiple Regression Analysis—A nonlinear multiple regression program, MULTI, developed by Yamaoka et al.,¹⁴ was used to carry out multiple regression analysis. The correlation coefficient (r) was calculated using the following equation

$$r = \left(1 - \frac{\text{ESS}}{\text{EMS}}\right)^{1/2} \quad (4)$$

where ESS is the sums of squares of the deviation of the theoretical values from the experimental values and EMS is the sum of squares of the deviation of the experimental values from their mean.

Statistical Analysis—The calculated maximal amount of non-freezing water in PVP and PVP–PEG mixtures was statistically

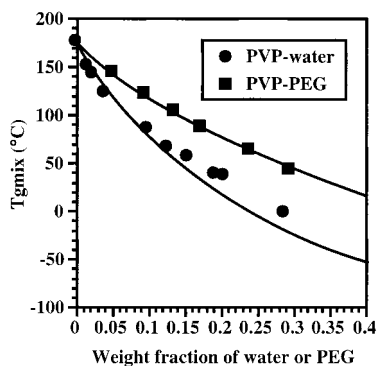


Figure 3—Effect of the weight fraction of water or PEG on the T_g^{mix} of PVP–water or PVP–PEG systems. The symbols represent experimental data points and the solid line represents the fit to the Gordon–Taylor equation (eq 2 in the text).

compared among each other using the Student's t test. Differences with $p < 0.05$ were considered significant.

Results and Discussion

Glass Transition Temperature of PVP–PEG and PVP–Water Binary Systems—Figure 3 shows the T_g value of PVP–water and PVP–PEG binary systems as a function of the weight fraction of water or PEG. The solid lines on the plots represent T_g values predicted by the Gordon–Taylor equation (eq 2). The T_g value decreases significantly with increasing weight fraction of water or PEG, showing that water as well as PEG acts as a good plasticizer. In the case of the PVP–PEG systems, the experimental T_g data fitted the predicted values well over the entire range studied. Therefore, it is considered that PVP and PEG mix ideally over the entire range studied (0–0.29 weight fraction of PEG). In the case of the PVP–water system, above a water fraction of around 0.1, the experimental T_g values for the PVP–water system were higher than predicted, whereas below this water fraction there was no difference between the experimental and theoretical T_g values. The results obtained for the PVP–water system are in excellent agreement with previous findings.⁸ It is considered that PVP and water are miscible ideally up to a water fraction of around 0.1, but they mix nonideally above this water fraction. In other words, it seems that the Gordon–Taylor equation is not suitable to predict the T_g values of the PVP–water system above a water fraction of around 0.1. There could be other factors affecting the systems, which are not taken into consideration in the Gordon–Taylor equation.

Glass Transition Temperature of PVP–PEG–Water Ternary Systems—Two amorphous PVP–PEG systems containing 10% and 20% PEG (0.09 and 0.17 weight fraction of PEG in the PVP–PEG systems, respectively) were chosen to determine the effect of water on the T_g values in the PVP–PEG–water systems. At these PEG fractions, PVP and PEG mix ideally, as stated above. Figure 4 depicts the T_g value of these two ternary systems of PVP–PEG–water as a function of the weight fraction of water. The solid lines on the plots represent values of T_g^{mix} predicted by the extended Gordon–Taylor equation (eq 2). As can be seen, the T_g data fitted the predicted T_g values well up to a water fraction of around 0.12 for the PVP–PEG 10%–water system and up to a water fraction of around 0.16 for the PVP–PEG 20%–water system. Therefore, it is suggested that these three components are miscible ideally with each other at a low water content. However, above a certain water content, deviations between the experimental and theoretical T_g values of the

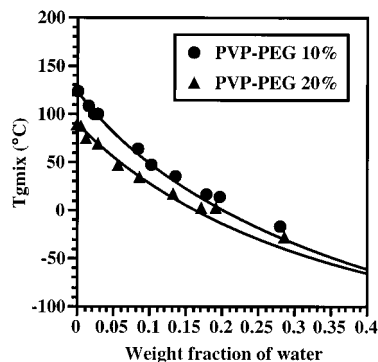


Figure 4—Effect of the weight fraction of water on the T_g^{mix} in PVP–PEG–water systems. The symbols represent experimental data points and the solid line represents the fit to the extended Gordon–Taylor equation (eq 2 in the text).

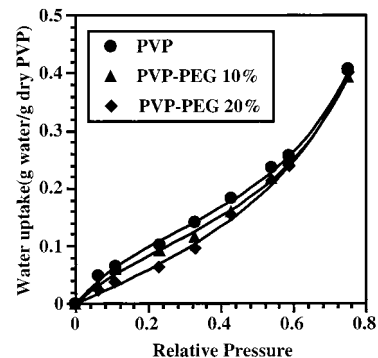


Figure 5—Water vapor absorption isotherms for PVP and PVP–PEG at 20 °C. The symbols represent experimental data points and the solid lines on the plot represent curve-fitted values using the GAB equation (eq 5 in the text).

PVP–PEG–water system were observed, as in the PVP–water system. It should be noted that the water fraction at which the deviations begin increases with the concentration of PEG (0%, 10%, 20%) in the sample.

Water Vapor Sorption Isotherms for PVP and PVP–PEG Mixtures—It is suggested that the miscibility between water and PVP or PVP–PEG systems changes at a certain water content based on the T_g studies. The interaction of water with other components has also been estimated by studies of water vapor sorption isotherms. W_m , the weight of adsorbed water required to form a complete monolayer on the solid surface, is one of the critical factors needed to characterize quantitatively the water sorption isotherms. W_m is calculated by fitting the sorption isotherm to the Brunauer–Emmett–Teller (BET) equation¹⁵ or the Guggenheim–Anderson–DeBoer (GAB) equation,^{16–18} which is an extension of the BET equation. The BET and GAB equations are generally applied to physical adsorption. The mechanism of water sorption to an amorphous solid like PVP is different from that of physical adsorption. However, even in an amorphous solid, it has been suggested that there is evidence indicating that at the point on the isotherm corresponding to the water content of W_m (apparent W_m), certain effects of water on solids change significantly and the apparent W_m value can be an important parameter relating to the interaction of polymer with water.^{19–21}

Figure 5 shows the water vapor sorption isotherms for PVP containing 0%, 10%, and 20% PEG at 20 °C. The water content at each RH decreases with increasing concentration of PEG in the samples and the water uptake is significantly inhibited by the addition of PEG at 20–50% RH. All the water sorption isotherms of PVP and PVP–PEG are sigmoidal in shape (type II²²). Therefore, the GAB equation,

given by eq 5, (where k is the GAB constant, W is the mass of gas sorbed per mass of dry solid at a relative pressure of p/p_0 , and C_B is a constant which reflects the overall free energy of sorption)

$$W = \frac{kW_m \frac{p}{p_0} C_B}{\left(1 - k \frac{p}{p_0}\right) \left(1 - k \frac{p}{p_0} + k C_B \frac{p}{p_0}\right)} \quad (5)$$

was fitted to the data and the apparent W_m values were obtained by multiple regression analysis, though mixtures such as the PVP-PEG system are different from the systems for which the GAB equation was originally intended. As shown in Figure 5, the calculated W values, which are represented as a solid line, fitted the experimental W values very well for PVP containing 0%, 10%, and 20% PEG systems with a correlation coefficient greater than 0.995. The values of apparent W_m calculated are 0.124, 0.133, and 0.173 g of water/g of solid (0.110, 0.117, and 0.147 weight fraction of water, respectively) for PVP containing 0%, 10%, and 20% PEG, respectively. The relative humidities at which the W value is equal to the calculated apparent W_m value, (the RH(W_m)) was 28%, 36%, and 48% RH for PVP containing 0%, 10%, and 20% PEG, respectively. The apparent W_m value increases with the concentration of PEG in the sample. This suggests that in the sample containing a higher concentration of PEG, the interaction with water changes significantly when a larger amount of water is sorbed (the apparent W_m).

As mentioned above, the deviation of the experimental T_g values from those predicted seems to begin at a higher weight fraction of water in the sample containing a higher content of PEG. Also, the apparent W_m values increase with increasing PEG concentration in the sample. It should be remembered that the experimental T_g values were measured using a nonisothermal method (DSC), whereas the W_m values were estimated from isothermal measurements (the sorption isotherms). However, both values, the apparent W_m values and the weight fraction at which the deviation of the experimental T_g values seems to begin, are similar, which suggests that water interacts ideally with the polymer up to the higher water content in the sample containing the higher amount of PEG.

The Maximal Amount of Nonfreezing Water in PVP and PVP-PEG Mixtures—When samples contain immiscible water, the system shows a melting peak of water at 0 °C or less during heating after prior cooling. This component of water in the system can be regarded as freezing water, which is classified into two types,^{23,24} type I, free, freezing water melting at 0 °C; and type II, loosely bound, freezing water with a melting point below that of pure water. Nonfreezing water is classified as type III. The PVP and PVP-PEG samples stored under conditions of RH up to 75% showed no melting peak of water in the DSC experiments. Consequently, no detectable freezing water exists in these systems, though some of them have the appearance of a transparent gel. Thus, to determine the interaction of water with PVP and PVP-PEG over a wide range, the melting peak of water in various concentrations of aqueous PVP and PVP-PEG solutions was detected using DSC, and the maximal amount of nonfreezing water which can be contained in the PVP-water and PVP-PEG-water systems was calculated.

Two methods have been applied to obtain the maximal amount of nonfreezing water in a polymer-water system.²⁵ Sung²⁶ reported that when there is a linear relationship between the enthalpies of water (J/g of dry polymer) and the ratio of water to polymer, the extrapolation to zero

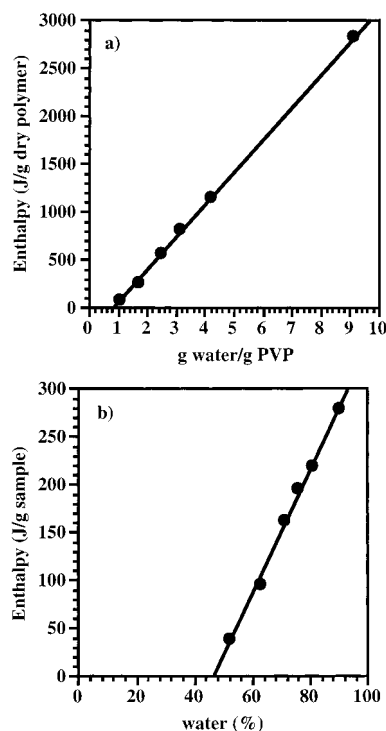


Figure 6—Relationship between (a) enthalpies of fusion and water/PVP ratio for PVP solutions (Sung's plot) and (b) enthalpies of fusion and water percentage for PVP solutions (Ford and Mitchell's plot).

enthalpy gives the maximal amount of nonfreezing water in the system. Ford and Mitchell²⁷ also reported that when a linear relationship exists between the enthalpies of water (J/g of sample) and the percentage of water in the system, the maximal amount of nonfreezing water in the system is calculated from the extrapolation to zero enthalpy. Figure 6a,b shows Sung's plot and Ford and Mitchell's plot for the PVP-water system. In both cases, there is a linear relationship between the enthalpies of water and the ratio of water to polymer or the percentage of water. From both Sung's plot and Ford and Mitchell's plot, the maximal amounts of nonfreezing water are calculated to be around 0.47 of the weight fraction of water, corresponding to around 5.4 mol of water per polymer repeating unit (PRU) of PVP. Although the experimental T_g values could not be measured due to the limitations of the cooling system (minimum temperature 223 K), it is expected that more than one T_g value would be detected in the sample containing freezing water due to its heterogeneity.^{12,28}

In the case of the ternary systems, Sung's method does not seem to be suitable for obtaining the maximal amount of nonfreezing water, because it is impossible to calculate the enthalpies of water based on J/g of dry polymer. Therefore, only the Ford and Mitchell method was applied to obtain the maximal amount of nonfreezing water. As shown in Figure 7, there is a linear relationship between the enthalpies of water (J/g of sample) and the percentage of water in both PVP-PEG 10% and 20% systems. The maximal amount of nonfreezing water is calculated to be 0.49 and 0.51 for PVP-PEG 10% and 20% systems. These results indicate that freezing water is detected above 0.47, 0.49, and 0.51 weight fraction of water for PVP containing 0%, 10%, and 20% PEG, respectively. These values were analyzed to be significantly different. It is suggested that as PEG interacts with larger amounts of water compared to PVP, larger amounts of water can exist as nonfreezing water by adding PEG to PVP.

The Miscibility between Water and PVP or PVP-PEG Systems—From the results obtained above, the

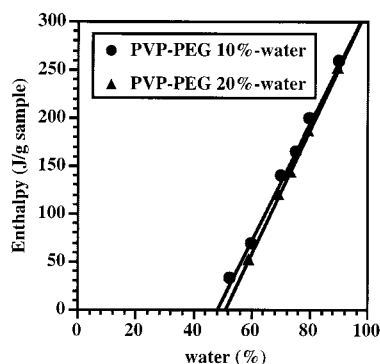


Figure 7—Relationship between enthalpies of fusion and water percentage for PVP-PEG solutions (Ford and Mitchell's plot).

miscibility between water and PVP can be expressed with certain assumptions as follows: up to the apparent W_m value (around 0.1 weight fraction of water), PVP and water mix ideally and the experimental T_g values of the PVP-water system can be estimated using the Gordon-Taylor equation. It has been reported that the interaction between the hydrophilic polymer and water may change according to the water content.⁶ For example, in the case of amylose-water systems, it was assumed that the polymer-water system formed by hydrogen bonds is more compact than the polymer-polymer system with less than 10% water content and that a looser network is formed due to the occurrence of water-water interactions at a higher water content. As the miscibility of PVP and water also relates to the hydrogen bonds between them, it is speculated that the interaction between PVP and water changes at the weight fraction of around 0.1. This water fraction corresponds to the ratio of two water molecules ($M_w = 18$) to three PRU of PVP (PRU of PVP = 111).

On the other hand, above a 0.47 water weight fraction of water, corresponding to around 5.4 mol of water per PRU of PVP, freezing water is detected in the PVP-water system. It is expected that more than one T_g value may be detected due to the heterogeneity in the system. At a weight fraction of water of 0.1–0.47, though water still exists as nonfreezing water in the system, the miscibility of water and PVP must have decreased as the experimental T_g value did not decrease as much as predicted. In the case of maize starch and hydroxypropylmethyl cellulose, it has been reported that three states of sorbed water, internally adsorbed water, monolayer-adsorbed water, and externally adsorbed water, could be estimated by analyzing the water sorption and desorption patterns using the Young-Nelson equations.^{25,29} The interaction between water and solid is considered to be significantly influenced by these states of water. In the case of the PVP-water system, as the hypotheses based on the Young-Nelson equations are inadequate, the three states of water cannot be calculated using the Young-Nelson equations.

In the PVP-PEG-water systems, though the interaction among the three components are more complicated, it is speculated that the miscibility between water and the PVP-PEG system can be expressed, as in the case of PVP, except that both the apparent W_m values (or water fraction at which the deviations of the T_g values begin) and the maximal amount of nonfreezing water increase with increasing concentration of PEG in the sample. In the PVP-PEG-water systems, it may fairly be presumed that the three components interact with each other by hydrogen bonds. The PRU of PEG (CH_2OCH_2 , PRU of PEG = 44) is smaller than the PRU of PVP (111) and PEG has more groups that may interact with water from the hydrogen bonds than PVP. Therefore, this may explain why PVP containing the higher concentration of PEG interacts with

water up to the higher water fraction (the apparent W_m and the maximal amount of nonfreezing water).

Conclusion

The interaction between water and PVP containing 0%, 10%, and 20% PEG was studied using DSC and water sorption isotherms. The miscibility between water and PVP seems to change according to the water content in the system. Up to the apparent W_m value (around 0.1 weight fraction of water), PVP and water mix ideally and the experimental T_g values of the PVP-water system can be estimated using the Gordon-Taylor equation. From a 0.1 weight fraction of water to 0.47, which is calculated as the maximal amount of nonfreezing water, although water still exists as nonfreezing water in the system, the miscibility of water and PVP must have decreased as the experimental T_g value did not decrease as much as predicted. On the other hand, at a water weight fraction above 0.47, freezing water was present in the system and it is expected that there may be more than one T_g value due to the heterogeneity in the system. All parameters, the water fraction at which the deviation of the T_g values begins, the apparent W_m value, and the maximal amount of nonfreezing water, increase with the concentration of PEG in the sample. This may be explained by the fact that PEG has more polymer repeating units, which may interact with water more than PVP.

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