Analysis of the Moisture Sorption Behavior of Amorphous Drug–Polymer Blends

Alfred C. F. Rumondor,[1,2] Hajime Konno,[1,3] Patrick J. Marsac,[1,4] Lynne S. Taylor[1]

[1]*Department of Industrial and Physical Pharmacy, School of Pharmacy, Purdue University, West Lafayette, Indiana*
[2]*Pharmaceutical and Analytical Research Development, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware*
[3]*Pharmaceutical Research and Technology Laboratories, Astellas Pharma, Inc., Yaizu, Shizuoka, Japan*
[4]*Materials Characterization and Technology Assessment, Merck & Co., Inc., West Point, Pennsylvania*

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ABSTRACT: Hydrophobic drugs are often formulated with hydrophilic polymers to form miscible blends called amorphous solid dispersions. The interaction of moisture with these blends is an important topic, both from stability as well as processing perspectives. In this study, the moisture sorption profiles of four different drug–polymer blends, [felodipine–poly(vinylpyrrolidone) (PVP), indomethacin–PVP, felodipine–hypromellose (HPMC), and felodipine–hypromellose acetate succinate (HPMCAS)] were experimentally determined at 25°C, and analyzed using various mathematical models. It was found that the moisture sorption profiles of the drug–polymer blends could not be reconstructed using the weight-averaged sum of the moisture sorbed by each of the components. Application of the Flory–Huggins model for ternary systems to extract drug–polymer interaction parameter (χ_{23}) values using known values of water–drug and water–polymer interaction parameters led to ambiguous conclusions about the systems' thermodynamics. χ_{23} values extracted for felodipine–PVP and indomethacin–PVP using this model ranged from −9.6 to 26.9 and −20.4 to 22.0, respectively. It is thought that the presence of specific drug–polymer interactions changed the water–drug and the water–polymer interactions in the system. Combined with the mathematically small contribution from the term encompassing χ_{23} to the predicted amount of moisture sorbed by the drug–polymer blends, it was concluded that this method cannot be used to unambiguously determine drug–polymer interaction parameters in solid dispersions. Instead, a model with a mean interaction parameter ($\chi_{1,23}$) that considers the drug and the polymer in the blend as a single unit was found to better describe the changing affinity of water for the solid matrix with a change in composition or polymer type. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 1055–1063, 2010

Key words: amorphous; drug–polymer blend; drug delivery systems; moisture sorption; Flory–Huggins

INTRODUCTION

Polymers are frequently used to aid in the delivery of drugs to the body. Recently, there has been a lot of interest in preparing miscible drug–polymer blends to improve the aqueous solubility and hence delivery of extremely water-insoluble crystalline drugs. The improved solubility and dissolution rate of these drug–polymer blends arises, in part, because the crystal lattice of the drug is destroyed by intimate mixing with the polymer to form the blend. The polymer with which the drug is blended serves to inhibit the crystallization of the drug to its more thermodynamically stable, but less soluble, crystalline form.[1–6] The majority of polymers used to form such drug–polymer blends, which are often referred to as amorphous solid dispersions, are somewhat hydrophilic with a high level of disorder and are therefore hygroscopic, resulting in blends that absorbs larger quantities of water as compared to the amorphous drug alone. This hygroscopicity can result in potentially large decreases in the glass transition temperature (T_g), which may lead to crystallization of the drug.[7,8] It is therefore important to understand the tendency of drug–polymer blends to sorb moisture.

Several different mathematical models, both empirical and mechanistic, have been implemented to predict the moisture sorption of binary amorphous drug–polymer blends. The simplest approach is to assume that the moisture sorption profile of a one-phase blend can be predicted using the weight-averaged sum of the moisture sorbed by each of the individual components. Shamblin et al. modeled the moisture sorption behavior of colyophilized amorphous systems comprised of sucrose–poly(vinylpyrrolidone) (PVP) and sucrose–poly(vinylpyrrolidone-*co*-vinylacetate) (PVP/VA) using this approach.[7]

Correspondence to: L. S. Taylor (lstaylor@purdue.edu).
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They reported good correlations between calculated and experimentally determined isotherms for mixtures containing 50 wt % PVP. Poor correlations were observed for systems containing 20 wt % PVP or systems containing PVP/VA above 32% relative humidity (RH), which they attributed to the crystallization of sucrose. Zhang and Zografi used the same approach in their examination of the moisture sorption isotherms of systems comprised of sucrose–PVP and trehalose–PVP.[9] Good correlations were again noted between experimentally determined and calculated moisture sorption isotherms based on the weight-averaged sum of the moisture absorbed by each components as long crystallization of the sugar was not observed. They then used the Flory–Huggins equation for three-component systems to further interrogate the systems, and extracted the interactions parameters (χs) for water–sugar, water–PVP, and sugar–PVP for these systems. The extracted Flory–Huggins χ values were consistent with miscible binary pairs (sugar–water, sugar–PVP, and water–PVP), in agreement with experimental observations.

Crowley and Zografi used a similar approach with amorphous miscible blends comprised of a hydrophobic drug (indomethacin, ursodeoxycholic acid, or indapamide) and PVP.[10] The authors reported good agreement between calculated and experimentally determined values for indomethacin–PVP systems containing 60–90% by weight PVP. However, the drug–polymer interaction parameters they extracted from fitting of the ternary Flory–Huggins equation to the moisture sorption data were in the range of 1.27–1.49, indicative of limited miscibility between the drug–polymer pairs. The authors commented these values were counterintuitive based on known miscibility of this drug–polymer system, for example as indicated by a single T_g for the mixtures,[11] as well as using infrared spectroscopy[12] and powder X-ray diffractogram analysis.[13] Subsequent studies have indicated that the indomethacin–PVP interaction parameter indeed appears to be much lower, consistent with a well-mixed binary system.[14]

In this work, several models for the prediction of moisture sorption by binary amorphous blends are evaluated. In particular, the validity of the Flory–Huggins equation for ternary systems is explored to explain the moisture sorption behavior of one-phase blends comprised of a hydrophobic drug and a hydrophilic polymer.

EXPERIMENTAL

Materials

Four model amorphous blends were used for this study: felodipine–PVP, felodipine–hypromellose (HPMC), felodipine–hypromellose acetate succinate (HPMCAS), and indomethacin–PVP. Felodipine was a generous gift from AstraZeneca, Södertälje, Sweden. HPMC (Pharmacoat® 606) and HPMCAS (AQOAT® AS-MF) were obtained from Shin Etsu Chemical, Tokyo, Japan. PVP K29/32 and indomethacin were purchased from Sigma-Aldrich, St. Louis, MO. Dichloromethane and ethanol were obtained from Mallinckrodt Baker, Paris, KY and PHARMCO-AAPER, Brookfield, CT, respectively.

Methods

Amorphous blends comprised of the model drug (felodipine or indomethacin) and the model polymer (PVP, HPMC, or HPMCAS) were prepared by solvent evaporation. The polymer was dried over phosphorous pentoxide for no less than 1 week, mixed with the drug as received in a glove-box flushed with dry air (RH $<$ 15%), and then dissolved in pure ethanol (indomethacin–PVP) or 1 : 1 (w/w) mixture of dichloromethane-ethanol (felodipine-containing systems). The solvent was then removed using a rotary evaporator apparatus (Brinkman Instruments, Westbury, NY). The resulting samples were placed under vacuum for at least 12 h before they were heated to 5°C above the melting temperature of the pure drug for about a minute to ensure that no crystalline material remained, cooled to room temperature, and then gently ground using a mortar and pestle in the glove-box. All samples prepared using this methodology have been previously demonstrated to form miscible blends with a single T_g.[8,10,15–17]

Moisture sorption isotherms of the samples were measured using a symmetrical gravimetric analyzer (SGA-100; VTI Corporation, Hialeah, FL) at 25°C. Approximately 10 mg material was loaded into the gravimetric analyzer, flushed with dry air (RH $<$ 2%) for 3 h at 25°C, and subsequently exposed to 5, 15, 25, 35, 45, 55, 65, 75, 85, and 95% RH in separate experiments. The samples were left at each RH until a plateau was reached; about 600 min for the pure amorphous drugs and about 1000 min for the drug–polymer blends. Reported vapor sorption isotherms are values recorded at the plateau of each individual experiment at each RH, at which point no evidence of crystallization was observed.

RESULTS AND DISCUSSION

The moisture sorption isotherms for PVP, HPMC, HPMCAS, amorphous indomethacin, and amorphous felodipine are shown in Figure 1. Only data where there was no evidence of drug crystallization during the experiment are reported. The results highlight differences in hydrophilicity between the

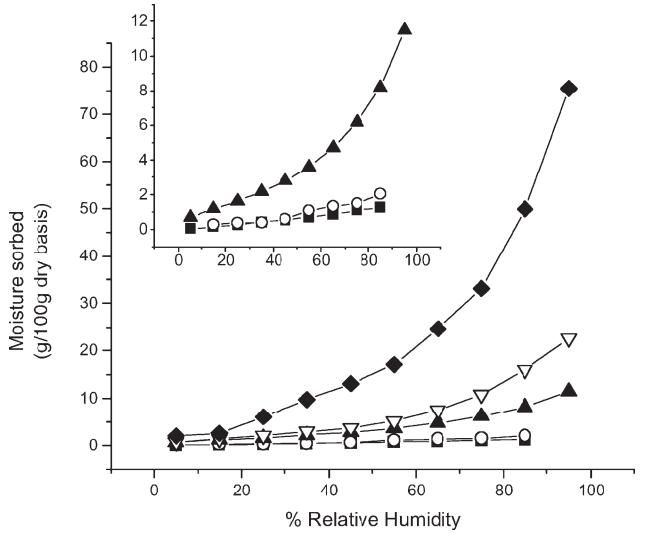

Figure 1 Moisture sorption isotherms of (◆) PVP, (▽) HPMC, (▲) HPMCAS, (○) amorphous indomethacin, and (■) amorphous felodipine at 25°C, with lines drawn to guide the eyes. The last three series are re-plotted in the inset to better show their values.

various compounds used in this study: PVP is quite hydrophilic, absorbing higher amounts of water than the other four compounds used in this study at the same RH and temperature. HPMC sorbs more water than HPMCAS, which is the least hygroscopic polymer. Comparing the two model drugs, indomethacin is slightly less hydrophobic than felodipine, absorbing more water at an equivalent RH.

The moisture sorption isotherms for felodipine–PVP, felodipine–HPMC, felodipine–HPMCAS, and indomethacin–PVP blends are shown in Figures 2–5. For each drug–polymer combination, the amount of moisture sorbed increased as the proportion of the hydrophilic component (polymer) in the mixtures was increased. The increases in the amount of moisture sorbed were higher for PVP-containing systems compared to the HPMC- or HPMCAS-containing model system at the same polymer content, presumably due to the higher polarity, and hence, hygroscopicity of PVP.

Mathematical model based on weight-averaged sum of the moisture sorption of individual components

The simplest model for predicting the moisture sorption of the drug–polymer blends is to use the weight-averaged sum of the moisture sorbed by each component. For this model to work, the miscible blend must behave like a physical mixture of the two components. At the molecular level, this approach requires that the functional groups which form specific interactions with water in the pure amorphous materials have the same ability to interact with moisture when present in the miscible blend. For the model systems studied here, it was found that the moisture sorption values predicted using this simple additivity model were much larger than values measured experimentally. The differences between predicted versus experimental values (normalized against the predicted values) for felodipine–PVP blend is shown in Figure 6. The largest discrepancies were observed at around 25% polymer (w/w). Similar trends were also obtained for indomethacin–PVP blends (results not shown). Crowley and Zografi observed similar results for different hydrophobic drugs and PVP,[10] and the authors suggested the relative size of the discrepancy was related to the formation of drug–polymer specific

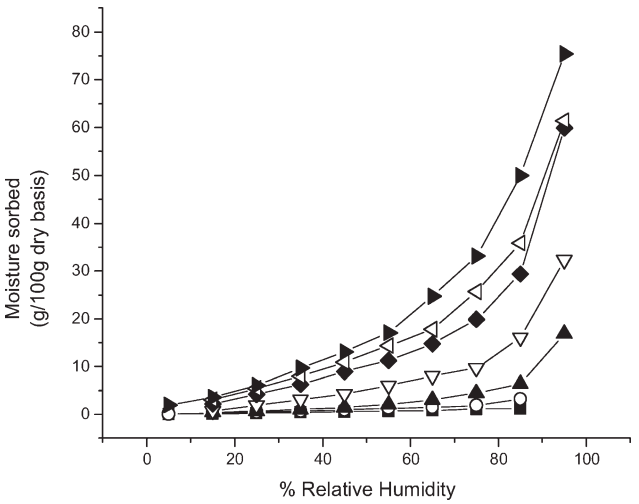

Figure 2 Amounts of moisture sorbed by felodipine-PVP solid dispersion systems containing (■) 0, (○) 10, (▲) 25, (▽) 50, (◆) 75, (◁) 90, and (▶) 100% PVP (dry weight basis), measured at 25°C.

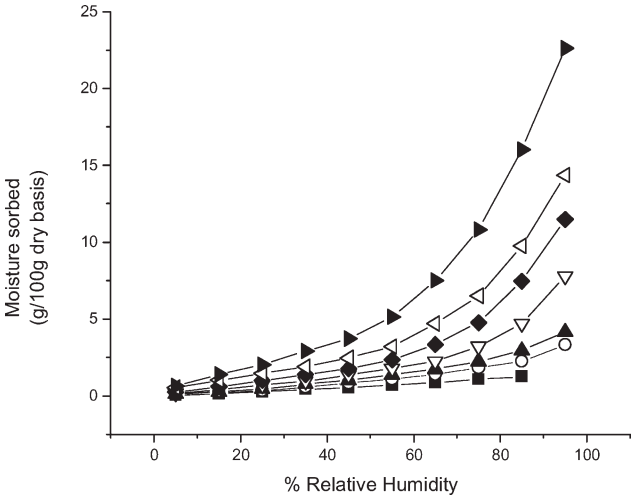

Figure 3 Amounts of moisture sorbed by felodipine-HPMC solid dispersion systems containing (■) 0, (○) 10, (▲) 25, (▽) 50, (◆) 75, (◁) 90, and (▶) 100% HPMC (dry weight basis), measured at 25°C.

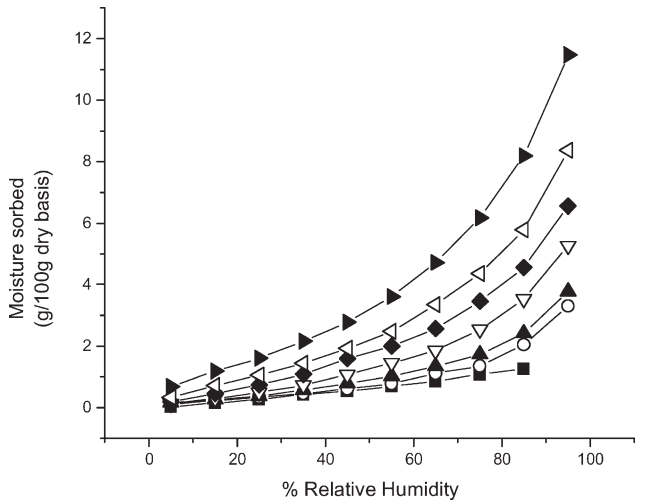

Figure 4 Amounts of moisture sorbed by felodipine-HPMCAS solid dispersion systems containing (■) 0, (○) 15, (▲) 25, (▽) 50, (◆) 70, (◁) 85, and (▶) 100% HPMCAS (dry weight basis), measured at 25°C.

interactions. They hypothesized that the largest difference should occur at compositions corresponding to an approximately 1 : 1 molar ratio of the hydrogen bond donors in the drugs and the hydrogen bond acceptor in the repeating units of PVP. These compositions would correspond to 76 : 24 and 78 : 22 weight ratios for indomethacin–PVP and felodipine–PVP, respectively, and is indeed around where the maximum reduction in moisture sorption is observed for our systems.

For HPMC and HPMCAS dispersions with felodipine, an additivity model again failed to predict the moisture sorption profiles. As for the hydrophobic drug–PVP model systems, experimentally measured moisture sorption values were lower than those

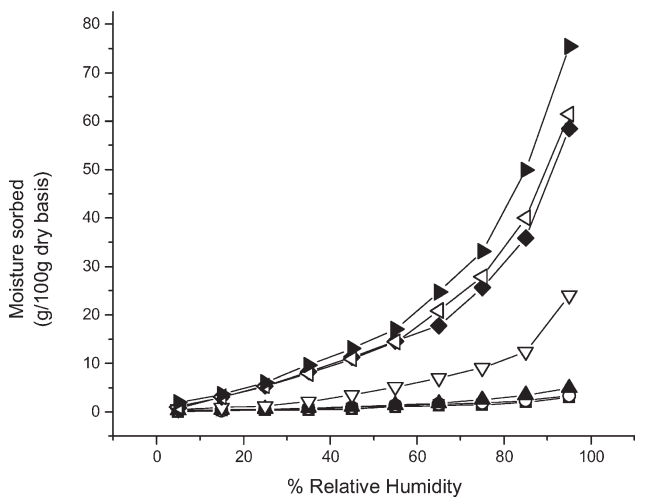

Figure 5 Amounts of moisture sorbed by indomethacin-PVP solid dispersion systems containing (■) 0, (○) 10, (▲) 25, (▽) 50, (◆) 75, (◁) 90, and (▶) 100% PVP (dry weight basis), measured at 25°C.

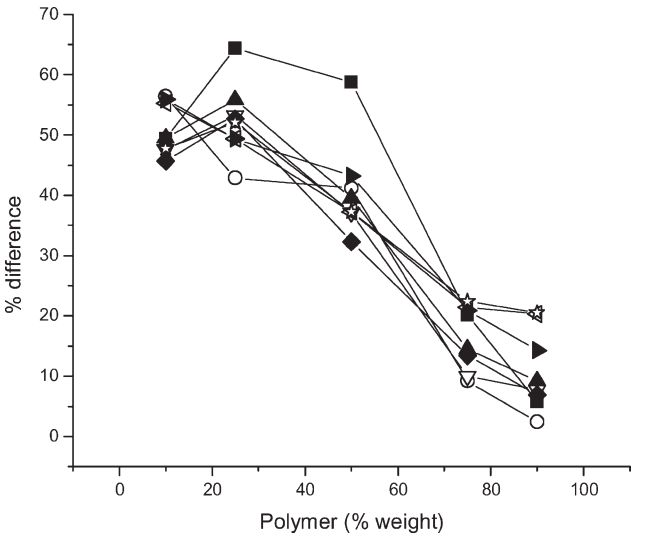

Figure 6 Differences between experimentally obtained moisture sorption values of felodipine-PVP against values predicted from weight-averaged amounts of moisture sorbed by the individual components (normalized against the predicted values) at (■) 15, (○) 25, (▲) 35, (▽) 45, (◆) 55, (◁) 65, (▶) 75, (☆) 85 % RH.

expected based on the additivity model, although the percentage reduction in moisture sorption was lower for these systems and much more dependent on RH. The largest discrepancies between predicted versus measured isotherms for felodipine–HPMC and felodipine–HPMCAS systems occurred between 50 and 70% (w/w) polymer levels, as shown in Figures 7 and 8. Unlike PVP, HPMC and HPMCAS have multiple hydrogen bond donors and acceptors

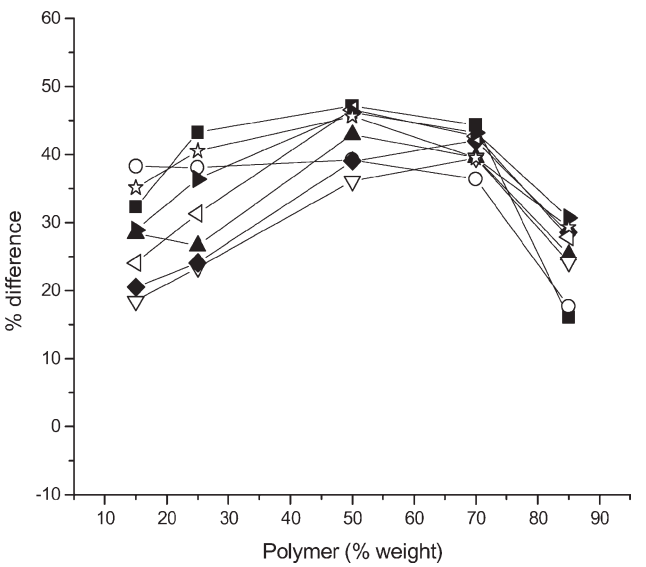

Figure 7 Differences between experimentally obtained moisture sorption values of felodipine-HPMC against values predicted from weight-averaged amounts of moisture sorbed by the individual components (normalized against the predicted values) at (■) 15, (○) 25, (▲) 35, (▽) 45, (◆) 55, (◁) 65, (▶) 75, (☆) 85 % RH.

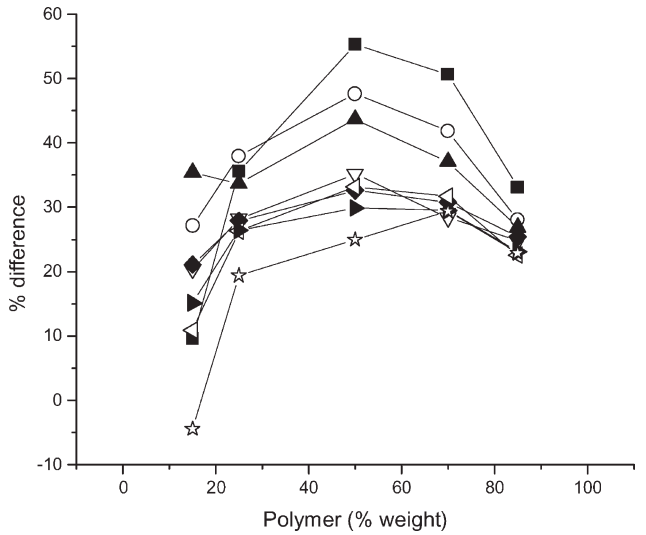

Figure 8 Differences between experimentally obtained moisture sorption values of felodipine-HPMCAS against values predicted from weight-averaged amounts of moisture sorbed by the individual components (normalized against the predicted values) at (■) 15, (○) 25, (▲) 35, (▽) 45, (◆) 55, (◁) 65, (▶) 75, (☆) 85 % RH.

per polymer repeating unit. In addition, it has been suggested that these polymers form weaker interactions with felodipine.[17] If the reduction in moisture uptake is indeed caused by a specific drug–polymer interaction, it is intuitive that blends with cellulose polymers would be less affected as they have multiple sites for hydrogen bonding with water and weaker drug–polymer interactions compared to the PVP systems. It is therefore reasonable to speculate that the magnitude of the discrepancy between the actual and predicted moisture sorbed is related to the nature of the drug–polymer interactions and how these drug–polymer interactions affect the ability of water to interact with the individual components.

Analysis of single-component isotherms using Flory–Huggins theory

Since it is apparent that the nature of the water-individual components interaction and the drug–polymer interactions affect the amount of moisture sorbed by the blends, it is useful to explore models, which incorporate these interactions. The first model that will be considered is the Flory–Huggins model for binary systems, which can be used to better understand the interactions between water and the individual components. This model can be extended to describe a ternary system, as described in the next section.

Flory and Huggins developed equations to try and understand the thermodynamics of polymer solutions.[18] Assuming the absorption of water into an amorphous solid can be treated as a dissolution process, the relative pressure of water vapor can be expressed as a function of vapor volume fraction absorbed in an equation based on the Flory–Huggins model[19,20]

$$\ln\left(\frac{p}{p_0}\right) = \ln \phi_1 + \left(1 - \frac{1}{x_{12}}\right)\phi_2 + \chi_{12}{\phi_2}^2 \qquad (1)$$

Here, subscripts 1 and 2 refer to water and the amorphous solid respectively. The activity of the moisture is given by ratio of the partial vapor pressure of moisture to the saturated vapor pressure (p/p_0), ϕ_1 is the volume fraction of water, ϕ_2 is the volume fraction of the amorphous solid, x_{12} is the relative molecular volume between the two components, and χ_{12} is the Flory–Huggins interaction parameter between water and the amorphous solid. If there is a net attraction between the two species, the value of χ_{12} would be negative. However, if there is a net repulsion between the two species, the value of χ_{12} would be positive. By comparing against the critical interaction parameter value for the binary system ($\chi_{12,c}$), χ_{12} values can be used to predict if a binary mixture will form a one-phase system over all compositions. For mixtures of a small molecule and a polymer (e.g., in polymer solutions), $\chi_{12,c}$ is approximately 0.5, whereas for mixtures of two small molecules, $\chi_{12,c}$ depends on the ratio of the molecular volumes between the two species. Different authors have used this approach to determine the χ_{12} between water and PVP assuming x to be infinity, and reported the value to be around 0.5.[19,20] Crowley and Zografi[10] used this approach for amorphous

TABLE I
List of Constants and Values Used in Calculations Performed

Compound	Felodipine (amorphous)	Indomethacin (amorphous)	PVP	HPMC	HPMCAS	Water
Density (g/cm^3)	1.28	1.335	1.11	1.285	1.285	1.00
Molecular weight (g/mol)	384.3	357.8	40,000	35,600	18,000	18.0
Molar volume (cm^3/mol)	300.2	268.0	36,036	27,704	14,008	18.0
Molecular volume (cm^3/mol)	5.0×10^{-22}	4.5×10^{-22}	6.0×10^{-20}	4.6×10^{-20}	2.3×10^{-20}	3.0×10^{-23}

Density and molecular weight values for amorphous felodipine, amorphous indomethacin, PVP, HPMC, HPMCAS, and water are taken from values reported in references.[14,16]

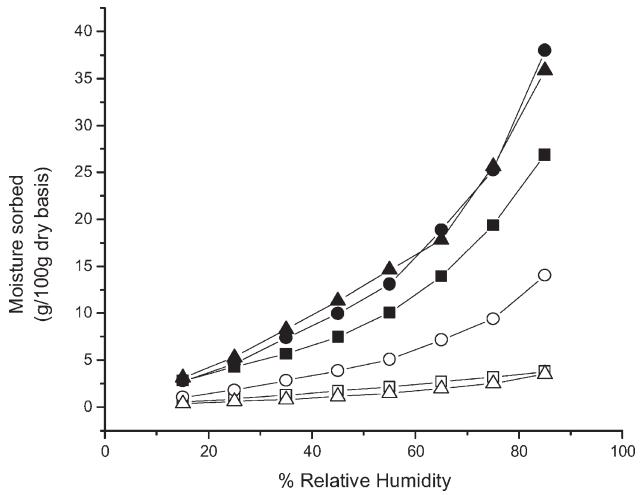

Figure 9 Moisture sorption profiles of indomethacin-PVP solid dispersion samples containing 25% (white) and 75% (black) polymer determined (▲,△) experimentally, (■,□) predicted by equation 2, and (●,○) from weight-averaged sum of the moisture sorbed by each of the systems' components.

indomethacin, and reported a χ_{12} value of 3.13 based on fitting at a single water content value at $p/p_0 = 0.8$, and $x = 2$.

Following a similar approach, experimentally measured moisture sorption data for amorphous felodipine and indomethacin are fitted into eq. (1). The values of the parameters used are listed in Table I. The values of x_{12}'s used in fitting the data to eq. (1) are the ratios between molecular volumes of felodipine-to-water (16.7) and indomethacin-to-water (14.9). Fitting was done using the complete moisture sorption isotherm data collected between $p/p_0 = 0.15$–0.85 or 0.95, by minimizing the sum of squared errors between predicted and experimentally determined $\ln(p/p_0)$ for a given amount of moisture sorbed. The correlation coefficients (r's) were better than 0.985 in all cases, indicating a good fit between values obtained using the Flory–Huggins model to experimental data. From each moisture sorption profile, an average value of water–drug interaction parameter was determined. The $\chi_{\text{water–felodipine}}$ value calculated was 3.27, whereas the $\chi_{\text{water–indomethacin}}$ obtained was 2.86. The large positive χ values obtained indicate unfavorable interactions between both drugs and water, as expected for hydrophobic drugs. The smaller χ_{12} value for indomethacin compared to felodipine indicates that indomethacin has slightly more favorable molecular interactions or mixing with water compared to felodipine.

When a similar approach was applied to the polymers used, the values obtained for $\chi_{\text{water–PVP}}$, $\chi_{\text{water–HPMC}}$, and $\chi_{\text{water–HPMCAS}}$ were 0.36, 1.33, and 1.62, respectively. The positive values larger than 0.5 obtained for HPMC and HPMCAS indicate unfavorable mixing with water, which again is in line with expectation when considering that both polymers are relatively insoluble in water.[21] On the other hand, the value obtained for PVP (which is similar, albeit slightly smaller, to values reported by other authors), emphasizes the fact that this compound is relatively more hydrophilic than the other model compounds used in the study.

Analysis of drug–polymer blend moisture sorption profiles using ternary Flory–Huggins theory

To predict the moisture sorption of the drug–polymer blends, it is necessary to employ a model that considers water-drug, water-polymer, and drug–polymer interactions, such as the ternary form of the Flory–Huggins model. If all three of the binary interaction parameter values are known, then the moisture sorption profile of the dispersion can be predicted using eq. (2), which describes the relationship between the relative vapor pressure of water and the volume fraction of water absorbed. Alternatively, if the moisture sorption profile has been experimentally determined, one of the binary interaction parameters can in principle be extracted by fitting the experimental data into the equation, assuming that the other two interaction parameters are known.

$$\ln\left(\frac{p}{p_0}\right) = \ln\phi_1 + (\phi_2 + \phi_3) - \frac{\phi_2}{x_{12}} - \frac{\phi_3}{13} + (\chi_{12}\phi_2 + \chi_{13}\phi_3)(\phi_2 + \phi_3) - \chi_{23}\frac{\phi_2\phi_3}{x_{12}} \quad (2)$$

Here, subscripts 1, 2, and 3 refer to water, drug, and polymer, respectively, ϕ_i is the volume fractions of the different components, χ_{ij} is the Flory–Huggins interaction parameters for components i and j, and x_{ij} is the molecular size ratio parameters for components i and j.

Since all of the binary interaction parameters for the indomethacin–PVP system are known from independent measurements, the moisture sorption profiles for indomethacin–PVP solid dispersions containing 25 and 75% polymer were predicted using eq. (2), and the results are shown in Figure 9. Values of $\chi_{\text{water–indomethacin}}$ and $\chi_{\text{water–PVP}}$ determined using eq. (1) were used, while $\chi_{\text{indomethacin–PVP}}$ (estimated from melting point depression measurements) was obtained from the literature.[14] Also shown in Figure 9 are the moisture sorption profiles predicted assuming an additivity model as well as the experimentally obtained profiles. It can be seen that the additivity model underpredicts the moisture sorbed for the system containing 75% polymer, and overpredicts the moisture sorption for the dispersion with 25% polymer. At 75% polymer, the experimental data is reasonably similar to the additivity model, whereas at 25% polymer, both the experimentally

TABLE II
Contributions of the Different Enthalpic Terms in the Right Hand Side of eq. (3) Expressed as Percentage of the Overall Adjustment

	% PVP (dry weight)	% Adjustment due to water–drug interactions	% Adjustment due to water–polymer interactions	% Adjustment due to drug–polymer interactions
Indomethacin–PVP	10	98.34	1.63	0.034
	25	95.19	4.73	0.081
	50	86.90	12.96	0.140
	75	68.97	30.87	0.160
	90	42.64	57.24	0.115
Felodipine– PVP	10	98.41	1.56	0.029
	25	95.38	4.55	0.070
	50	87.38	12.50	0.123
	75	69.88	29.98	0.143
	90	43.68	56.22	0.105

observed results and the FH predictions are much lower than the additivity model.

To further analyze the impact of the various terms in eq. (2), the contributions of the different terms to the amount of water sorbed by the solid matrix were analyzed by first rewriting the equation as:

$$\ln \phi_1 = \ln\left(\frac{p}{p_0}\right) - (\phi_2 + \phi_3) - \frac{\phi_2}{x_{12}} - \frac{\phi_3}{13} - \chi_{12}\phi_2(\phi_2 + \phi_3) - \chi_{13}\phi_3(\phi_2 + \phi_3) + \chi_{23}\frac{\phi_2\phi_3}{x_{12}} \quad (3)$$

The first five terms on the right hand side of eq. (3) show that the volume fraction of water sorbed by an amorphous solid dispersion depends on the activity of water (which in turn is related to the storage RH) as well as the contributions of the volume fractions of the drug and the polymer to the entropy of the system. However, the combined effects of including only these five terms will result in either an overprediction or underprediction of the amount of moisture sorbed for nonideal systems where there is a nonzero enthalpy of mixing. The last three terms of the equation adjust the prediction by taking into account how favorable the interactions of water with the individual components are as well as the drug–polymer interactions. Favorable water–drug or water–polymer interactions would lead to negative values of χ_{12} or χ_{13}, which then gives an overall positive contribution to the amount of water sorbed. On the other hand, favorable drug–polymer interactions (negative χ_{23} values) will reduce the predicted amounts of water sorbed.

In the case of indomethacin–PVP and felodipine–PVP, the combined contributions from the first five terms in the equation overpredicted the amount of moisture sorbed by the solid matrix, suggesting that there are unfavorable enthalpic contributions. Including the positive χ_{12} and χ_{13} values (unfavorable interactions with water, particularly in the case of the drug) as well as the negative χ_{23} values (favorable drug–polymer interactions) brought the predicted moisture sorption profile closer to actual values. The contributions from the last three terms in the right hand side of eq. (3) for these model systems, expressed as percentage of the overall adjustment attributed to the enthalpic part of the equation, are listed in Table II.

For both systems, it was found that up to 75% PVP (w/w), the majority of the reduction in the amount of water sorbed by the solid dispersion system can be attributed to the more hydrophobic component in the system, i.e., the drug. Only at the highest level of PVP investigated (90%, w/w) can more of the reduction in the amount of water sorbed be attributed to the polymer. In addition, the contribution from the term encompassing the drug–polymer interaction parameter is negligible for all cases. This result highlights the insensitivity of the ternary Flory–Huggins equation to the drug–polymer interaction parameter term, as was also noted by Zhang and Zografi.[9] Mathematically, this means that while drug–polymer interactions do affect the amount of moisture sorbed by the drug–polymer blends, their contributions is dwarfed by the contributions from the hygroscopicity of the individual components.

In applying eq. (2) to either predict moisture sorption profiles from the independently measured binary interaction parameters or to fit the experimental moisture sorption data to extract χ_{23} values, it is assumed that water–drug, water–polymer, and drug–polymer interactions in the ternary systems are the same as in the binary systems. In other words, the presence of the third component does not change the interactions of the binary systems. However, it is unlikely that these assumptions are true and in reality, the presence of drug–polymer interactions would most likely have changed the ability of water to interact with either the drug or the polymer and

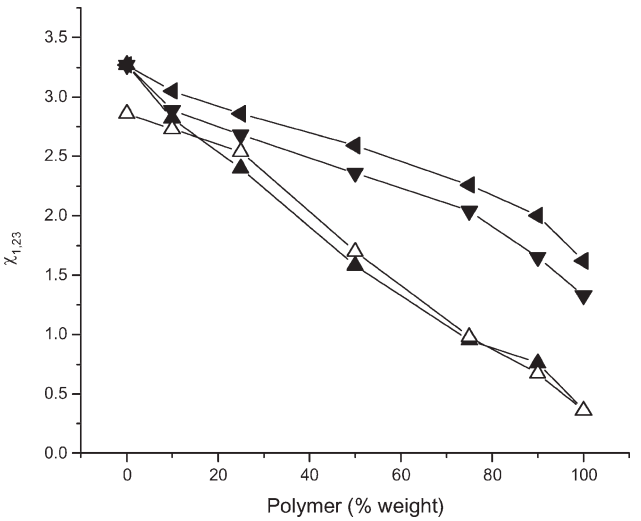

Figure 10 Values of interaction parameters between water and the solid matrix ($\chi_{1,23}$) calculated for (△) indomethacin-PVP, (▲) felodipine-PVP, (▼) felodipine-HPMC, and (◀) felodipine-HPMCAS solid dispersion systems.

the presence of water will change the drug–polymer interactions. Several literature examples exist that illustrate how the interaction of a solvent with a solid matrix can be influenced by the nature of the intermolecular interactions of the matrix components. Gupta and Prausnitz observed a greater extent of solvent absorption by acrylonitrile–butadiene copolymers than either polyacrylonitrile or polybutadiene.[22] This enhanced solvent absorption was attributed to intermolecular repulsion between the heterosegments in the copolymer that was shielded by the solvent, making solvent sorption favorable. Chang et al. report the opposite phenomenon for the water vapor sorption of blends of PVP and poly (acrylic acid).[23] In this work, the authors noted that the miscible polymer blend absorbs less moisture than would be expected based on the individual polymer moisture sorption profiles, and attribute the reduced moisture sorption of the blend to the hydrogen bonding interactions formed between the two polymers. Liu et al. have reported that the solubility of toluene in poly(methylmethacrylate) is decreased when butanone is present.[24] Because of the relatively small contributions of the χ_{23} term as shown by our contribution analysis above, small changes in χ_{12} or χ_{13} in the presence of the other component will result in large changes in χ_{23}, thus drug–polymer interaction parameter values obtained by fitting to experimental data may not be physically meaningful or even show the correct trend, as inferred by Crowley and Zografi.[10] For example, χ_{23} estimates obtained by fitting experimental moisture sorption profile to eq. (2) for felodipine–PVP ranged from −9.6 to 26.9, whereas the values for indomethacin–PVP ranged from −20.4 to 22.0.

Analysis of drug–polymer blend moisture sorption profiles using Flory–Huggins equation with the mean parameter approach

It has been pointed out that the value of the polymer–polymer interaction parameter determined in a ternary system is very dependent on the solvent in which it is measured,[25] and that the binary interaction parameters might change in a ternary system as discussed earlier. Thus in their study of polymer blends, Sabzi and Boushehri,[26] Eliassi and Modarress,[27] and Csaki et al.[28] used a modified approach to evaluate solvent–polymer–polymer blends using Flory–Huggins theory. Following theoretical formalism developed by Panayiotou and Vera,[29] they determined $\chi_{1,23}$, which can be regarded as a *mean parameter* or a *mixed interaction parameter*, characterizing the solvent-segment interactions in solutions of chemically different molecules. The values of $\chi_{1,23}$ can be obtained from the pseudobinary equation:

$$\ln a_1 = \ln \phi_1 + \left(1 - \frac{1}{x_{23}}\right)\phi_{23} + \chi_{1,23}\phi_{23}^2 \qquad (4)$$

This approach can be extended to the drug–polymer blends by considering the mean parameter as an estimate of the affinity between the solvent (water) and the mixture of solids (drug and polymer), which is considered as one unit. In this approach, the assumption that χ_{12} and χ_{13} remain unchanged in the presence or absence of drug–polymer interactions can be relaxed.

By fitting the moisture sorption isotherm data obtained for felodipine–PVP, felodipine–HPMC, felodipine–HPMCAS, and indomethacin–PVP to eq. (4), average values of $\chi_{1,23}$ can be determined, as shown in Figure 10. For this purpose, only moisture sorption isotherm values collected between 15 and 65% RH was used for felodipine–PVP, since this system has been shown to exhibit moisture-induced drug–polymer immiscibility at high RHS.[30] The values of χ_{12} and χ_{13} (water–drug and water–polymer interaction parameters) calculated as a function of water content by fitting experimentally obtained values to eq. (1) are also included.

It can be observed that for all four systems, $\chi_{1,23}$ values calculated decreased as the ratio of polymer-to-drug was increased. This can be interpreted as an increase in the affinity of water to the solid mixture as the percentage of polymer (the hydrophilic component) in the mixture was increased. It can also be observed that the reduction in $\chi_{1,23}$ values as a function of percentage of polymer added was larger for PVP-containing systems compared to HPMC- and HPMCAS-containing systems. This result can be explained by the fact that PVP is more hygroscopic than HPMC or HPMCAS, as previously concluded.

Note that in this approach, the drug–polymer blend is considered as a new solid matrix, with different properties or combined interactions with water compared to the individual components. This assumption seems more appropriate for drug–polymer blends where intimate molecular level mixing between the drug and the polymer molecules have been shown, for example as shown for the model systems used in this study.[16] This method is particularly useful since it does not require *a priori* knowledge about the binary interaction parameters between water and the individual components.

CONCLUSIONS

It was found that the amount of moisture sorbed by several miscible drug–polymer blends containing a hydrophobic drug and a hydrophilic polymer was much lower than the weight-averaged sum of the moisture sorbed by each of the individual components. In addition, while Flory–Huggins theory was successfully applied to model the moisture sorption profile of several single component amorphous solids, care must be taken when using the same model for drug–polymer blends. Direct application of the Flory–Huggins model for ternary systems to extract drug–polymer interaction parameter (χ_{23}) values using known values of water–drug and water–polymer interaction parameter values for two model systems investigated led to erroneous values; using this method, drug–polymer interaction parameter (χ_{23}) values extracted for felodipine–PVP and indomethacin–PVP ranged from -9.6 to 26.9 and -20.4 to 22.0, respectively. It is hypothesized that these results are caused by the incorrect assumption that the presence of drug–polymer interactions would not change drug–water and polymer–water interactions, combined with a mathematically small contribution from the term encompassing χ_{23} to the predicted amount of moisture sorbed by the solid dispersions. A modified Flory–Huggins ternary model that employs a mean interaction parameter was also evaluated. This model considers the drug and the polymer in a blend as one unit, and illustrates the changing affinity of water to the solid matrix as a function of polymer content and type. Application of this model clearly shows that the affinity of water to the solid matrix increases with an increasing weight proportion of the polymer, as well as with increasing polymer hygroscopicity.

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