Pharmaceutical Research, Vol. 10, No. 9, 1993

Research Article

The Use of Solution Theories for Predicting Water Vapor Absorption by Amorphous Pharmaceutical Solids: A Test of the Flory–Huggins and Vrentas Models

Bruno C. Hancock[1] **and George Zografi**[1,2]

Received November 17, 1992; accepted March 1, 1993

The limitations of traditional gas adsorption models for describing water vapor sorption by amorphous pharmaceutical solids are described and an alternative approach based on polymer solution theories is proposed. The approach is tested by comparing *a priori* predicted isotherms with literature data for the poly(vinylpyrrolidone)(PVP)–water system. The well-known Flory–Huggins model is able to describe the water vapor sorption isotherm only when the PVP–water mixture is in the rubbery state (i.e., above its glass transition temperature). However, a newer model developed by Vrentas and coworkers, which takes into account the plasticizing effect of water on the polymer, is able to describe the entire form of the isotherm. Consideration of the parameters in this model allows a number of critical variables to be identified and also enables the characteristic shape of the water vapor sorption isotherm to be explained.

KEY WORDS: water vapor; moisture; sorption; amorphous; solution theory; glass transition temperature; plasticization.

INTRODUCTION

The tendency for pharmaceutical solids to sorb significant amounts of water vapor over a wide range of relative humidities and temperatures is well documented (1), as is the ability of such residual water to affect many of the critical physical and chemical properties of these solids (2). Typically the equilibrium water content of a solid (as a function of relative humidity at constant temperature) is information obtained during the preformulation and formulation stages of pharmaceutical development. Of particular interest in the context of this report is the situation where water vapor is absorbed into amorphous or partially amorphous solids. Such materials include many polymeric excipients [e.g., poly(vinylpyrrolidone), starch, microcrystalline cellulose] and small molecules (e.g., drugs, sugars) that have experienced high energy processing such as milling, drying, and compaction (2). The amount of water that is sorbed by these solids is greater than that which can be accounted for by surface adsorption because water is taken up into the bulk of the solid material. Usually the greater the polarity of the solid, and hence the greater the solubility of water in the solid, the greater is the extent of water uptake under any particular conditions.

Typically the water vapor absorption isotherm for an amorphous solid exhibits the form depicted in Fig. 1, with two deviations from linearity, one at high relative humidities and the other at low relative humidities. The deviation at low relative humidities usually appears as a "shoulder" and is typical of "Type II" isotherms observed for gas adsorption processes (3). This is in contrast to "Type III" gas adsorption isotherms, where no initial shoulder occurs. In view of the similarity of the water vapor absorption isotherms to those obtained from gas adsorption experiments, it has been very common to fit water vapor sorption data to equations originally derived for gas adsorption processes. By far the most popular approach has been to use the well-known BET equation (4):

$$W = \frac{W_m C_B(p/p_0)}{[1 - (p/p_0)][1 - (p/p_0) + (C_B(p/p_0))]} \quad (1)$$

where W is the mass of water absorbed per unit mass of solid, p/p_0 is the relative vapor pressure of the water (100 p/p_0 = % relative humidity), and W_m and C_B are constants.

For gas adsorption W_m is defined as the mass of gas forming a complete monolayer on the solid surface, and it is usually taken to represent the point or region on the isotherm where the initial shoulder occurs. The use of the BET equation and its extensions (e.g., the GAB equation) for evaluating water vapor sorption by amorphous pharmaceutical solids has been reviewed extensively (e.g., Ref. 5). It appears that at water contents in the region of W_m, a number of important and critical effects of water on solid properties occur (e.g., Refs. 6 and 7). However what exactly gives rise to the initial shoulder in the isotherm that so critically affects these solid properties has not been well understood.

Recent studies concerned with the hydration of amor-

---

[1] School of Pharmacy, University of Wisconsin—Madison, Madison, Wisconsin 53706.

[2] To whom correspondence should be addressed.

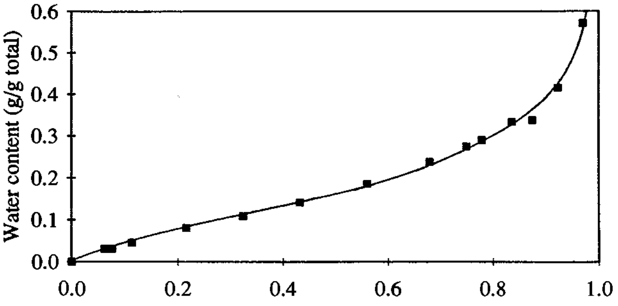

Fig. 1. A typical water vapor sorption isotherm for an amorphous pharmaceutical solid (PVP K30; 30°C) (from Ref. 9).

phous solids (8) have demonstrated that water vapor absorption is associated with a significant plasticizing effect by water, as reflected by significant reductions in the glass transition temperature (T_g) of the solid. Work from this laboratory (9,10) with poly(vinylpyrrolidone) (PVP)–water systems has demonstrated that the deviation from linearity on the absorption isotherm at higher relative humidities corresponds to a water content (W_g) which is sufficient to lower the glass transition temperature of the solid to that of its environment. Thus the sharp rise in water uptake observed in this region occurs as the amorphous solid converts from a highly viscous glassy state to a much less viscous rubbery state. It is noteworthy that for a number of materials, a fairly constant relationship is noted between the points W_g and W_m over a significant temperature range, suggesting that W_m is also somehow linked to the plasticizing effect of water on the amorphous polymer (9,10).

The use of the BET equation for water vapor absorption data, although useful for identifying the point W_m, is really only a nonpredictive curve-fitting exercise that does little to advance our understanding of the molecular processes occurring as water is taken up into amorphous solids. It clearly does not take into account the significant plasticizing effect of water or any structural changes in the solid as water is absorbed. If one considers the absorption process to be completely analogous to the solution process, then it should be possible to use basic solution theories to model the data and to gain a better understanding of water vapor absorption into amorphous pharmaceutical solids. In this paper such an approach is described. Specifically, polymer solution theories from the literature are used to predict the water vapor sorption behavior of a typical amorphous pharmaceutical solid (PVP) from first principles (without any adjustable parameters or curve fitting constants), and then these isotherms are compared with previously reported experimental data (9,11).

THEORETICAL CONSIDERATIONS AND RESULTS

The Flory–Huggins Theory

Perhaps the best-known and most widely used theory of polymer solution processes is due to Flory and Huggins (12). These authors developed their theory based on a statistical mechanical analysis of a polymer in solution using a lattice model. Assuming that the solution process is driven by a minimum free energy requirement, it was shown that the partial specific free energy of a penetrant, such as water, in the system can be calculated using the following equation:

$$\overline{G}_1 = \overline{G}^{O}{}_{1(T1P1)} + RT[\ln\phi_1 + \phi_2 + \chi\,\phi_2{}^2]/M_1 \tag{2}$$

where $\overline{G}_1$ is the partial specific free energy of the penetrant, $\overline{G}_1{}^{O}$ is the standard partial specific free energy of the penetrant (at temperature $T1$ and pressure $P1$), R is the universal gas constant, T is the experimental temperature, ϕ_1 is the volume fraction of solvent, ϕ_2 is the volume fraction of polymer, χ is the Flory–Huggins polymer–solvent interaction parameter (a constant), and M_1 is the molecular weight of the solvent. The polymer–solvent interaction parameter (χ) is a measure of polymer–solvent compatibility and reflects the nonideality of the system. A large value of χ indicates poor interaction, whereas a low value indicates strong interaction. χ values are usually determined by viscometric, osmotic, or light-scattering measurements and have been tabulated for a large number of different polymer–solvent combinations (e.g., Ref. 13).

Equation (2) can be rearranged into a form that gives the partial pressure of the solvent as a function of the solvent content of the system [Eq. (3)] and thus it allows standard vapor sorption isotherms to be predicted from first principles (14):

$$p/p_O = \phi_1 \exp\{(1 - 1/x)\phi_2 + \chi\,\phi_2{}^2\} \tag{3}$$

where p/p_O is the partial vapor pressure of the solvent and x is the ratio of molar volumes of the solvent and the polymer.

The form of the isotherm that is predicted by Eq. (3) is shown in Fig. 2. The relative molecular volume (x) and the polymer–solvent interaction parameter (χ) are clearly important variables. For most polymers mixed with water we consider the polymer to be much larger than the water molecule and therefore the isotherm takes the form shown where x = infinity. In these circumstances the Flory–Huggins model predicts a positive deviation from linearity at high vapor pressures but no "shoulder" at low vapor pressures (i.e., a Type III isotherm).

The validity of the Flory–Huggins model for describing water vapor absorption into amorphous pharmaceutical solids can be tested by comparing the predicted isotherm with experimental data from the literature. Figure 3 shows data

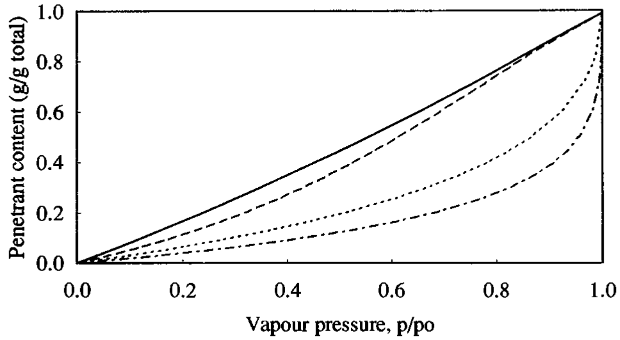

Fig. 2. The form of water vapor sorption isotherms predicted by the Flory–Huggins model (x = ratio of molar volumes of penetrant and polymer, χ = polymer–solvent interaction parameter). (——) $x = 1$, $\chi = 0.0$; (---------) $x = 1$, $\chi = 0.5$; (··········) $x = \infty$, $\chi = 0.0$; (-·-·-·-·-·-) $x = \infty$, $\chi = 0.05$.

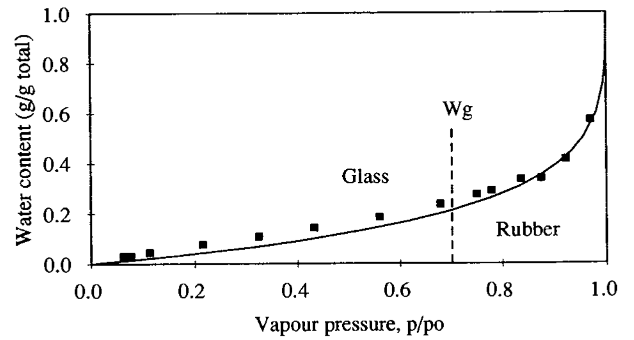

Fig.3. Comparison of the experimental water sorption data and the Flory–Huggins model for PVP K30 at 30°C (χ = 0.5). (■) Data; (——) Flory–Huggins equation.

for the poly(vinylpyrrolidone) (PVP K30)–water system at 30°C (9,10) and a Flory–Huggins plot derived using a χ value of 0.5 obtained from the literature (15). Overall the agreement between the experimental data and the predicted isotherm is very good, especially considering that the Flory–Huggins theory was developed for freely mobile polymers rather than for polymers that are restricted in their movement (e.g., in the glassy state). The agreement between theory and experiment is best when the experimental temperature is significantly greater than the glass transition temperature of the mix and is worst at the lower water contents where the system is in the glassy state. Again, this result is not surprising since the Flory–Huggins model was developed for nonpolar polymer–solvent systems at high solvent concentrations and these conditions are not met by PVP absorbing small amounts of water in the glassy state. Some authors (e.g., Refs. 13 and 15) have tried to improve the fit of the theoretical isotherm at low vapor pressures by allowing χ to vary with solute concentration. Unfortunately this approach does not add to our understanding of the changing molecular properties of the system since it reduces χ to an arbitrary fitting parameter rather than a well-defined and independently derived constant. The true Flory–Huggins model is thus capable of giving an approximate prediction of the experimental data for the whole water vapor sorption isotherm but is least accurate in the region of interest for most pharmaceutical applications (i.e., at low partial vapor pressures).[3]

Vrentas' Theory

Recent work by Vrentas and co-workers (16,17) concerned with the diffusion of small molecules in glassy polymers has used concepts related to free volume theory (18) to account for nonideal volumetric changes in a glassy polymer brought about by the presence of a low molecular weight penetrant. These nonideal volume changes occur as a direct result of structural changes in the polymer with increasing penetrant concentration and, provided that the processing history of the polymer in question is known, can be described in terms of a classical plasticization effect (19–21). The nonideal volume changes cause nonideal changes in the free energy of the system, and as the spontaneous sorption of vapor by a solid is a free energy-controlled process, the model can be used to describe vapor sorption processes (22).

The total specific free volume of a glassy polymer can be thought of consisting of the occupied or "true" volume of the polymer molecule, the interstitial free volume trapped within its three-dimensional structure, and the hole free volume between the molecules which is available for diffusion, side chain movement, etc. The magnitude of each of these free volumes is determined by the processing history of the polymer and the storage conditions at any given time. Vrentas proposed that the sorption of a penetrant by a polymer results in a "nonideal" hole free volume increase that is less than that calculated by summing the hole free volumes of the two components. This net excess loss in hole free volume is due to local rearrangement of the glassy polymer as the penetrant enters the system and interacts with the polymer. Assuming that there is no accompanying change in the occupied or interstitial free volumes, the magnitude of the nonideal hole free volume change can be related to changes in the total volume of the system. This can be measured directly or can be estimated using an equation that relates these changes to the variation of the glass transition temperature of the mix with increasing penetrant concentration (19–21):

$$\Delta \bar{V} = -(dT_{gm}/dw_1)w_1 w_2 \bar{V}_2{}^{o}{}_{Tg2}(\alpha_2 - \alpha_{2g}) \qquad (4)$$

where $\Delta \bar{V}$ is the excess specific volume of the polymer–penetrant mixture, dT_{gm}/dw_1 is the change in T_g of the mixture with varying penetrant mass fraction (w_1), w_2 is the polymer mass fraction, $\bar{V}_2{}^{o}{}_{T_g2}$ is the specific volume of the pure polymer at its T_g, α_2 is the thermal expansion coefficient of the rubbery polymer, and α_{2g} is the thermal expansion coefficient of the glassy polymer.

For several materials of pharmaceutical interest such volumetric changes have been measured directly and found to be of the order of a few percent [e.g., cellulose (23), poly(methylmethacrylate) (24), elastin (25)]. The volumetric

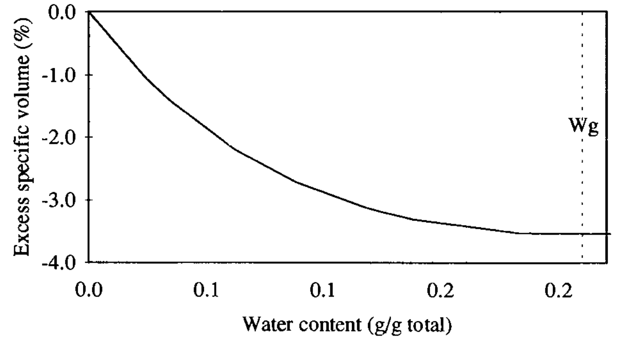

Fig. 4. Nonideal volume changes predicted for the PVP K30–water system using Eq. (4) (see text).

---

[3] In some processing situations (e.g., freeze drying, wet granulation) high relative vapor pressures will be encountered and the system can be above its glass transition temperature for some time. While this is an important situation which needs to be understood, the product will almost always be dried and then stored at lower vapor pressures.

changes predicted for the PVP–water system using Eq. (4) are shown in Fig. 4 and are of a similar order of magnitude. As a consequence of the nonideal volumetric changes that occur on mixing the glassy polymer and the penetrant, the equation used to calculate the partial specific free energy of the penetrant in the mix [see Eq. (3)] must include an additional term to account for these changes:

$$\overline{G}_1 = \overline{G}^{O}{}_{1(T1P1)} + RT\,[\ln\phi_1 + \phi_2 + \chi \cdot \phi_2{}^2]/M_1 + w_2{}^2\,[\delta\overline{G}^{O}{}_{2g}/\delta w_1]_{(T1P1)} \quad (5)$$

where $\overline{G}^{O}{}_{2g}$ is the partial specific free energy of the polymer in the glassy state. The last term in this equation quantifies the effect that the volumetric changes have on the free energy of the system and can be calculated from the glass transition temperature data in a manner analogous to that used in Eq. (4):

$$[\delta\overline{G}^{O}{}_{2g}/\delta w_1]_{(T1P1)} = (\overline{C}_{pg} - \overline{C}_p)\,(dT_{gm}/dw_1)\,((T/T_{gm}) - 1) \quad (6)$$

where $\overline{C}_{pg}$ is the specific heat capacity of the mix in the glassy state and $\overline{C}_p$ is the specific heat capacity of the mix in the rubbery state.

For any given system $\overline{C}_{pg} - \overline{C}_p$ is effectively constant and therefore the free energy change, $\delta\overline{G}^{O}{}_{2g}/\delta w_1$, is directly related to the change in glass transition temperature of the polymer with increasing water content, dT_{gm}/dw_1. A typical plot of glass transition temperature versus water content (for PVP) is shown in Fig. 5 (9) along with the line of best fit through the data. Such plots usually show a significant change in T_g at low water contents, with a leveling-off in the response as the water content increases (8), and many explanations have been proposed for the form of this relationship (e.g., Refs. 26 and 27). It is generally thought that at low water contents the solid–water interaction is very strong, resulting in a marked plasticizing effect. As the water content increases, the strength of the solid–water interaction decreases, and the plasticizing efficiency of the water is reduced. Eventually the affinity of the water for the solid decreases so much that the water preferentially associates with itself (28). It has been suggested that for certain materials (e.g., proteins) the plasticizing effect may stop when the hydrogen bonding capacity of the solid is exceeded. Obviously the nature and strength of the water–solid interaction depend upon the identity of the solid, and for certain materials there may be little tendency to interact. It is notable that this situation does not occur very often and even materials that are considered to be strongly hydrophobic will interact with water strongly enough to experience a significant plasticizing effect.

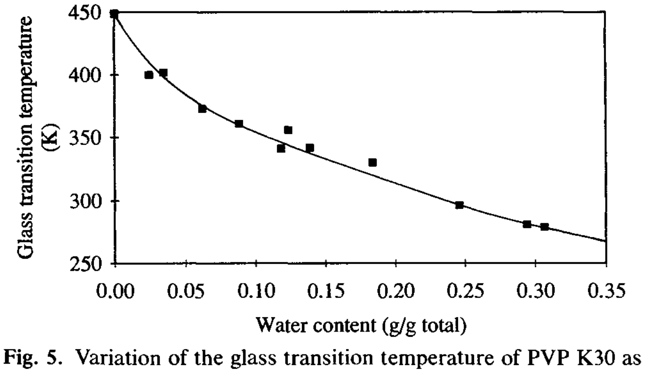

Fig. 5. Variation of the glass transition temperature of PVP K30 as a function of water content (from Ref. 9).

Finally, by combining Eqs. (5) and (6) and rearranging in terms of the vapor pressure of the penetrant, we obtain the Vrentas equation:

$$p/p_O = \phi_1 \exp\,[(1 - (1/x))\,\phi_2 + \chi\phi_2{}^2]\,\exp f \quad (7)$$

where

$$f = \{M_1 w_2{}^2\,(\overline{C}_{pg} - \overline{C}_p)\,(dT_{gm}/dw_1)\,((T/T_{gm}) - 1)\}/RT$$

This equation is very similar to the Flory–Huggins equation but contains one additional term, exp f. In this term are all those factors that reflect the changing structure of the polymer–penetrant mixture below its glass transition temperature. As each of these terms can be obtained independently of vapor sorption measurements, the model is considered to be a truly predictive one. (Note that when T is equal to T_g the exp$f$ term disappears and the equation reduces to the Flory–Huggins equation).

From the mathematical form of Eq. (7) it can be demonstrated that it is the magnitude of the exp f term which determines the shape of the water vapor isotherm below T_g. Furthermore, as all the components of this term except dT_{gm}/dw_1 are constant for any given experimental temperature, it is the dT_{gm}/dw_1 function which is most critical in determining the shape of the isotherm below T_g (a significant change in the value of dT_{gm}/dw_1 would produce a large shoulder on the isotherm, whereas a constant, linear relationship would produce no shoulder at all). Therefore it is the solid–water interactions that determine the efficiency of the plasticization process which are primarily responsible for both of the deviations from linearity in the water vapor sorption isotherms of amorphous solids. The initial extent of water uptake by the solid is directly related to the strength of the water–solid interaction at low vapor pressures and the "shoulder" on the isotherm occurs as a result of the changing interaction between the solid and the aqueous phases as the vapor pressure increases. Eventually, although the level of interaction becomes reduced, the solid gains enough energy from the sorption process to undergo a phase change from the glassy to the rubbery state and this is accompanied by a significant increase in the efficiency of water uptake into the solid (i.e., the second deviation from linearity on the isotherm).

The practical utility of the Vrentas model and Eq. (7) was originally demonstrated only for a polycarbonate–carbon dioxide system (22). The required parameters for the PVP–water system at 30°C can be obtained from the literature (9) (Table I) and thus a predicted isotherm can be compared with experimental data. Values for dT_{gm}/dw_1 were obtained from the line of best fit in Fig. 5 and it was assumed, as in the original model, that the processing histories of all the polymer samples were effectively identical. Although not

Table I. Values of the Parameters Used in the Flory–Huggins and Vrentas Calculations

PVP	
Source	PVP K30, General Aniline Film Corp., NJ
$\bar{V}$	8×10^{-7} m^3 g^{-1}
T_g	449 K (9)
$\bar{C}_p$-$\bar{C}_{pg}$	0.2117 J g^{-1} K^{-1} (9)
α-α_g	4.8×10^{-4} K^{-1} (13)
Water	
M	18
T_g	135 K (9)
PVP–water	
x	∞
χ	0.50 (15)
dT_{gm}/dw_1	In the range 1500 to 100 K (9) (see Fig. 5)

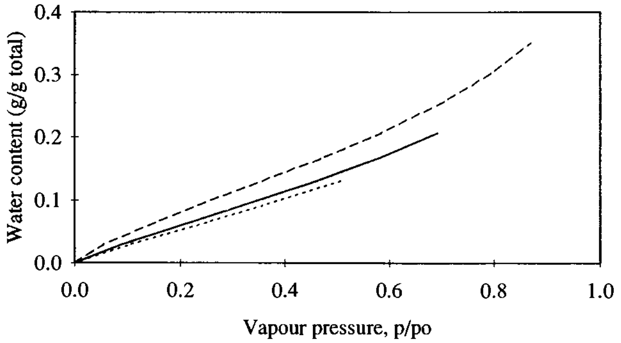

Fig. 7. Water vapor sorption isotherms for PVP K30 at different temperatures predicted using the Vrentas model (χ = 0.5). (——) 60°C; (··········) 30°C; (---------) −30°C.

a perfect fit, the isotherm predicted using the Vrentas model (Fig. 6) represents a significant improvement over that derived using the Flory–Huggins theory when the polymer is in the glassy state, and because of the mathematical form of Eq. (7), the Vrentas model is also able to predict directly the initial shoulder on the isotherm at low relative humidities, which the Flory–Huggins model cannot.

Another advantage of the Vrentas model over the Flory–Huggins model is that it permits an estimation of the effect of temperature on the form of the sorption isotherm. For the PVP–water system a decrease in temperature should cause an overall increase in absorption and increase the size of the initial shoulder (Fig. 7) (this prediction does not take into account any change in χ with temperature so it can be considered to be only a qualitative prediction). Over a normal working temperature range of 20–60°C the model and the experimental data (9–11) are in very close agreement. For temperatures less than the freezing point of water, the Vrentas model significantly underestimates the extent of water vapor absorption. This is believed to be because water can undergo crystallization at such low temperatures (8) and this behavior is not accounted for in the theoretical model.

CONCLUSIONS

The sorption of water vapor by amorphous and partially amorphous pharmaceutical polymers can be predicted from first principles using models based on solution theories. The Flory–Huggins model enables sorption isotherms to be predicted for polymers that are in the rubbery state; the Vrentas model enables sorption isotherms to be predicted for polymers in both the glassy and the rubbery states by taking into account structural changes in the glassy polymer as water is absorbed. The Vrentas model also provides some extra insight into the mechanisms of the water vapor process and highlights those factors that are responsible for determining the shape of the isotherm at low relative humidities. Although experimental data have been presented only for one solid–liquid system in this paper, the widespread utility of the approach described can be readily appreciated. The traditional concepts of "bound" and "unbound" water appear to be inapplicable to water vapor sorption by amorphous pharmaceutical solids; instead a mutual miscibility or "plasticizer" model should be utilized since it allows a continuum of chemical, physical, and energetic states to be considered. The prediction of those temperatures and water contents where significant structural changes or phase transitions occur is likely to be of benefit in many aspects of drug formulation and research. Fortuitously the data required for such predictions are already available for a wide range of pharmaceutical materials (e.g., cellulose, gelatin, cellulose polymers) or can be easily obtained (e.g., for new chemical entities) using conventional characterization techniques (e.g., differential scanning calorimetry, viscometry). While the models described cannot be considered to be universal because of the unique way in which water interacts with amorphous materials, they can provide an insight into the mechanisms of water–solid interactions that cannot be obtained by the simple measurement of sorption isotherms over a limited range of temperatures. The careful use of the knowledge gained from such theories should assist in identifying those factors involving residual water in amorphous solids that are critical in formulation and processing.

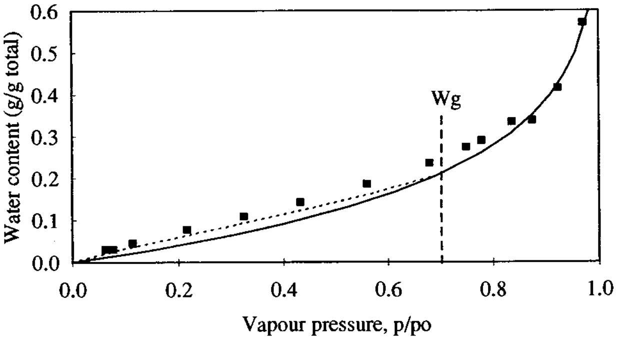

Fig. 6. Comparison of the experimental water sorption data and the Vrentas model for PVP K30 at 30°C (χ = 0.5) (■) Data; (··········) Vrentas equation; (——) Flory–Huggins equation.

ACKNOWLEDGMENTS

The authors express their appreciation to Professor H. Yu, Chemistry Department, University of Wisconsin–Madison, for helpful discussions and to the Purdue/Wisconsin Joint Industrial Program for financial support. B.C.H. acknowledges a travel grant from the Wellcome Trust.

NOMENCLATURE

1 (subscript)	Solvent/penetrant/diluent/plasticizer
2 (subscript)	Solute/polymer/solid/substrate
α	Coefficient of thermal expansion
BET	Brunauer, Emmett, and Teller gas adsorption theory
C_B	BET constant
$\bar{C}_p$	Specific heat capacity
χ	Flory–Huggins interaction parameter (a constant)
exp	Natural logarithm
f	Vrentas' equation function
ϕ	Volume fraction
g (subscript)	Glassy
$\bar{G}$	Specific free energy
GAB	Guggenheim, Anderson, and De Boer gas adsorption theory
m	Mixture
M	Relative molecular mass
p/p_o	Partial vapor pressure
T_g	Glass transition temperature
T	Experimental temperature
$\bar{V}$	Specific Volume
w	Weight fraction
W	Mass of water per unit mass of solid
W_m	BET monolayer capacity
W_g	Glass transition water content
x	Ratio of molar volumes of polymer and solvent

REFERENCES

1. J. Callahan, G. Cleary, M. Elefant, G. Kaplan, T. Kensler, and R. Nash. Equilibrium moisture content of pharmaceutical excipients. *Drug. Dev. Indust. Pharm.* 8:355–369 (1982).
2. C. Ahlneck and G. Zografi. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int. J. Pharm.* 62:87–95 (1990).
3. P. C. Hiemenz. *Principles of Colloid and Surface Chemistry*, Marcel Dekker, New York, 1986.
4. S. Brunauer, P. H. Emmett, and E. Teller. Adsorption of gases in multimolecular layers. *J. Am. Chem. Soc.* 60:309–319 (1938).
5. G. Zografi. States of water associated with solids. *Drug Dev. Indust. Pharm.* 14:1905–1926 (1988).
6. M. J. Kontny and C. A. Mulski. Gelatin capsule brittleness as a function of relative humidity at room temperature. *Int. J. Pharm.* 54:79–85 (1989).
7. G. W. Radebaugh, S. R. Babu, and J. N. Bondi. Characterisation of the viscoelastic properties of compacted pharmaceutical powders by a novel non-destructive technique. *Int. J. Pharm.* 57:95–105 (1989).
8. H. Levine and L. Slade. Glass transitions in foods. In H. G. Scwartzberg and R. W. Hartel (eds)., *Physical Chemistry of Foods*, Marcel Dekker, New York, 1992, pp. 83–219.
9. C. A. Oksanen. *The Interaction of Water with Amorphous Solids*, M.Sc. thesis, and *Molecular Mobility in Mixtures of Absorbed Water and Solid Poly(vinylpyrrolidone)*, Ph.D. thesis, University of Wisconsin—Madison, 1989 and 1992.
10. C. A. Oksanen and G. Zografi. The relationship between the glass transition temperature and water vapor absorption by poly(vinylpyrrolidone). *Pharm. Res.* 7:654–657 (1990).
11. A. P. MacKenzie and D. H. Rasmussen. Interactions in the water-polyvinylpyrrolidone system at low temperatures. In H. H. G. Jellinek (ed.), *Water Structure at the Water Polymer Interface*, Plenum Press, New York, 1972, pp. 146–172.
12. P. J. Flory. *Principles of Polymer Chemistry*, Cornell University Press, New York, 1953.
13. J. Brandrup and E. H. Immergut (eds.). *Polymer Handbook*, Wiley, New York, 1975.
14. B. E. Eichinger and P. J. Flory. Thermodynamics of polymer solutions. Part 1. Natural rubber and benzene. *Trans. Faraday Soc.* 64:2035–2052 (1968).
15. M. A. Cohen Stuart. *Flexible Polymers at a Solid-Liquid Interface: The Adsorption of Polyvinylpyrrolidone onto Silica*, Ph.D. thesis, Wageningen University, Wageningen, The Netherlands, 1980.
16. J. S. Vrentas and J. L. Duda. Diffusion of small molecules in amorphous polymers. *Macromolecules* 9:785–790 (1976).
17. J. S. Vrentas and J. L. Duda. Diffusion in polymer-solvent systems. 1. Re-examination of the free volume theory. *J. Polym. Sci.* (*Polym. Phys. Ed.*) 15:403–416 (1977).
18. M. H. Cohen and D. Turnbull. Molecular transport in liquids and glasses. *J. Chem. Phys.* 31:1164–1169 (1959).
19. J. S. Vrentas, J. L. Duda, and H.-C. Ling. Antiplasticization and volumetric behaviour in glassy polymers. *Macromolecules* 21:1470–1475 (1988).
20. J. S. Vrentas and C. M. Vrentas. Volumetric behaviour of glassy polymer-penetrant systems. *Macromolecules* 22:2264–2266 (1989).
21. J. S. Vrentas and C. M. Vrentas. Predictions of volumetric behaviour for glassy polymer-penetrant systems. *J. Polym. Sci.* (*Polym. Phys. Ed.*) 28:241–244 (1990).
22. J. S. Vrentas and C. M. Vrentas. Sorption in glassy polymers. *Macromolecules* 24:2404–2412 (1991).
23. E. Filby and O. Maass. The volume relations of the system cellulose and water. *Can. J. Res.* 7:162–177 (1932).
24. D. T. Turner. Polymethylmethacrylate plus water: sorption kinetics and volumetric changes. *Polymer* 23:197–202 (1982).
25. M. Scandola, G. Ceccorulli, and M. Pizzoli. Water clusters in elastin. *Int. J. Biol. Macromol.* 3rd April: 147–149 (1981).
26. J. M. Pochan, C. L. Beatty, and D. F. Pochan. Different approach for the correlation of the Tg of mixed amorphous systems. *Polymer* 20:879–886 (1979).
27. T. S. Chow. Molecular interpretation of the glass transition temperature of polymer-diluent systems. *Macromolecules* 13:362–364 (1980).
28. F. Franks. Water solubility and sensitivity—hydration effects. In C. A. Finch (ed.), *Chemistry and Technology of Water Soluble Polymers*, Plenum Press, New York, 1981, pp. 157–178.