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INVESTIGATIONS REGARDING THE DETERMINATION OF GLASS TRANSITION TEMPERATURES FROM MOISTURE SORPTION ISOTHERMS

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ABSTRACT

Moisture sorption isotherm and glass transition temperature (T_g) data on polyvinylpyrrolidone (PVP) of molecular weights less than or equal to 40,000 as well as PVP containing added plasticizers were collected to examine the possibility of extracting T_g values from moisture sorption data. Moisture sorption isotherms generated for PVP of various molecular weights were similar to those previously reported. The moisture sorption isotherm for PVP-K15 containing added vinylpyrrolidone (VP) and methylpyrrolidone (MP) were predicted reasonably well by simple addition of their respective isotherms with that of PVP-K15. The T_g values for PVP as a function of moisture was similar to that found previously. Decreasing polymer molecular weight or the addition of plasticizers (VP or MP) reduced the T_g of the polymer system, displacing the T_g to lower temperatures. When the moisture content to give a T_g of 25°C (W_g) was indicated on the isotherm, W_g shifted downward with decreasing molecular weight or increasing plasticization by VP or MP while the shape of the isotherm was not distinguishably altered. Consequently, W_g, and thus T_g, would be difficult to extract from the moisture sorption isotherm.

INTRODUCTION

Interest in the concept of glass transition has increased during recent years. The applicability of glass transition principles has permeated from polymer and material science into such areas as food science, pharmaceutics, and biotechnology. The physical, and possibly chemical, stabilization of foods, drugs, and lyophilized biological materials is a primary reason for the increase in glass transition research. Tablet properties (1), crystallization of excipients or drugs (2,3), collapse of lyophilized formulations (4,5), and free flowability of powders (6) are aspects of pharmaceutical formulations influenced by the glass transition.

The glass transition is a physical change in the properties of an amorphous material promoted by the addition of heat or the uptake of low molecular weight substances (i.e., plasticizers). Below the glass transition temperature (T_g), a material is in the glassy state which is described as rigid yet brittle, having a high internal viscosity and very low mobility and diffusion (7-9). As the temperature increases through and above the T_g, the glassy material becomes soft or rubbery, with the viscosity and modulus decreasing by a factor of a thousand and molecular mobility increasing sharply (7-9). As mentioned, a glassy substance can become rubbery by the uptake of plasticizers. Thus, moisture sorption into polymeric systems is a plasticizing phenomenon as shown with oligosaccharide systems (10).

Moisture sorption isotherms depict the relation between water activity (i.e., relative vapor pressure) and equilibrium moisture content. Moisture sorption is influenced by several factors including dissolution of solutes, capillary effects, and the interaction of water with chemical groups on the surface (11). These surface interactions are responsible for the monolayer as determined by the Brunauer-Emmett-Teller, BET, (12) or Guggenheim-Anderson-DeBoehr, GAB, (11,13) equations. The GAB equation is shown below where a_W is the water activity, M is the moisture content, m_o is the monolayer, and C and k are energy terms associated with the sorption process (11,13):

$$M=\frac{m_o kCa_W}{(1-ka_W)(1-ka_W+kCa_W)} \tag{1}$$

Although semi-empirical, the GAB remains to be frequently used. Additional thermodynamic aspects of moisture sorption have been discussed previously (14).

It has also been suggested that moisture sorption isotherms are influenced by mechanosorption and macroscopic properties, such as modulus (15-18). If these play a role in equilibrium moisture sorption, then a glassy material would be expected to have different equilibrium sorption properties than the same material in the rubbery state. Oksanen and Zografi (16) have observed that the upper inflection point of moisture sorption isotherms for polyvinylpyrrolidone (PVP-K30) occurs near the point where the moisture content reduces the T_g to the temperature of the isotherm. This implies that glass transition temperatures may be able to be extracted from equilibrium moisture sorption data. Using moisture sorption data to obtain glass transition temperatures is currently being attempted in industrial drug development. At the 1993 annual meeting of the American Association of Pharmaceutical Scientists, the application of this concept was mentioned both in a short course on water-solid interactions (19) and in a symposium on the freeze-drying of pharmaceuticals (20), again indicating its current use.

Vrentas and Vrentas (17) proposed a model to predict the impact of structural changes encountered during relaxation on equilibrium sorption of penetrants into glassy polymers; their model was derived from the Flory-Huggins equation. Sorption isotherm predictions, using this model, for carbon dioxide into polycarbonate were in reasonable agreement with experimental data. Hancock and Zografi (18) used this model to characterize moisture sorption into PVP and concluded it was able to describe the observed trend of the entire sorption isotherm. The combined Vrentas/Flory-Huggins equation, in the form of moisture as the penetrant, is shown in equation (2).

$$a_W = v_1 e^{[v_2 + \chi(v_2)^2]} e^F \tag{2}$$

In this equation, a_W is the water activity, v_1 is the volume fraction of water, χ is the polymer-solvent interaction parameter, v_2 is the volume fraction of polymer, and

$$F = \frac{M_1(w_2)^2(\Delta C_p)(dT_{g(m)}/dw_1)[(T/T_{g(m)})-1]}{RT} \tag{3}$$

In the above equation, M_1 is the molecular weight of water, w_2 is the weight fraction of polymer, ΔC_p is the change in heat capacity from the glassy state to the rubbery state, $dT_{g(m)}/dw_1$ is the slope of the glass transition diagram, T is the temperature, $T_{g(m)}$ is the glass transition temperature, and R is the ideal gas constant. Thus, it may appear that T_g values can be determined from a mathematical manipulation of moisture sorption data using equations (2) and (3).

The prediction of T_g values from moisture sorption data, if possible, would enable T_g values to be estimated for systems in which the T_g has been difficult to measure by differential scanning calorimetry (e.g., globular proteins). The ability to determine T_g values from equilibrium moisture sorption data could be effectively investigated in the absence of secondary temperature effects if studied at constant temperature. Two approaches can be explored, the use of varying polymer molecular weight and the addition of non-aqueous plasticizers. Both approaches will enable shifting the T_g while maintaining a constant temperature. Thus, the purpose of this project was to evaluate the potential for using moisture sorption isotherms for estimating glass transition temperatures.

MATERIALS & METHODS

Materials. Polyvinylpyrrolidone (PVP-K15), having a number average molecular weight 10,000, was obtained from Sigma (St. Louis, MO) as was PVP-K30, having a number average molecular weight of 40,000. The PVP-K15 and PVP-K30 were both used as received. Vinylpyrrolidone (VP) and methylpyrrolidone (MP) were selected as non-aqueous plasticizers because of their structural similarities to PVP. VP (Aldrich, Milwaukee, WI) and MP (Janssen Chimica, Belgium) were used as received. Salts employed as saturated solutions included LiCl, $MgCl_2$, K_2CO_4, NaCl, and KCl from Mallinckrodt (Paris, KY) as well as $Mg(NO_4)_2$ and $CoCl_2$ from Sigma.

Sample Preparation. Concentrated solutions (350-450 mg/mL) of PVP-K15, 94% PVP-K15 with 6% VP, 88.8% PVP-K15 with 11.2% VP, 89.7% PVP-K15 with 10.3% MP, and 79.7% PVP-K15 with 20.3% MP were prepared (w/w basis). The solutions were dripped via a syringe with a 22 gauge needle into a beaker containing liquid nitrogen. The frozen pellets were lyophilized in a chamber lyophilizer (The Virtis Company, Inc., Gardiner, NY) for 2 d at 20 mtorr and 25°C. These samples were then stored over drierite until further use. The amount of plasticizer lost due to volatilization during lyophilization was minimal, resulting in approximate final concentrations of 6% and 11% VP and 10% and 20% MP. A portion of PVP-K15 was dialyzed using a 3500 MWCO tubing for 48 hr and four 1500 mL washes with purified water. The first dialysate containing components below a molecular weight of 3500 was lyophilized in a tray for 2 d at 20 mtorr and 35°C. The lyophilized powder was stored over drierite. Initial moistures for the lyophilized samples containing PVP-K15 were determined by Karl Fischer to be 1 to 2.5%, prior to storage over drierite. The initial moisture of PVP-K30 was 4 to 4.5% as determined gravimetrically by transferring to a vacuum desiccator containing drierite at 40°C for 4 d.

Moisture Sorption. Samples of the dried material were weighed into glass vials and stored in desiccators over saturated salt solutions. The PVP samples were found to equilibrate after 4 days, as determined by no change in mass at subsequent times. Moisture sorption isotherms were constructed, correcting for the initial moisture content; the apparent monolayer values were calculated using the GAB equation.

The amount of MP volatilized during moisture equilibration from the 20% MP/PVP-K15 system was evaluated by HPLC. The MP/PVP system was dissolved into water. The resulting solution was injected into a 25/75 methanol/water mobile phase and passed through two 10 cm 5 μm C-18 columns in series at 1 mL/min. MP eluted at 5.3 min and was detected at 229 nm. The percent MP remaining in samples equilibrated at a water activities of 0.33 and 0.75 as compared to the non-equilibrated sample were 77% and 88%, respectively. The sample at water activity 0.75 collapsed, which together with the reduced vapor pressure of MP due to the sorbed moisture, retained MP better than the sample at water activity 0.33. The amount of VP volatilized would be expected to be less than MP because VP is less volatile. In addition, the glass transition temperature of these systems indicated significant plasticizer remained after moisture equilibration.

Due to the volatility of pure VP and MP, traditional moisture sorption isotherms for VP and MP could not be determined. Thus, solutions containing known mass fractions of water and VP or MP were prepared and the water activity measured using a Hygroscop DT (Rotronic Instrument Corp., Huntington, NY). The instrument was calibrated using saturated salt solutions of known water activities and rechecked after exposure to the mixtures to rule out possible errors due to the potential interaction of MP and VP with the sensor.

Glass Transition Determination. Samples of the equilibrated material as well as the dry material were analyzed for glass transition temperatures (T_g) by differential scanning calorimetry (DSC) using a Perkin Elmer DSC-4 (Perkin Elmer Corporation, Norwalk, CT). Samples were hermetically sealed into aluminum pans to prevent moisture loss. The pans held 3 to 15 mg depending upon bulk density. The scan rate was set at 5°C/minute. The temperature range of the DSC run depended upon the expected glass transition temperature. Low moisture samples of PVP-K15 were ran from 20 to 120°C while PVP-K30 was ran from 50 to 200°C. For higher moisture samples, the temperature range was changed to -40 to 50°C. The glass transition was identified as an endothermic baseline shift upon heating the sample which was reversible upon a rescan. Reweighing of the pan with sample after the DSC run indicated no change in mass (i.e., no moisture loss). The onset T_g value was used in this study.

RESULTS AND DISCUSSION

Moisture Sorption. The moisture sorption into the PVP systems were similar. The GAB monolayer values of the systems ranged from 10 to 21 g water/100 g solids, while the upper inflection range occurred at 20 to 25 g water/100 g solids (Table 1). These values are larger than those found previously using the BET equation (16,21). As PVP molecular weight decreased, the amount of equilibrium moisture sorption showed a trend toward lower values, which were minimally discernible (see Figure 6 later). This effect was also shown by the insignificant drop in the monolayer values as a function of decreasing molecular weight ($P > 0.05$). The trend toward decreasing penetrant sorption with decreasing molecular weight was also observed with carbon dioxide sorbing into polystyrene (22).

The moisture sorption isotherms for plasticized PVP-K15 were also quite similar to that of PVP-K15. The equilibrium moisture content of systems containing 6 and 11% VP was slightly less at a given water activity than pure PVP-K15 as seen by the monolayer value for the 11% VP system being significantly lower ($P < 0.05$) than the PVP-K15 system and the 6% VP system. This was indicative of a mixture containing two components of different moisture sorption capabilities. VP has a lower moisture sorption than PVP-K15 while MP has a higher moisture sorption (Figure 1). PVP-K15 containing 10 and 20% MP had isotherms which crossed over that of PVP-K15, having a higher moisture content at water activities of greater than 0.4 to 0.5. The monolayers for the MP systems were not significantly different ($P > 0.05$) from the monolayers of other systems. Despite the small shifts in moisture content at a given water activity, the isotherms for the seven systems were quite similar.

If a mixture of two substances has minimal interactions, then the composite moisture sorption isotherm can be generated by summing the moisture mass fractions of the individual isotherms at each water activity (13). Figure 2 shows the predicted moisture sorption isotherms based on summing the individual isotherms of MP and PVP-K15 for the 10% MP system and VP and PVP-K15 for the 11% VP system. There was good agreement between the predicted sorption isotherm and the actual sorption data. The additive nature of the plasticized polymer isotherms suggests that the reduction of the glass transition temperature by nonaqueous plasticizers had a minimal effect on water uptake.

Glass Transition Temperatures. In the dry state, the T_g values of LMW-PVP (MW < 3500), PVP-K15, and PVP-K30 were 45°C, 100°C, and 180°C, respectively. As moisture was sorbed, the T_g decreased as expected. The current T_g data is consistent with the other data in the literature (16,21,23). The T_g increased as molecular weight increased as expected based on polymer theory (7). For PVP, the critical molecular weight above which the T_g becomes independent of molecular weight is around 40,000 (16,21). The influence of molecular weight on the T_g values of PVP at different moisture contents is depicted in Figure 3.

Both of the low molecular weight additives, VP and MP, act as plasticizers, reducing the glass transition temperature at a given moisture content. In the dry state, the T_g of PVP-K15 systems containing 6% VP, 11% VP, 10% MP, and 20% MP were 63, 50, 45, and 30°C, respectively, as compared to the T_g of 100°C for pure PVP-K15. The impact of moisture on the glass transition diagrams of the PVP plasticized with VP is shown in Figure 4. However, the dramatic influence of non-aqueous plasticization on the T_g was not parallelled on the moisture sorption isotherm.

TABLE 1.

Moisture Contents (g H_2O/100 g solids) Associated with Monolayer, Upper Inflection Point, and Glass Transition of PVP Systems.

Sample	GAB Monolayer	Range of Upper Inflection from Isotherm	Moisture Range for T_g = 25°C (W_g)
PVP-K30	17.1	20-25	26-32
PVP-K15	16.4	20-25	15-20
PVP (MW<3500)	14.8	20-25	5-10
PVP-K15 (6% VP)	21.3	20-25	8-12
PVP-K15 (11% VP)	9.6	15-20	5-10
PVP-K15 (10% MP)	16.3	20-25	5-10
PVP-K15 (20% MP)	21.3	20-25	1-4

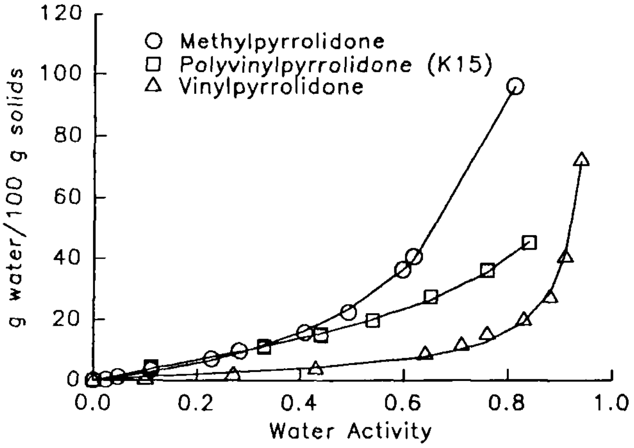

FIGURE 1.

Moisture Content as a Function of Water Activity for PVP-K15, Methylpyrrolidone, and Vinylpyrrolidone at 25°C as fit by the GAB Equation.

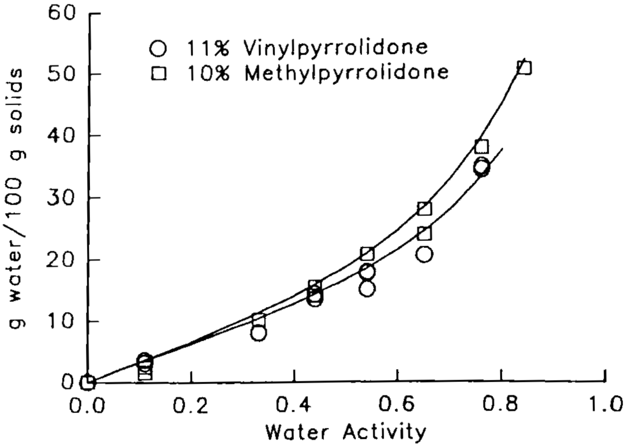

FIGURE 2.

Moisture Sorption Data and Curve Predicted Using Summation of Individual Isotherms for PVP–K15 with 10% Methylpyrrolidone and PVP–K15 with 11% Vinylpyrrolidone at 25°C.

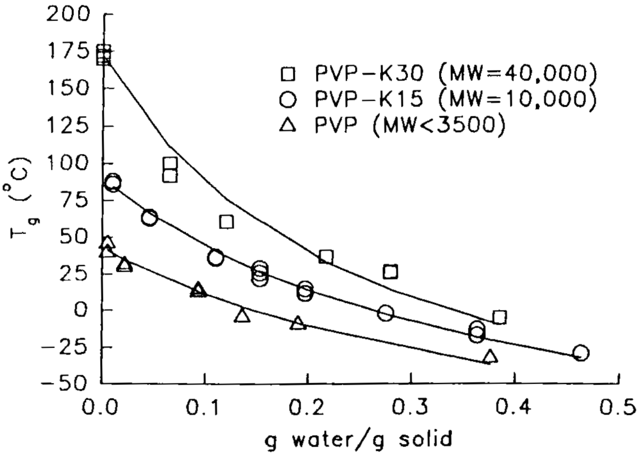

FIGURE 3.
Glass Transition Temperatures of PVP having Different Molecular Weights as a Function of Moisture Content.

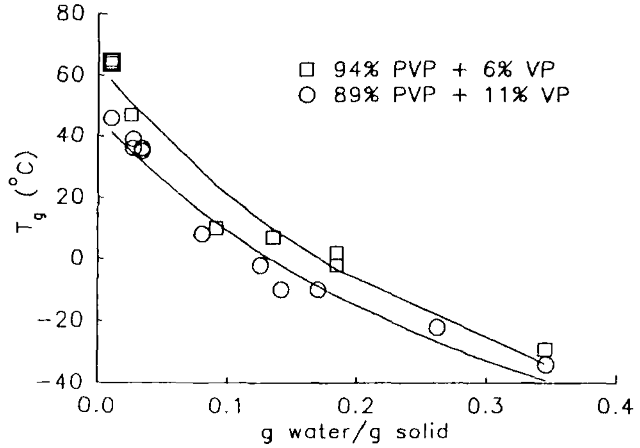

FIGURE 4.
Glass Transition Temperatures of PVP/VP Blends as a Function of Moisture Content.

Combined Moisture Sorption/Glass Transition. Table 1 lists the monolayer values, visual estimation of the upper inflection range of the moisture sorption isotherms, and the moisture content yielding a glass transition temperature of 25°C (W_g) for the current PVP systems. Again, the monolayer values for the PVP systems were between 10 and 20 g water/100 g solids. The range of the upper inflection point was around 20 to 25 g water/100 g solids. Little difference existed among the PVP moisture sorption isotherms as discussed earlier. However, the moisture content to produce a system having a T_g = 25°C varied tremendously between the systems. As the concentration of VP or MP increased, the value of W_g continually decreased. Figure 5 shows the composite moisture sorption isotherm for PVP-K15 with and without the two concentrations of MP plotted along with the value of W_g to illustrate the results.

As the molecular weight of PVP decreased, the value of W_g also decreased while the isotherms remained virtually identical. This is demonstrated in Figure 6, which is the composite moisture sorption isotherm for the PVP samples of different molecular weights with the values of W_g superimposed. Oksanen and Zografi showed that the values of W_g and the monolayer moisture content both changed with temperature (16). However, both of these parameters change similarly as a function of temperature. At constant temperature, PVP of different molecular weights have monolayers which are virtually the same while values of W_g differ dramatically. Thus, as seen in Table 1 and Figures 5 and 6, it is improbable that glass transition temperatures, as modified by nonaqueous plasticizers or polymer molecular weight, can be determined from the monolayer or inflection points from the moisture sorption isotherms.

These results suggesting that glass transition data cannot be extracted from moisture sorption isotherms appear to contradict the ability of the combined Vrentas/Flory-Huggins equation to successfully describe the moisture sorption isotherm for PVP-K30 using glass transition data (18). However, the general application of the

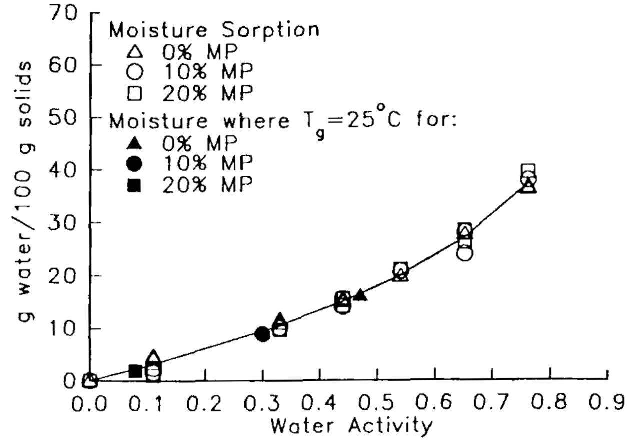

FIGURE 5.

Composite Moisture Sorption Isotherms for PVP-K15/MP Systems at 25°C fit by the GAB Equation with Glass Transition Moisture Contents Superimposed.

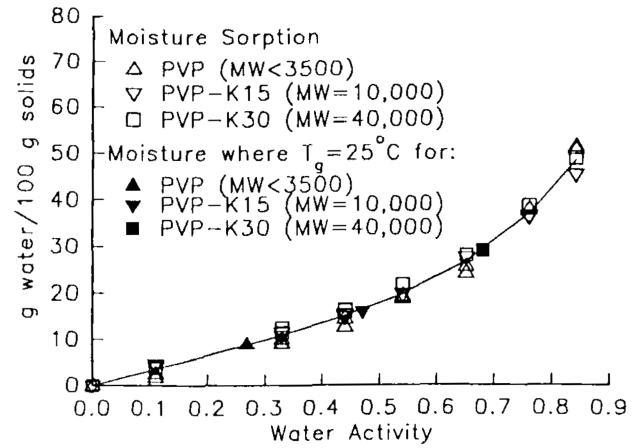

FIGURE 6.

Composite Moisture Sorption Isotherms for PVP Systems at 25°C fit by the GAB Equation with Glass Transition Moisture Contents Superimposed.

Vrentas/Flory-Huggins equation for calculating glass transition temperatures requires the solvent-polymer interaction parameter, χ, and the slope of the glass transition diagram, $dT_{g(m)}/dw_1$. If the instantaneous slopes of the glass transition diagram were known, there would be no need to calculate T_g from moisture sorption data (i.e., the T_g's would already be known as well). Thus, while the combined Vrentas/Flory-Huggins equation may provide the fundamental basis for describing the shape of the PVP-K30 sorption isotherm using glass transition data (18), it would be extremely difficult to mathematically extract glass transition temperatures from the moisture sorption isotherm without extensive knowledge about the system.

CONCLUSIONS

The extent or importance of a relationship between equilibrium moisture sorption and glass transition requires continued research. However, based on data from these hydrophilic systems, the simple extrapolation of glass transition data from moisture sorption isotherms, either visually or mathematically, is not accomplished without a much more extensive evaluation of the system's properties. Thus, attempting to extract the glass transition temperature from moisture sorption isotherms, as has been suggested (16), could lead to incorrect formulation or processing decisions in pharmaceutical research and development.

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