Thermodynamics of Water–Solid Interactions in Crystalline and Amorphous Pharmaceutical Materials

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ABSTRACT: Pharmaceutical materials, crystalline and amorphous, sorb water from the atmosphere, which affects critical factors in the development of drugs, such as the selection of drug substance crystal form, compatibility with excipients, dosage form selection, packaging, and product shelf-life. It is common practice to quantify the amount of water that a material sorbs at a given relative humidity (RH), but the results alone provide minimal to no physicochemical insight into water–solid interactions, without which pharmaceutical scientists cannot develop an understanding of their materials, so as to anticipate and circumvent potential problems. This research was conducted to advance the science of pharmaceutical materials by examining the thermodynamics of solids with sorbed water. The compounds studied include nonhygroscopic drugs, a channel hydrate drug, a stoichiometric hydrate excipient, and an amorphous excipient. The water sorption isotherms were measured over a range of temperature to extract the partial molar enthalpy and entropy of sorbed water as well as the same quantities for some of the solids. It was found that water–solid interactions spanned a range of energy and entropy as a function of RH, which was unique to the solid, and which could be valuable in identifying batch-to-batch differences and effects of processing in material performance. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2772–2783, 2014
Keywords: water sorption; water in solids; hygroscopicity; hydration; thermodynamics; solid state; crystallinity; amorphous

INTRODUCTION

Water sorption of pharmaceutical materials is considered as an important, sometimes critical, factor that affects selection of the salt and crystal form of a drug substance, manufacturing and performance of solid dosage forms. In this honorary edition of Journal of Pharmaceutical Sciences, devoted to Professor George Zografi, it is noted that he along with colleagues and students began to investigate the water sorption properties in the 1970s, building a prototype moisture sorption system to evaluate pharmaceutical materials.[1] In 1988, Prof. Zografi reviewed the critical aspects of water–solid interactions from a fundamental, scientific perspective, highlighting the distinction between adsorption in crystalline and absorption in amorphous solids, capillary condensation, deliquescence, and formation of hydrates[2]—physicochemical factors that continue to challenge the development of drug products 25 years later. Over the years, it has been recognized that water sorption can affect powder bulk density, blending, flow and compaction,[3–5] capsule mechanical properties,[6] tablet hardness,[7–9] disintegration[7,10–12] and dissolution,[10–14] excipient compatibility,[15–17] and chemical stability.[18–20] The moisture properties of pharmaceutical solids are an important part of package selection.[21–23] Many commercial drug products contain a storage statement on the label around moisture protection, and may contain a desiccant or special packaging, underscoring water's relevance to detrimental changes that it can produce on storage.

Most drugs are crystalline solids that generally sorb only a small amount of water from the atmosphere, for example, 0.1%–0.2% water at a relative humidity (RH) as high as 90%. The reason for the low sorption level is that water molecules mainly have access to the solid surface, not to the bulk of crystalline particles. After only a few layers of water molecules deposit onto a surface, the sorbed water properties start to approach that of bulk water, that is, the vapor pressure or RH approaches 100%. For example, if a crystalline solid has a typical specific surface area of 0.5–1 m^2/g, using water's area of 0.10 nm^2/molecule value,[24] one molecular layer would occur at a water content of 0.03%. Considering that multilayers can form before a monolayer is established, it is not too surprising that at a few multiples of 0.03%, the RH will approach 100%, which is consistent with the high humidity water content of crystalline solids in the 0.1%–0.2% range. The important physical perspective is that although the moisture level is small for crystalline solids, water molecules occupy a significant fractional coverage of a solid's surface even at a moderate RH of 50%.

Another important aspect of water sorption is that it can vary from one batch of drug or excipient to another, and in cases where the moisture level is critical, the water sorption profile becomes an important characterization technique for raw materials. There can be energetic and micromeritic reasons for the water sorption level variation. Typically, raw materials are also tested for particle size and specific surface area, and the results can be used to try to normalize the moisture sorption profile by these properties, for example, water content per unit of surface area. It is also possible to analyze a moisture sorption isotherm in terms of the Brunauer–Emmett–Teller (BET) equation to extract a C_B value related to energy of adsorption of the first layer or the Guggenheim-Anderson-de Boer (GAB) equation to extract C_G and K values related to adsorption energies of the first and an intermediate layer.[25,26] Both models also provide the W_m parameter formally related to monolayer capacity, and although it does not provide specific surface areas in accord with values from N_2 gas adsorption, it can have interpretive value.[27] The BET or GAB sorption energy parameters fail to give the complete characterization of a vapor's interaction with

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a solid, in particular water's energetic interaction with a drug or excipient. Specifically, the BET or GAB models do not incorporate interactions between adsorbed vapor molecules, in particular water–water interactions, which presumably are an important factor in the sorption process as the RH increases, especially for the water molecule that exhibits strong H-bonding with itself. Indeed, IR spectroscopic experiments of moisture sorption on NaCl have shown H-bonding of water with itself at submonolayer coverage.[28] It is in fact well established from sorption calorimetry experiments that heats of sorption vary continuously as the vapor pressure (or RH in the case of water) of the probe increases, indicating that a single energy parameter such as C_B can miss important detail in characterizing water–solid interactions.[25,29]

Sorption calorimetry is less commonly used in routine characterization of drug substances and raw materials. In contrast, automated water sorption equipment is a standard technique that requires minimal sample preparation and effort, making it more appropriate for routine characterization. The main data obtained by the water sorption technique is water weight versus RH. Although it is necessary to quantify the water content of materials and the isotherm provides practical value in characterizing their "hygroscopicity,"[30] the isotherm contains far greater information regarding water–solid thermodynamic interactions. In this research, a more detailed analysis of water sorption isotherms is executed. The water sorption isotherms were measured for several anhydrous crystalline solids, an isolated site hydrate, a channel hydrate, and an amorphous polymer. Specifically, the compounds selected represent "nonhygroscopic" anhydrous drugs (genistein, indomethacin, and griseofulvin), the nonhygroscopic excipient lactose monohydrate, the hygroscopic channel hydrate erythromycin A dihydrate, and the hygroscopic amorphous excipient polyvinylpyrrolidone (PVP K29-32). The water sorption isotherm data were analyzed to provide partial molar enthalpy and partial molar entropy of sorbed water, as well as the partial molar quantities for the solid component in the case of PVP and erythromycin A dihydrate. It was the intent of this research (1) to illustrate and execute the methodology and (2) to provide the interpretation of the thermodynamics of pharmaceutical solids with sorbed water.

THEORETICAL BACKGROUND

Crystalline solids are generally thought to adsorb water because of minimal pathways for water to penetrate the particle bulk. However, it is possible that some of the critical distinctions in crystalline materials arise from defects or imperfect crystallinity, which leads to water absorption in addition to adsorption. In this context, the theoretical analysis should not be limited to or assume only adsorption. It is in fact unnecessary and certainly undesirable to make such limiting assumptions in the theoretical analysis.

The chemical potential (μ) of water vapor can be readily calculated from its vapor pressure (p). The most common standard state for sorption studies is water vapor at its saturation vapor pressure p^0. Using this standard state, the chemical potential is

$$\mu = \mu^0 + RT\ln p/p^0 \tag{1}$$

Although this equation calculates the chemical potential of water vapor relative to vapor at the saturation pressure at temperature T, if the water sorption experiment allows equilibrium to be established, the chemical potential of sorbed water is equal to that of the vapor, in which case, the equation also calculates the chemical potential of water in the solid relative to the vapor at p^0. Also, as the chemical potential of pure liquid water is the same as water vapor at saturation (p^0), the equation can be expressed more specifically to denote the condensed phases involved:

$$\mu_w = \mu_l^0 + RT\ln p/p^0 \tag{2}$$

in which w is for sorbed water and l is for liquid water at its saturation pressure p^0. The quantity p/p^0 is also referred to as the water activity (a_w), which, in turn, when multiplied by 100 is defined as the RH. In a water sorption experiment, p/p^0 or a_w is fixed and the water content of the solid is measured. The p/p^0 value is changed and water content is measured over a range from $p/p^0 = 0$ to typically 0.9. The isotherm establishes the relation of p/p^0 to water content, which in this analysis will use water mole fraction X_w.

$$\frac{p}{p^0} = a_w = f(X_w) \tag{3}$$

Thus, the chemical potential of sorbed water can be calculated as a function water composition.

$$\mu_w = \mu_l^0 + RT\ln f(X_w) \tag{4}$$

The relation of chemical potential of sorbed water to composition is important when combined with standard thermodynamic relations that calculate enthalpy and entropy. From the defining relationship for free energy applied to partial molar functions with liquid water as the reference state:

$$\mu_w - \mu_l^0 = \overline{H}_w - H_l^0 - T\left(\overline{S}_w - S_l^0\right), \tag{5}$$

in which H is enthalpy and S is entropy and overbars signify partial molar quantities. The partial temperature derivatives at constant total atmospheric pressure (P, not water vapor pressure p) and water composition then provide the entropy and enthalpy:

$$\left[\frac{\partial\left(\mu_w - \mu_l^0\right)}{\partial T}\right]_{P,X_w} = -\left(\overline{S}_w - S_l^0\right) \tag{6}$$

and

$$\left[\frac{\partial\left[\left(\mu_w - \mu_l^0\right)/T\right]}{\partial(1/T)}\right]_{P,X_w} = \left(\overline{H}_w - H_l^0\right). \tag{7}$$

These equations illustrate how partial molar entropy and enthalpy at the given water mole fraction can be calculated from moisture sorption isotherms at multiple temperatures. Rather than working with chemical potential in Eq. (7), this function when expressed in terms of water vapor pressure yields

$$\left[\frac{\partial \ln p}{\partial(1/T)}\right]_{P,X_w} = \frac{\left(\overline{H}_w - H_l^0 - \Delta H_{vap}\right)}{R}, \tag{8}$$

in which ΔH_{vap} is water's heat of vaporization, which has the value 44.0 kJ/mol at 25°C.[31] Integration of this equation, taking advantage of weak temperature dependence of enthalpy differences over a small temperature range, results in

$$\left[\ln p\right]_{P,X_w} = \frac{\left(\overline{H}_w - H_l^0 - \Delta H_{vap}\right)}{R}\frac{1}{T} + \text{constant.} \quad (9)$$

This equation instructs us to create isosteres (constant amount sorbed) of ln p versus $1/T$, the slope of which gives the partial molar enthalpy of water relative to the bulk water molar enthalpy. In surface science literature, a derivation of Eq.(9) is given by a different approach, and the negative of the enthalpy terms is referred to as the isosteric heat, which uses the vapor as the reference state.[32] In this research for water sorption, the emphasis is on liquid water as the reference state and in particular on partial molar quantities. It is only the partial molar enthalpy of water that depends on its mole fraction and will vary with increasing RH as the water content increases. In addition, the partial molar entropy of sorbed water can be calculated from the heat and measured chemical potential using

$$\overline{S}_w - S_l^0 = -\frac{\mu_w - \mu_l^0}{T} + \frac{\overline{H}_w - H_l^0}{T}. \quad (10)$$

These relations are used in this research to quantify the partial molar enthalpy and entropy of sorbed water in several crystalline drugs and an amorphous polymer.

Additionally, it is possible to calculate the partial molar thermodynamic functions of the solid phase (s) component using the Gibbs–Duhem equations for constant temperature and pressure processes.

$$X_w d\overline{H}_w + X_s d\overline{H}_s = 0 \quad (11)$$

$$X_w d\overline{S}_w + X_s d\overline{S}_s = 0 \quad (12)$$

$$X_w d\mu_w + X_s d\mu_s = 0 \quad or \quad \mu_s = \overline{H}_s - T\overline{S}_s \quad (13)$$

These equations are used when water is absorbed into the bulk of the material, which in this research will be applied to PVP and erythromycin.

EXPERIMENTAL

The crystalline solids analyzed are: genistein (DSM lot SI06068001, 98+%), griseofulvin (MP Biomedical lot M5796, 97.5%), indomethacin (Sigma lot BCBF9122V, 99+%), erythromycin A dihydrate (Fluka lot SZBB105XV, 95.4%, water content 4.5%), lactose monohydrate (Foremost Farms lot 8509122912, #312 impalpable, NF grade), and PVP K29-32 (Sigma lot 074K0109, USP grade).

Water sorption isotherms were measured using an automated ambient pressure balance system (model TGA Q5000SA; TA Instruments, New Castle, DE). In our laboratory, this equipment exhibits an ultralow ±0.1 μg balance noise baseline, making it well suited to measure water uptake of crystalline solids even below 10% RH, although most of the emphasis on results from this research is for data above 10% RH. The balance was checked with a certified 50 mg weight prior to each measurement. Periodically, RH, as set by the equipment's mass flow controller valves, was verified by measuring the deliquescence of salts, specifically $LiCl{\cdot}H_2O$ (11.3% RH), $MgCl_2{\cdot}6H_2O$ (32.8% RH), NaBr (57.6% RH), NaCl (75.3% RH), KCl (84.2% RH), and KNO_3 (93.6% RH). The deliquescence points were measured to within 1% RH of the reference values. Although the mass flow controller valves can continuously open or adjust in sub-1% increments, the smallest increments used in these experiments was 2% RH, with the exception of erythromycin A dihydrate, for which 1% RH increments were used at low RH.

Isotherms were measured at 5°C, 15°C, 25°C, and 35°C for the purpose of determining the partial molar enthalpy of water. The isotherm at each temperature was measured three times and all 12 isotherms were used in enthalpy determination by regression analysis according to Eq. (9). The method involved a drying phase at 60°C/0% RH (40°C/0% RH for lactose monohydrate) followed by an equilibration stage at 25°C (typically 180–360 min), step scanning from 0%–40% RH in 2% increments and 40%–90% RH in 5% increments. Erythromycin A dihydrate was step scanned from 0% to 10% RH in 1% increments and then 10% to 90% RH in 5% increments because of the large water uptake at the lowest 0%–10% RH range. The equilibrium criterion for crystalline solids was not more than 0.002% weight change over 40 min or a total time of 120 min, with erythromycin A dihydrate as an exception using a total time of 1080 min because of slow equilibration in the low 0%–10% RH range. For PVP, the equilibrium criterion was not more than 0.002% weight change over 40 min or a total time of 360 min because of slower equilibration, particularly above 40% RH.

RESULTS

The materials examined in this research were characterized by X-ray powder diffraction (XRPD) to identify crystalline form (results not shown). The XRPD patterns demonstrated that genistein is the only crystalline form documented in the literature,[33] griseofulvin is Form I,[34] indomethacin is the γ form,[35] α-lactose monohydrate is the only known polymorph of the anomer, erythromycin A dihydrate is the channel hydrate form,[36] and PVP K29-32 is amorphous.

To illustrate the basic dataset used in the analysis, the water sorption isotherms for genistein are given in Figure 1a. The error bars are one standard deviation for three repetitions. Genistein is the lowest water sorbing material in these experiments and illustrates that the measurements were able to quantify water sorption isotherms as a function of the temperature range examined, 5°C–35°C, within the variation of the experiments.

The isotherms were fit to a cubic spline function and isosteres were created over the range of measured water mole fractions, $X_w = 0.00004$–0.01 for genistein. An example isostere is given in Figure 1b.

The water sorption isotherms for all of the compounds at 25°C are given in Figure 2. Note that for PVP, the water mole fraction is calculated using the vinylpyrrolidone molecular weight, so that a mole fraction of 0.5 represents 1 mole of water to 1 mole of monomer. In the isotherm for indomethacin, there is a small step-like feature at 50% RH, the relevance of which will be explained in the *Discussion* section. The isotherm

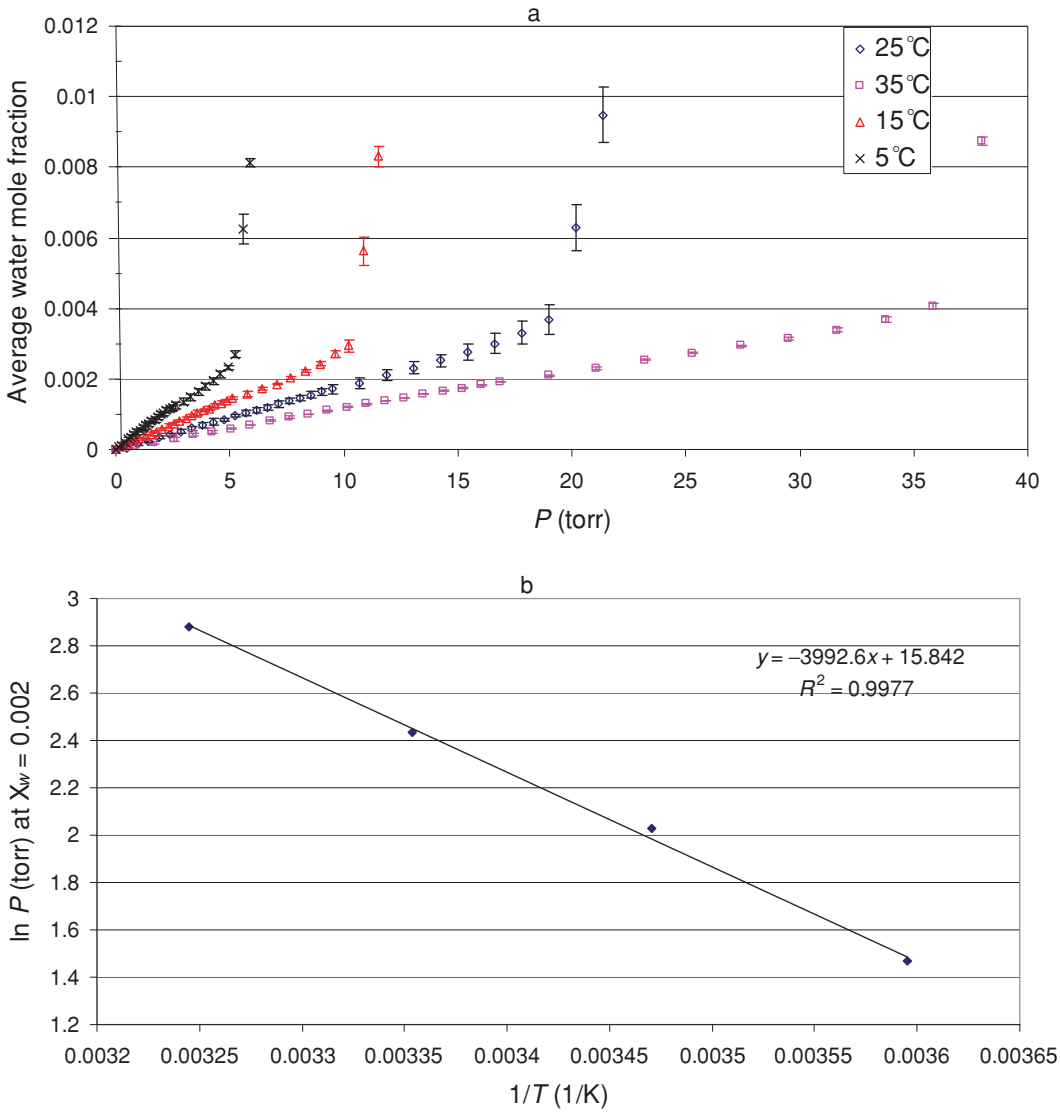

Figure 1. Water sorption isotherms (a, top) of genistein and an isostere (b, bottom) at $X_w = 0.002$.

for erythromycin illustrates its channel hydrate nature, where almost all of the water is sorbed below 10% RH.

The partial molar enthalpy and entropy of sorbed water (relative to bulk liquid water at its saturation pressure) for each of the solids are presented in Figure 3. Notice that of the crystalline solids—genistein, griseofulvin, indomethacin, and lactose monohydrate—genistein, indomethacin, and lactose monohydrate generally display endothermic water enthalpy relative to bulk water. Griseofulvin is distinctive in its slightly exothermic water enthalpy. The channel hydrate erythromycin exhibits highly exothermic water enthalpy up until the channels are filled, and the amorphous polymer PVP also exhibits significant exothermic water enthalpy compared to bulk water.

Given that lactose is a monohydrate with potential to dehydrate partially on the surface in the drying process, it was subjected to drying at 25°C in addition to the 40°C result presented in Figure 3. The partial molar enthalpy profiles of lactose dried at the two conditions are presented in Figure 4. Although the average 25°C drying curve is slightly more endothermic at low water sorption, the results are within experimental variability. If the drying condition affected enthalpy, it could not be detected in the experiments.

For PVP, given that moisture is sorbed in the bulk of the solid, it is also possible to calculate its partial molar enthalpy, entropy, and chemical potential, as well as the full mixing heat, entropy, and free energy. The partial molar and mixing quantities are presented in Figure 5.

Erythromycin sorbs water into the bulk channels at lower RH, but as the water content increases and the channels fill, the added water accumulates more on the surface. Given the more homogeneous bulk distribution of water at lower RH, the Gibbs–Duhem equations can be used to quantify erythromycin's contribution to enthalpy, entropy, and chemical potential. In particular, the ultralow partial molar entropy of water found in the channels, approximately −100 J/K-mol, warrants more complete analysis, so the partial molar entropy of erythromycin and overall mixing entropy were calculated and are presented in Figure 6. Notice the negative entropy change

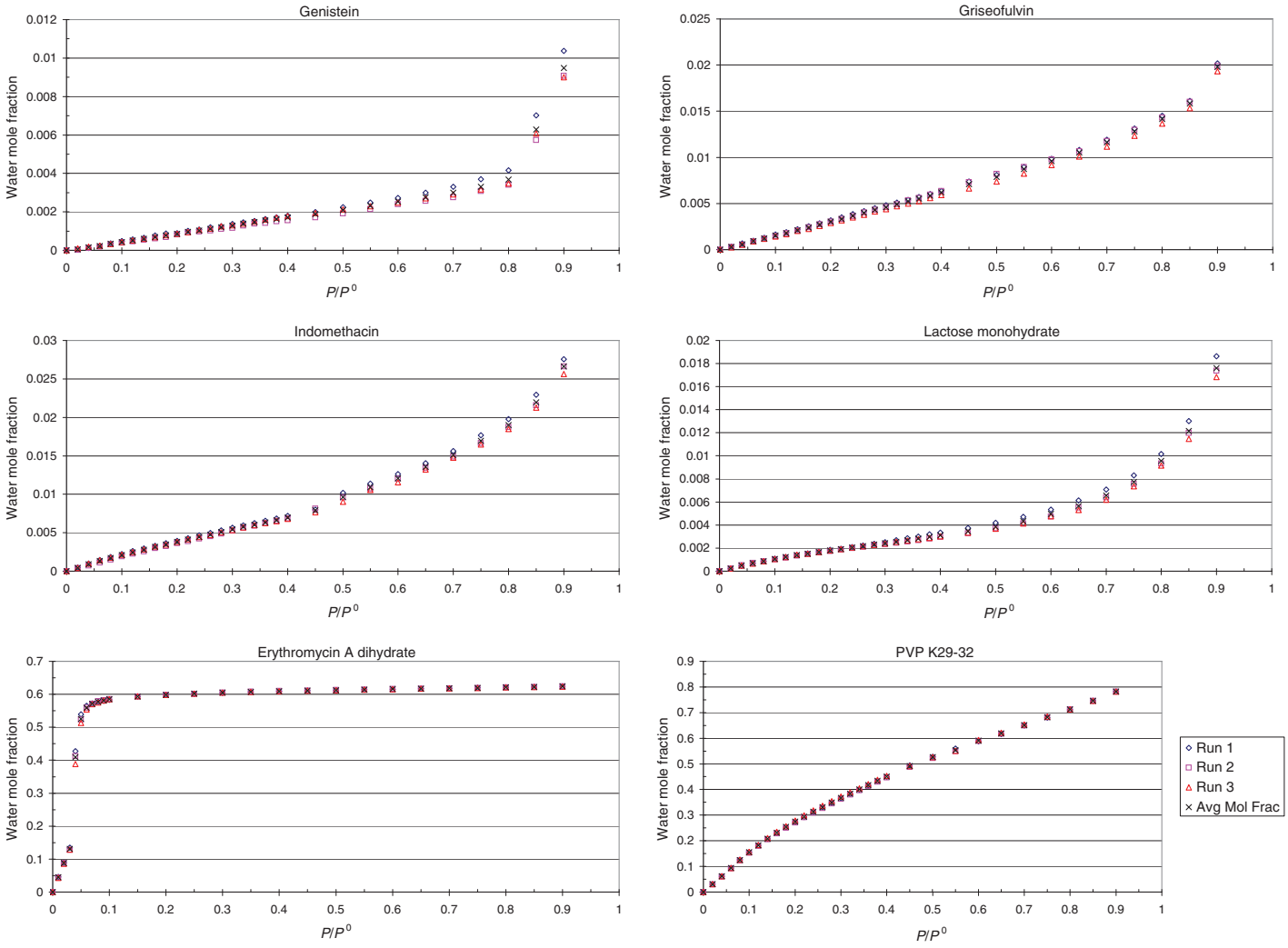

Figure 2. Water sorption isotherms at 25°C.

on mixing that arises from the large decrease in water's entropy and only small increase in erythromycin's entropy, an effect to be elaborated on in the *Discussion* section.

For the other crystalline solids, given that sorbed water is not homogeneously distributed in the solid, but is more concentrated on the surface, the bulk Gibbs–Duhem relations were not applied.

DISCUSSION

A general feature of all materials is a distinctly different water enthalpy at low sorption level that approaches the liquid water enthalpy with increasing moisture sorption (Fig. 3). For the particular batch of indomethacin, there is a second interaction energy that appears at intermediate sorption level, $X_w = 0.0125$ (55% RH). In the case of amorphous PVP, there is a very constant interaction energy over a broad range of water up to about 1 mol water:1 mol monomer, above which the water enthalpy approaches that of liquid water. At $X_w = 0.6$, the RH is 60%, which was shown in previous work to be the point at which T_g is reduced to the temperature of the experiment for PVP K30.[37] Thus, above $X_w = 0.6$, PVP glass converts to the concentrated, viscous solution.

The enthalpy results for genistein, indomethacin, and lactose (Fig. 3) illustrate at low sorption levels (e.g., near $X_w = 0.002$) that the H_2O–solid interaction is endothermic relative to the enthalpy of bulk liquid water. At low sorption level, the ratio of water molecules interacting with the solid relative to H_2O–H_2O interactions is higher. Even if the H_2O–solid interaction were as strong as H_2O–H_2O, one would expect an endothermic enthalpy because of the more interfacial (or two-dimensional) nature of the interaction relative to a full three-dimensional system. If the H_2O–solid interactions were weaker than H_2O–H_2O, then an even more endothermic water enthalpy would be observed. Weak H_2O–solid interactions should result in less restricted motions, which generally tighten quantum mechanical energy level spacing in the translations, rotations, and vibrations, which in turn increases the Boltzmann population accessing the greater number of energy levels, thereby increasing water's partial molar entropy. This effect is consistent with the observed partial molar entropy rankings for genistein, indomethacin, and lactose monohydrate, which follows that of partial molar enthalpy. For genistein and indomethacin at $X_w \sim 0.002$, water's enthalpy is ~12,000 J/mol and entropy is ~40–60 J/K-mol. For lactose at $X_w \sim 0.002$, water's enthalpy is lower at ~6000 J/mol, which reflects a stronger H_2O–solid

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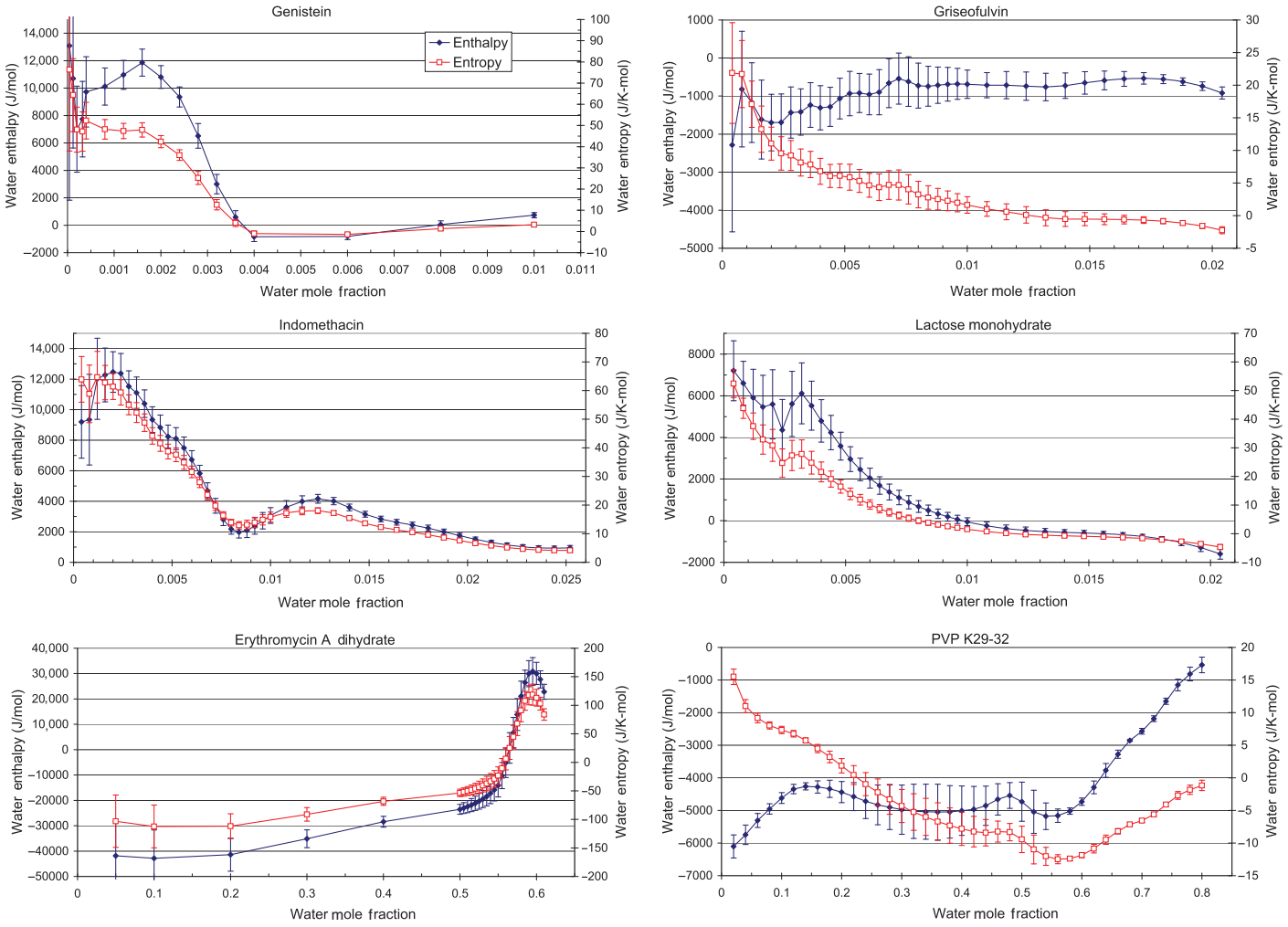

Figure 3. Partial molar enthalpy and entropy of sorbed water at 25°C.

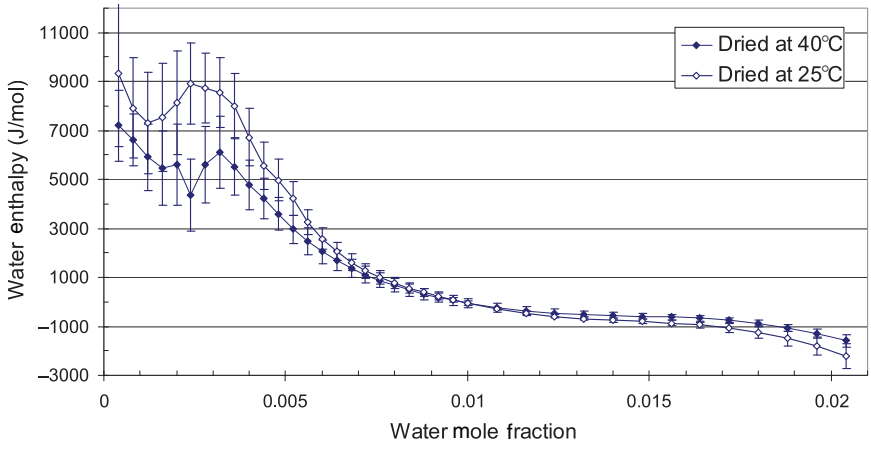

Figure 4. Partial molar enthalpy of water sorbed on lactose monohydrate with drying at 25°C and 40°C.

interaction compared with genistein and indomethacin, and exhibits correspondingly lower entropy of ~30 J/K-mol.

The enthalpy results for griseofulvin (Fig. 3) demonstrate a slightly exothermic enthalpy at low sorption level compared with bulk liquid water. At low amounts of sorption where H_2O–solid interactions are dominant, if the forces are much stronger than H_2O–H_2O, the enthalpy will be lower than that of liquid water, which evidently appears to be the case for H_2O–griseofulvin and could reflect strong H-bonding. It is also possible that some absorption occurs even at low water content to

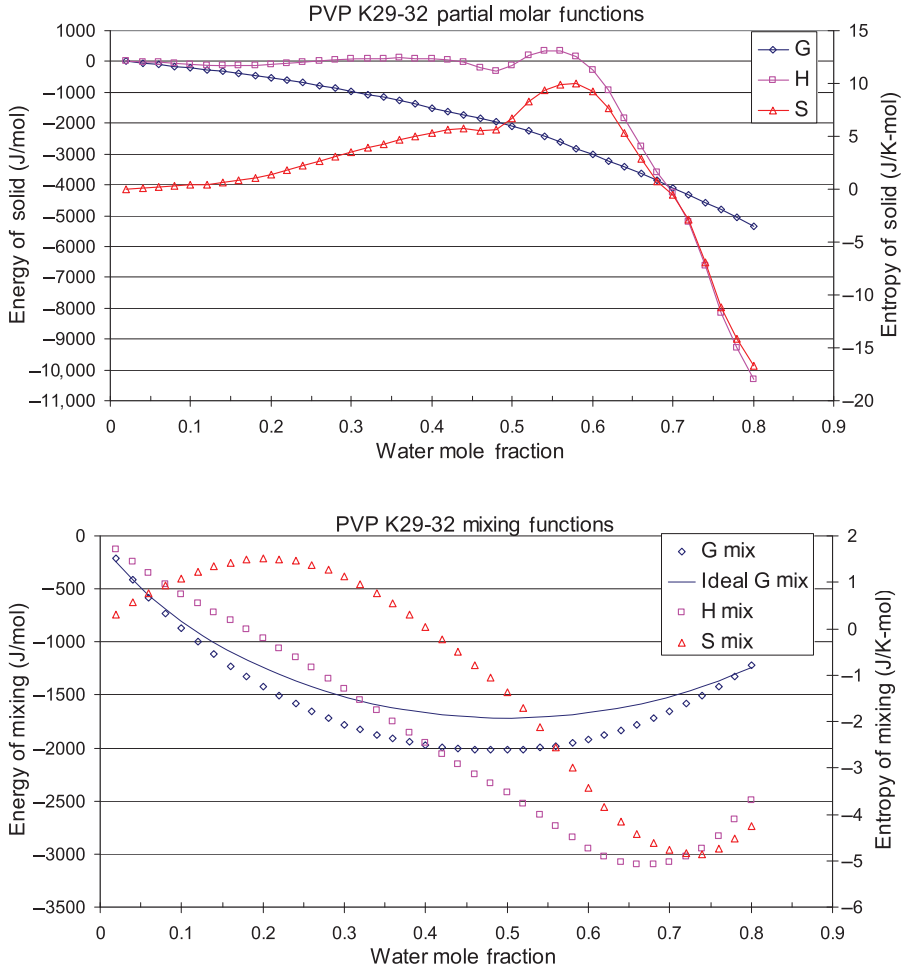

Figure 5. Polyvinylpyrrolidone K29-32 partial molar quantities (top) and overall mixing functions (bottom).

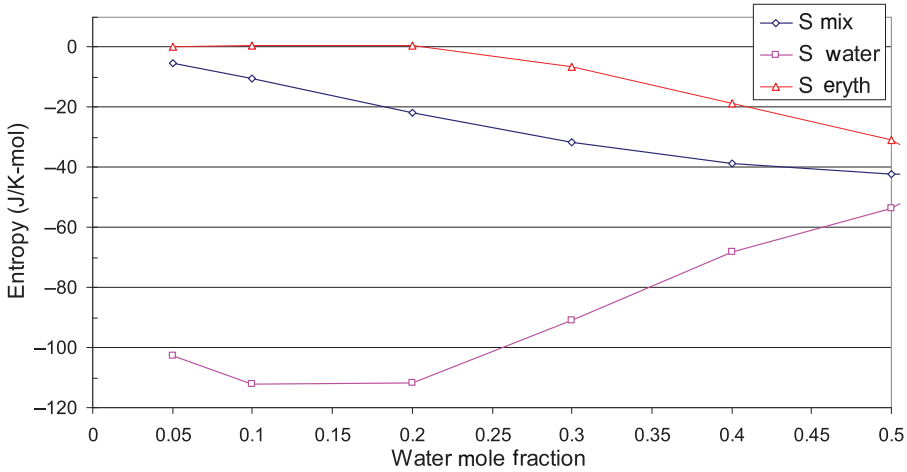

Figure 6. Erythromycin partial molar and mixing entropy functions for the channel filling regime.

account for the lower enthalpy, that is, greater three-dimensional interaction exists because of features such as surface and bulk defect sites. Such strong forces may also lead to more constrained motions and lower entropy. This effect is observed with griseofulvin, which has a partial molar enthalpy of approximately −1500 J/mol and partial molar entropy of ~20 J/K-mol at $X_w \sim 0.002$ (RH ~10%). In comparison to the other crystalline solids—genistein, indomethacin, and lactose as described above—water in grisoefulvin exhibits the lowest partial molar enthalpy and entropy. Clearly, the entropy is lower for water when it exhibits a stronger interaction with the solid phase, whether it arises from fundamentally stronger intermolecular forces or from surface and crystal structure features, which thermodynamics alone cannot distinguish.

Another consequence of a strong H_2O–solid interaction is that as RH increases and the water content rises, water's partial molar enthalpy will not asymptotically approach that of bulk water. With just several water layers at higher RH, the H_2O–solid interaction contribution is significant to the overall enthalpy that includes H_2O–H_2O association. In this case, it is expected that water's partial molar enthalpy will remain negative with regard to bulk water, which is observed for griseofulvin and is consistent with water's exothermic enthalpy at low RH that remains exothermic at higher RH.

It should be noted along these lines that a partial molar enthalpy close to that of bulk liquid water at low sorption level or RH is interpreted to reflect strong H_2O–solid interaction, not comparable, considering that in a more two-dimensional adsorbed state, water is lacking significant lateral interaction, and for its enthalpy to be near that of bulk liquid water, its attractive force with the solid must be strong. It is possible that this effect may not be because of a fundamentally stronger interaction force of water with a drug molecule, but could arise from a more three-dimensional sorption state involving crystal defects and surface amorphous content.

For the crystalline solids (except erythromycin), at low sorption level it is generally observed that water's entropy is higher than that of bulk liquid water (Fig. 3). Evidently, there are sufficient degrees of freedom in water molecule motions compared with bulk water to result in higher entropy. One factor may be the strong H-bonding in liquid water that in itself results in the bulk liquid's low entropy. A smaller presence (not complete absence) of this orienting, more generally motion-constraining force in H_2O–solid interactions, could produce higher entropy even in the two-dimensional adsorbed regime of low water content. As the water content increases for these crystalline solids, water's entropy decreases. This drop in entropy is readily explained by reduction of available sites or space as well as increased H_2O–H_2O interactions such as H-bonding that limit motional freedom. In terms of space limitation, the more constrained motions have wider quantum mechanical energy level spacing and consequent reduction in the number of accessible microstates. The statistical mechanical model of adsorption clearly illustrates how the entropy should decrease at higher sorption level. In the relation, for N_s molecules adsorbed on a solid surface with N_{sites} available sites, the chemical potential and partial molar entropies are

$$\mu_s = kT\left[\ln\left(\frac{N_s}{N_{sites}-N_s}\right) - \frac{\varepsilon}{kT} - \ln\left(Q_s^{tr,2D}Q_s^{vib}Q_s^{int}\right)\right] \quad (14)$$

$$\bar{S}_s = -\frac{\partial\mu_s}{\partial T} = k\ln\left(\frac{N_{sites}-N_s}{N_s}\right) + k\ln\left(Q_s^{tr,2D}Q_s^{vib}Q_s^{int}\right) + kT\frac{\partial\ln\left(Q_s^{tr,2D}Q_s^{vib}Q_s^{int}\right)}{\partial T} \quad (15)$$

in which ε is the adsorbate–adsorbent interaction energy and the Q_s quantities are the adsorbate partition functions for translation (two-dimensional), vibration, and molecular internal degrees of freedom.[38] It is evident from the first term that the partial molar entropy of the adsorbed gas is high at lower N_s and decreases with increasing adsorption, in particular as the available number of sites (N_{sites}–N_s) decreases. This effect is analogous to the reduction in entropy of bulk phases with reduced volume, arising from widened energy level spacing and reduction in accessible microstates.

As the water level increases for griseofulvin and lactose, and to a lesser extent genistein, the partial molar entropy of water drops below the value for bulk water (Fig. 3). In this regime, with the significant reduction of available sites on/in the solid, water's entropy is reflecting H_2O–solid and H_2O–H_2O interactions less confounded by the available space factor. Although there are more H_2O–H_2O interactions at higher water sorption, those water molecules directly interacting with the solid and perhaps one or two layers above evidently exhibit more constrained motions that results in a net entropy lower than that of liquid water. In effect, water will exhibit more structure because of the H_2O–solid interaction, that is, more "ice-like," than in pure liquid water. This result is observed with griseofulvin and lactose more than for genistein, and is consistent with the ranking of the partial molar entropies of these solids. In fact, for griseofulvin, at high water content, the water enthalpy approaches −500 J/mol and entropy −2 J/K-mol. Ice has an enthalpy of −6000 J/mol and entropy of −20 J/K-mol relative to liquid water, implying qualitatively that any structure arising from the strong H_2O–griseofulvin interaction is about 500/6000 = 1/12th (enthalpy) or 2/20 = 1/10th (entropy) that of ice.

Indomethacin exhibits a distinct feature in a second rise in water's enthalpy (Fig. 3) at intermediate water content (X_w = 0.0125, 55% RH). At low water level, the enthalpy is positive and decreases with increasing RH, which is due to H_2O–H_2O interactions. At intermediate RH, enthalpy and entropy start to increase and go through a maximum before decreasing again toward the pure water values. The maximum in enthalpy and entropy could arise from a capillary condensation effect. For example, intraparticle pores or interparticle contact points could serve as a source for condensation at approximately 50% RH if the pore radius were of the order of 1.5 nm, according to the well-known Kelvin equation

$$\ln\frac{p}{p^0} = -\frac{2\gamma V_m}{rRT}, \quad (16)$$

in which γ and V_m are water's surface tension and molar volume, respectively, T is temperature, R is the ideal gas constant, and r is the pore radius.[2] Given the 1.5 nm size of such pores, the condensed water would exhibit significant interfacial properties, and the enthalpy would be a compensation of the less favorable (more endothermic) H_2O–indomethacin and more favorable H_2O–H_2O interactions. As the pores are so small and there are two water–solid interfaces, it is reasonable to consider that the relative proportions of H_2O–indomethacin and H_2O–H_2O interactions are such that enthalpy could become more endothermic. This interpretation is also consistent with the second rise in water's partial molar entropy. The extra space that becomes available and the extra motional freedom of the weakly interacting H_2O–indomethacin sites are compensated with the lower entropy of the H_2O–H_2O interaction, resulting in a net, small increase in entropy. Above the second maximum, water's enthalpy and entropy start to decrease as more water is sorbed and the proportion of H_2O–H_2O interaction increases toward that of bulk water. The water sorption isotherm of indomethacin is provided in Figure 2 to illustrate a small step at 45%–50% RH that likely arises from a capillary condensation effect. Further support for this interpretation is that

the step-like feature is reversible upon desorption at 5%–10% lower RH (i.e., ~40%–35% RH), and then upon second sorption is still present at the 45%–50% RH region (data not shown). Indomethacin is the only material that exhibited this effect, which is not expected to be a general feature, but is likely to be unique to the process used in making this batch, or even as specific as a process variation for this particular batch. The small-step feature could be dismissed in a single water sorption scan as noise, but multiple scans at multiple temperatures and thermodynamic analysis have revealed its underlying significance.

For the crystalline solids (except erythromycin), it is observed that H_2O–H_2O interactions become significant above $X_w \sim 0.002$ (Fig. 3), where the enthalpy of water begins its approach to the bulk water value. Below $X_w \sim 0.002$, there is variation in enthalpy that could reflect "inherent heterogeneity" of the solid surface or interior access sites, but is difficult to detect because of the noise in the data at these ultralow water contents. Considering the common specific surface area of these crystalline solids as 0.5–1 m^2/g and water's area of 0.10 nm^2/molecule,[24] the estimated surface coverage—that is, area covered by water divided by total area—at $X_w = 0.002$ is approximately 20% or larger, and from the water sorption isotherms (Fig. 2), $X_w = 0.002$ corresponds to RH approximately 10%–40% depending on the material. Thus, it is not surprising that water's enthalpy and entropy start to change significantly above mole fractions of $X_w \sim 0.002$, as the surface coverage would be greater than 20%, where H_2O–H_2O interactions could be expected to influence the thermodynamics. In a recent publication using inverse gas chromatography, inherent surface heterogeneity was detected below a surface coverage of 12%,[39] which is consistent with the results for water sorption in this research in that it appears any inherent surface heterogeneity if present is below 20% surface coverage. In the case of PVP, the moisture mass uptake is significant even at the lowest RH, and any variation is not expected to be noise related (notice small error bars in Fig. 3), so the more exothermic heat that arises at $X_w < 0.15$ is likely representative of stronger H_2O–PVP interactions.

Water sorption into the amorphous material PVP exhibits overall negative partial molar enthalpy compared with pure water (Fig. 3). Below $X_w = 0.15$, water's enthalpy is more negative and from $0.15 < X_w < 0.6$, the enthalpy plateaus at about −5000 J/mol, a value close to the enthalpy of ice compared with water (−6000 J/mol). At $X_w > 0.6$, just above 1 mol of water to 1 mol of vinylpyrrolidone monomer, the enthalpy starts to rise and approach that of pure water. This rise coincides with the glass transition temperature that is lowered to near 25°C at about $X_w = 0.6$ or 60% RH.[37] Thus, above $X_w = 0.6$, the H_2O–PVP mixture becomes a concentrated viscous solution and H_2O–H_2O interactions become increasingly noticeable in terms of enthalpy. Above $X_w = 0.15$ (10% RH), where the enthalpy plateau zone starts, water's entropy is negative relative to pure water, but starts to approach that of pure water above T_g (at $X_w = 0.6$). As water undergoes bulk absorption into PVP, the partial molar enthalpy and entropy of PVP were calculated using the Gibbs–Duhem equations, and are presented in Figure 5. The partial molar enthalpy of PVP remains close to that of the pure, dry glass up to T_g ($X_w = 0.6$), and then becomes increasingly negative in the concentrated solution regime. The closeness of PVP's enthalpy to the dry material in the glassy state is noteworthy, and likely indicates that the "homogeneous" bulk absorption of water is not completely at a molecular level, but that water penetrates into interfacial regions that separate local structural domains, referred to as "microstructure."[40] This model envisions more dense local domains in which the polymer molecules exhibit local order in the packing separated by less dense interfacial regions. This distribution of water in the space between domains would result in fewer H_2O–PVP contacts than a true molecular mixture. Another feature suggesting that water "mixing" in the glass is not completely at the molecular level is the trend in partial molar entropy of water and PVP. Water's entropy drops from 15 J/K-mol at low RH, passes through 0, and then becomes negative with regard to bulk water, all within the glassy phase leading up to T_g. This trend appears to be due to water increasingly interacting with itself. In effect, at low RH, water is in a dilute state in the microstructure (higher entropy), and then progresses to a liquid water-like state (entropy close to that of bulk water), and finally becomes more ice-like as the microstructure space is exhausted at RH = 60%, at which T_g sets in. In fact, water's entropy approaches −15 J/K-mol, a value similar to that for ice relative to liquid water ($\Delta S_{cryst} = -20$ J/K-mol at 0°C). During this evolution of the filling of the microstructure, water's chemical potential is increasing, which would drive more water into PVP's locally ordered domains, eventually resulting in T_g reduction to 25°C. Note that PVP's entropy initially only slowly increases with RH in the glassy phase up to $X_w = 0.6$, maxing out at approximately 10 J/K-mol (Fig. 5, top). This gradual rise in PVP's entropy is consistent with water's gradual penetration into the local domains with increasing chemical potential. If water were completely mixing with PVP from the start at the lowest RH, one would expect PVP's entropy to rise more rapidly as the RH increases. Thus, water's inability to molecularly mix with PVP at low RH is explicable by its low enthalpy and sufficiently high entropy in the microstructure environment, resulting in too low of a chemical potential to significantly distribute into the denser packed glass domains. In the research on structure in amorphous pharmaceuticals,[40] the authors noted that XRPD provides the structural information within the domains and that other methods such as vapor sorption should better probe the interfacial microstructure. The partial molar enthalpy and entropy results appear to support this concept. In a later article on structure of PVP in the presence of sorbed water, the positions of the two halos in the XRPD pattern gradually changed with increasing water content, representing evidence for "clustering" of water in PVP.[41] The partial molar enthalpy and entropy findings support the conclusions of the structural changes in the H_2O–PVP system reported in earlier work. Molecular dynamics simulation of water in PVP has also indicated clustering to be present at a water content of 10% (w/w),[42] which corresponds to 30% RH or X_w approximately 0.3 (Fig. 2). From Figure 3, it is evident that at this level of water, the partial molar entropy has just dropped below that of bulk water, indicating that molecular modeling has captured this feature. One last interesting point is that the overall free energy of H_2O–PVP mixing is close to ideal (Fig. 5), but this result is an unusual compensation of very nonideal heat and entropy of mixing arising from the nonhomogeneous microstructure of PVP.

Erythromycin is distinct from the other crystalline solids in that its crystal structure contains channels.[36] Water can be reversibly removed from the channels without significant alteration of crystal structure by drying at low RH, which was

intentionally carried out in this experiment. At low water content, the partial molar enthalpy of water is remarkably negative (approximately −40,000 J/mol) with respect to liquid water because of the channel structure (Fig. 3). The rise in enthalpy at increasing RH is apparently because of the filling of the channels. As the water level approaches the dihydrate stoichiometry, water's enthalpy reaches a maximum value that is positive (~30,000 J/mol). The high, positive water enthalpy reflects a particularly weak H_2O–erythromycin surface interaction, weaker than for all other drugs examined in this research. This finding makes the incredibly exothermic enthalpy of channel filling all the more remarkable. The partial molar entropy of water follows that of enthalpy, with an ultralow value of approximately −100 J/K-mol at low water content. Negative entropy with regard to pure liquid water is expected because of the crystalline nature of water in the channels. Both the enthalpy and entropy of water in the channels are significantly lower than for ice compared with liquid water, as for ice $\Delta H_{\text{cryst}} = -6000$ J/mol and $\Delta S_{\text{cryst}} = -20$ J/K-mol at 0°C. It may appear impossible that water's entropy could be 100 J/K-mol lower than that of water or approximately 80 J/K-mol lower than that of ice. Indeed, liquid water's third law absolute entropy at 25°C is 70.0 J/K-mol,[43] and for erythromycin's channel water entropy to be 100 J/K-mol lower signifies that it has a negative partial molar entropy, specifically −30 J/K-mol. Negative partial molar quantities simply indicate that as material is added, the thermodynamic property decreases. In particular, as water is added to dehydrated erythromycin, the total entropy decreases. This effect occurs because the added water does not increase the partial molar entropy of erythromycin much, and the water molecules in the confined space of the channels exhibit very restricted motions, resulting in a net total entropy decrease on mixing, more analytically expressed as

$$\overline{S}_{\text{w}} = \left(\frac{\partial S}{\partial n_{\text{w}}}\right)_{T,P,n_{\text{s}}} \approx \frac{\Delta S}{\Delta n_{\text{w}}} < 0. \tag{17}$$

The partial molar entropies of water, erythromycin, and the total entropy change on mixing are plotted in Figure 6 to illustrate this unusual feature of negative entropy of mixing.

Finally, it is noted that the results of this research were based on drying the materials at 60°C/0% RH so that the thermodynamics could be assessed from the dry state up through the highest water contents. For lactose monohydrate, drying was initially conducted at 40°C/0% RH to try to minimize any crystalline water loss that might introduce defects that could affect the thermodynamics of water sorption, although given the dehydration temperature is approximately 140°C, it seemed unlikely that 40°C drying would influence the subsequent moisture sorption profile. To assess drying in more detail, lactose monohydrate was dried at 25°C/0% RH. It was found that there were no significant changes in the water sorption isotherms and the corresponding water enthalpy and entropy (enthalpy comparison provided in Fig. 4). Uncovering that the thermodynamic functions are affected by sample history does not invalidate the analysis, but on the contrary may provide critical insight into variability in a material's properties upon processing operations that could be important in performance and changes on stability. Thus, the analysis presented in this article may be useful for individual cases of problem solving where detrimental effects of moisture are observed. It is also possible, perhaps expected, that the thermodynamic functions will be different batch-to-batch, which could be important in understanding processing and performance variability for a material.

CONCLUSIONS

This research has illustrated the complete thermodynamic characterization of sorbed water for crystalline solids as well as the amorphous polymer PVP. Although models such as the GAB equation can fit water sorption profiles of crystalline solids well, the average energy of H_2O–solid interactions obtained from the analysis obscures the detailed distribution of H_2O–solid energies as demonstrated in the partial molar enthalpy of sorbed water reported in this article. The results of this research have demonstrated that the partial molar enthalpy of sorbed water can range from positive to negative values relative to the molar enthalpy of liquid water, depending on the solid and presumably the surface chemistry of the crystals.

Crystalline solids were found to exhibit distinctive H_2O–solid interactions at the lowest levels of water uptake near $X_{\text{w}} \sim 0.002$ (RH ~10%–40%). Water's enthalpy was determined to be endothermic (relative to liquid water) for some crystalline solids (genistein, indomethacin, and lactose monohydrate) and exothermic for others (griseofulvin). It was revealed that above this lower RH regime, H_2O–H_2O interactions become apparent as enthalpy and entropy values approach those of pure liquid water. It was also demonstrated that the partial molar entropy of water on crystalline solids (except channel hydrates) is positive at low sorption level, but can become negative with respect to bulk water at higher RH because of structuring effects at the water–solid interface and minimal available sites. The erythromycin channel hydrate case is distinctive in that water's partial molar entropy is negative even at lowest water sorption level and RH, presumably because of the strong structuring effect in channels.

Inherent heterogeneity of the crystalline solid surfaces examined in this research, if present, appears to be at low surface coverage of less than approximately 20%. The RH associated with this surface coverage depends on the material's surface area and water content, and for the compounds examined in this research is estimated to be approximately 10%–40%. It is important to consider this finding when probing surface heterogeneity at ultralow levels by surface analysis techniques. Although heterogeneity may be detected under very dry conditions, the material at the normal RH range of 20%–75% may have sufficient moisture to have completely covered higher energy sites. Thus, detected heterogeneity may not easily correlate with processing or performance challenges for the material.

For the amorphous polymer PVP K29-32, water's enthalpy is significantly exothermic relative to liquid water with a relatively constant value up to the RH at which the glass transition temperature is observed. Also, PVP's enthalpy is unchanged from the pure polymer value throughout the glassy phase. The near constancy of both water and PVP's enthalpy is consistent with the microstructural model of glasses in which water penetrates into interfacial space around structurally coherent domains. Also consistent with the microstructural model is water and PVP's partial molar entropy trends with increasing RH, which indicate significant interaction of water with itself, a result that would be unusual if the glass were a homogeneous solid with sorbed water molecularly mixing with polymer chains.

Overall, the findings of this research are certainly not intuitive. There is a wealth of detail in the thermodynamic interactions of sorbed water in pharmaceutical solids. It is expected that an increased understanding of the partial molar enthalpy and entropy of sorbed water may be important in the characterization of crystalline and amorphous solids, especially in understanding batch-to-batch differences in physicochemical property factors that influence processing and performance of capsules and tablets, as well as changes in performance on stability.

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This article honors Emeritus Prof. George Zografi, whose lifelong devotion to science, research, teaching, and mentoring both humbles and inspires us. From early on, Prof. Zografi understood the importance of water and its interaction with solids and surfaces in pharmaceutics, which he pursued with his students throughout his career, enlightening the pharmaceutical literature with great scientific achievements and practical applications. The research in this article would not have been conceived without the inspiration from Prof. Zografi's accomplishments. Borrowing the first line from Lord Byron, with the rest motivated by Prof. Zografi's career:

Water, water everywhere
So often it confuses us
With the complexity of its interactions
In solids ordered and amorphous

Prof. Zografi did his part to reduce the confusion and illuminate the complexities, and it has been a privilege to conduct this research to attempt to build upon his accomplishments with water–solid interactions.

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