Drug Development and Industrial Pharmacy, 27(3), 227–240 (2001)

RESEARCH PAPER

Thermodynamic Analysis of Water Interaction with Excipient Films

A. S. Achanta,[1,*] P. S. Adusumilli,[1] K. W. James,[1]
and C. T. Rhodes[2]

[1]*SmithKline Beecham Consumer Healthcare, Parsippany, NJ 07054*
[2]*Applied Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881*

ABSTRACT

The interaction of water with excipients that can form moisture-protective coatings was examined earlier by the application of theoretical models. In this study, thermodynamic analysis of water-excipient film systems has been performed to elucidate the mechanistic details of the water-excipient interaction. Partial molal free energies, enthalpies, and entropies were computed for films of lipidic (glyceryl behenate, GB) and polymeric (polyvinyl alcohol, PVA) coating excipients using the temperature dependence of the adsorption process. The analysis of free energy changes showed that excipient films were not inert participants in the water sorption process. The isoteric heats of adsorption confirmed that water formed hydrogen bonds with the excipient films and allowed estimation of number of hydrogen bonds per water molecule. This result also provided the reason for hysteresis during drying. A comparative evaluation of the application of theoretical models and thermodynamic analysis revealed that results obtained from both approaches were not always complementary. An exponential relationship was found to exist between sorption microrate constants and water activity for the PVA films at all temperatures.

KEY WORDS: Dynamic vapor sorption; Moisture barrier films; Sorption thermodynamics; Water-solid interaction.

---

[*] To whom correspondence should be addressed. Fax: 973-889-2390. E-mail: anand.s.achanta@sb.com

www.dekker.com

INTRODUCTION

The quantity and state of moisture present in a pharmaceutical excipient can influence profoundly the performance of the final dosage form of which it is a component. This is particularly important for excipients that can encapsulate solid dosage forms to offer protection from the adverse effects of moisture. Hence, it is important to study the interaction of water with excipient films that are applied to form a moisture-protective coating over the drug-laden substrate. In an earlier report, water sorption behavior of films of glyceryl behenate (GB), a hydrophobic waxy excipient, and of a formulation of polyvinyl alcohol (PVA), a novel polymeric aqueous film coating excipient for moisture-protective applications, was described using the powerful new technique of dynamic vapor sorption (DVST) (1).

Previously, established theoretical models of sorption and desorption were used to understand the water-excipient film interaction as a function of temperature and film thickness. Although application of theoretical models is analytically useful, it does not facilitate comprehensive characterization because of the limited validity of assumptions on which the model was developed. Hence, an investigation of the thermodynamics of water-excipient film systems is necessary to clarify the process of water sorption/desorption. It is the objective of this report to perform a complete thermodynamic analysis of the process by which water interacts with GB and PVA films as temperature varies. Further, the results of this analysis will elucidate the mechanism by which water interacts with these excipient films. A second objective is to perform a comparative evaluation of the results obtained through the application of theoretical models and thermodynamic analysis.

Materials and Methods

GB (Compritol 888 ATO, lot A17008) and PVA (Opadry AMB OY-B-28920, lot 5066503) were obtained from Gattefossé, Saint Priest, France, and Colorcon, West Point, PA, respectively. Films of GB and PVA of varying thicknesses (thin and thick) were cast. The sorption/desorption isotherms for GB and PVA thin films at $T = 293, 303$, and 313 K are presented in Figures 1 and 2,

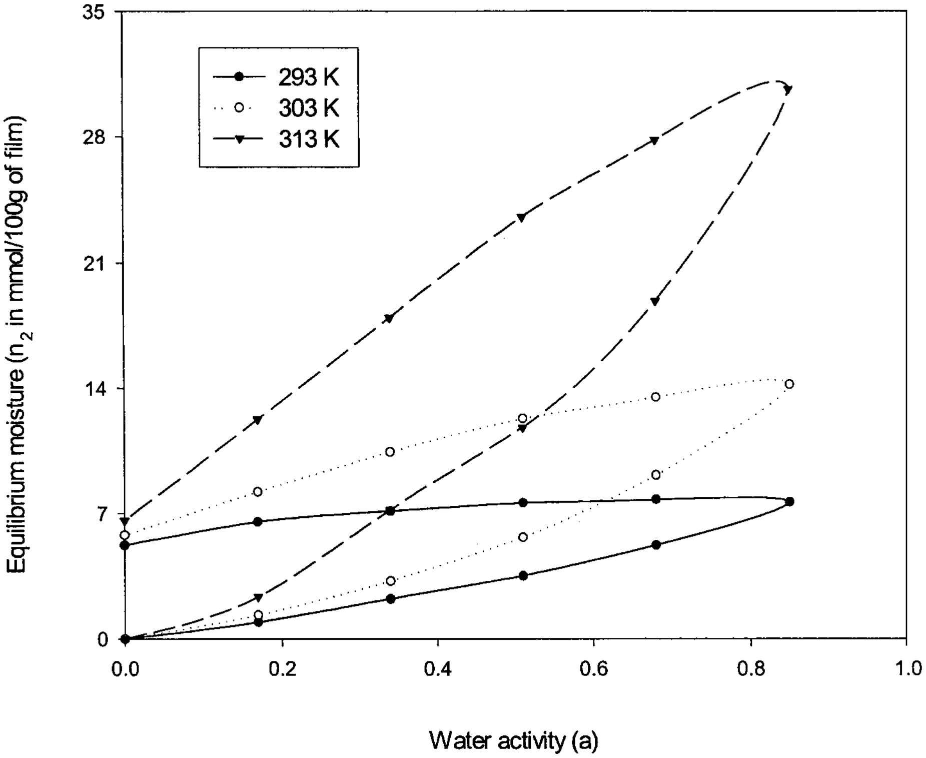

Figure 1. Sorption isotherms for GB thin film at various temperatures. Values of equilibrium moisture are mean of $n = 3$.

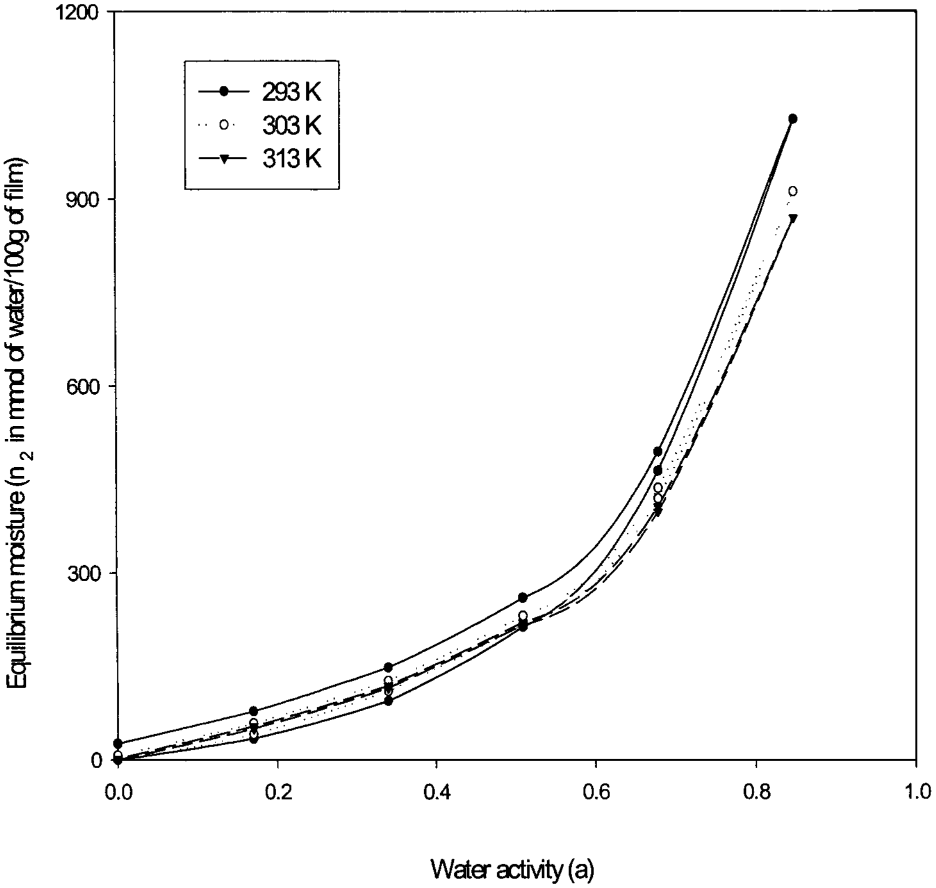

Figure 2. Sorption isotherms for PVA thin film at various temperatures. Values of equilibrium moisture are mean of $n = 3$.

respectively. The thick films were studied for comparison at $T = 303$ K only. The smoothed adsorption and desorption data were obtained from the isotherms by extrapolating the water activity values corresponding to amount of water (n_2 in mmol water/100 g of film) by manual graphing. An example of the smoothed adsorption data is shown in Table 1. All details of the experimental methods have been described in an earlier report and are not repeated here (1).

Theoretical

The method of Tabibi and Hollenbeck based on the thermodynamic theory developed by Copeland and Young has been used to study the thermodynamics of water-excipient film systems (2,3). Standard free energy relations were used to calculate the following thermodynamic properties:

$$\Delta G_2 = RT(\ln a)$$

$$n_1 \Delta G_1 = -RT \int_0^a n_2 d(\ln a)$$

$$\Delta G = n_1 \Delta G_1 + n_2 \Delta G_2$$

$$\Delta G_{2h} = RT \ln\left(\frac{a_d}{a_s}\right)$$

The subscripts 1 and 2 have been used to represent the excipient film (adsorbent) and water (adsorbate), respectively. ΔG_1 and ΔG_2 are the relative partial molal free-energy changes of the excipient and water, respectively; n_1 and n_2 are the number of moles of excipient and water involved in the sorption process respectively; ΔG is the integral free-energy change associated with the

Table 1.

An Illustrative Example of Smoothed Adsorption Data Shown for Water-GB Thin Film System at $T = 293$ K

n_2 (mmol/100 g of Film)	Water Activity	n_2 (mmol/100 g of Film)	Water Activity
0.00	0.000	4.00	0.560
0.25	0.040	4.25	0.595
0.50	0.085	4.50	0.620
0.75	0.135	4.75	0.640
1.00	0.165	5.00	0.665
1.25	0.210	5.25	0.685
1.50	0.240	5.50	0.710
1.75	0.275	5.75	0.740
2.00	0.305	6.00	0.760
2.25	0.345	6.25	0.770
2.50	0.375	6.50	0.785
2.75	0.405	6.75	0.805
3.00	0.450	7.00	0.825
3.25	0.485	7.25	0.840
3.50	0.500	7.50	0.850
3.75	0.535		

adsorption process; a is water activity; R is the universal gas constant; and T is absolute temperature. $\Delta G_{2\mathrm{h}}$ is the free-energy change of water associated with the hysteresis phenomenon, and a_d and a_s denote the water activity during desorption and sorption phases, respectively. The quantity $n_1\Delta G_1$ was determined graphically by plotting (n_2/a) versus a, and the area under the curve was computed using the trapezoidal rule (4). The temperature dependence of the sorption process was used to compute the isoteric (equal coverage) heats of adsorption in the following manner:

$$\Delta H = \left[\frac{\partial\left(\frac{\Delta G}{T}\right)}{\partial\left(\frac{1}{T}\right)}\right]$$

The appropriate free-energy changes were used to compute the corresponding ΔH values for water, excipient film, and total process. The general definition of entropy:

$$\Delta S = \left(\frac{(\Delta H - \Delta G)}{T}\right)$$

was used to compute the entropy changes using the appropriate enthalpy and free-energy changes for the water-excipient film systems at various temperatures.

RESULTS AND DISCUSSION

Free Energy Changes

Relative partial molal free-energy change of water (ΔG_2), weighted relative partial molal free-energy of water ($n_2\Delta G_2$), and excipient film ($n_1\Delta G_1$) along with the integral free-energy of adsorption (ΔG) were computed. Figures 3 and 4, respectively, present ΔG_2 as a function of water sorbed for GB and PVA thin films at different temperatures. The relative partial molal free-energy change of water reflects the difference between adsorption of one mole of water on the excipient film and water, i.e., pure water is used as the standard state. As expected, the greater the dryness of the excipient film, the larger this quantity (ΔG_2), with the negative sign indicating the spontaneous nature of the adsorption process. From Figure 3, for the GB thin film, two points of inflection may be noted at all temperatures in the otherwise monotonous curves. At $T = 313$ K, the inflection points occur at approximately 3 and 8 mmol water/100 g of film. These inflections possibly reflect the completion of monolayer formation and subsequent additional layers of water sorption. For PVA thin film, the inflection points were recorded at approximately 100 and 250 mmol water/100 g of film. Examination of similar plots for thin and thick films of GB and PVA revealed a dramatic difference only in the case of PVA. The

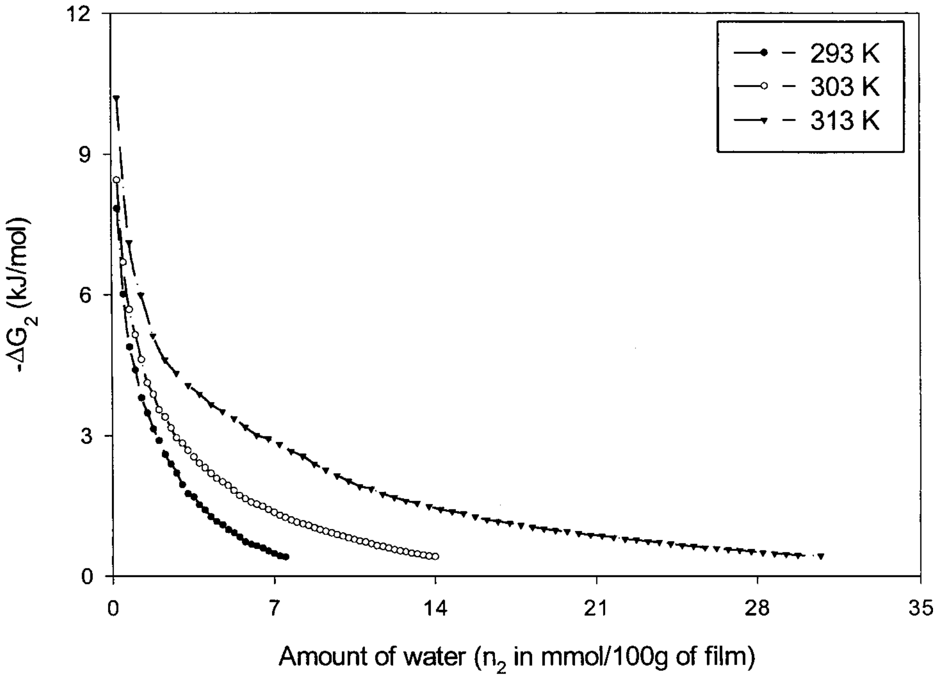

Figure 3. Relative partial molal free energy of adsorbed water on GB thin film at various temperatures.

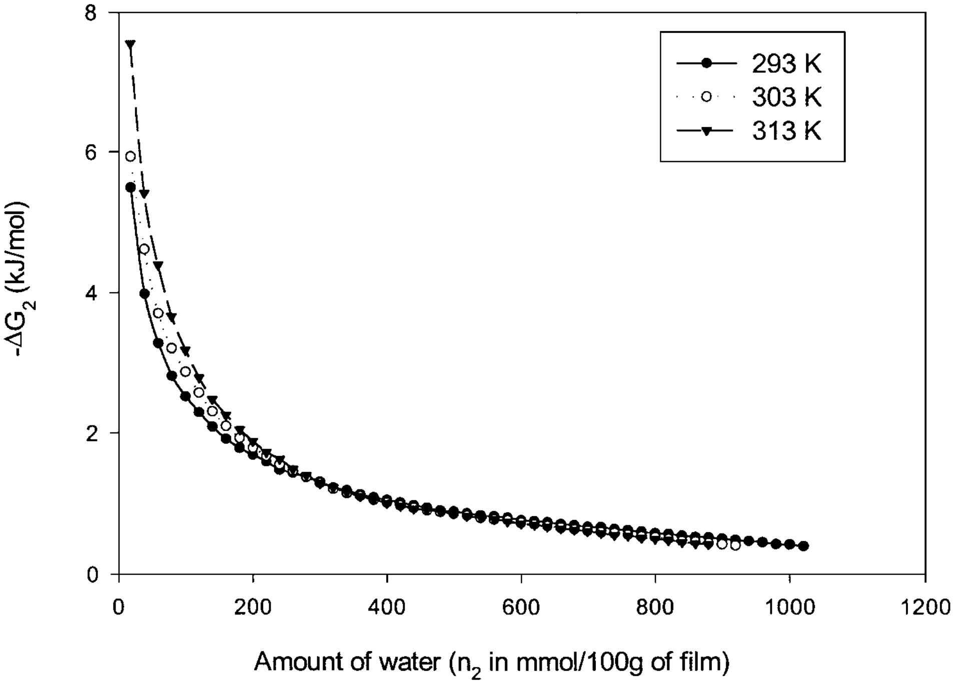

Figure 4. Relative partial molal free energy of adsorbed water on PVA thin film at various temperatures.

thick PVA film displayed a very low ΔG_2 value, suggesting that the drying of the thin film before conducting the sorption experiment was more successful.

The contribution of water to the overall free-energy change associated with the adsorption process is given by the product $n_2\Delta G_2$. Although the thermodynamic quantities of water are important, they do not fully characterize the adsorption process unless the adsorbent (excipient film) is inert. Hence, it is desirable to examine the relative partial molal free-energy change of the adsorbent, ΔG_1, but unfortunately the term $n_1\Delta G_1$ cannot be separated. The quantity n_1 denotes the number of moles of the excipient in the film surface that actually participate in the adsorption process. Because it is impossible to determine the number of layers of the excipient film involved in the sorption process, n_1 cannot be determined. Also, n_1 is not constant and varies with n_2. Hence, the effect of adsorption on the adsorbent and adsorbate has been studied by comparing the quantities $n_1\Delta G_1$, $n_2\Delta G_2$, and ΔG. These quantities for GB and PVA thin films at $T = 303$ K are presented in Figures 5 and 6, respectively.

For both films, the quantity $n_2\Delta G_2$ decreases initially to attain a minima (approximately 4 mmol water/100 g of GB film and 200 mmol water/100 g of PVA film). After additional water sorption, there is a plateau region that is followed by an increasing trend in the quantity. It seems useful to divide the $n_2\Delta G_2$ curve into three distinct regions: region A, representing the decreasing part up to attainment of minima; region B, indicating the plateau region; and region C, indicating the increasing trend in $n_2\Delta G_2$. It is believed that these three regions signify completion of monolayer, formation of intermediate layers, and finally bulk water, respectively. Also, in region A the most dramatic changes occur for water because the film is dry initially and the magnitude of $n_2\Delta G_2$ at the minima is suggested to be an indicator of the affinity of water to the solid. Comparison of $n_2\Delta G_2$ minima at $T = 303$ K for GB and PVA thin films (approximately 10 J/mol for GB film and 400 J/mol for PVA film) shows that water has greater affinity for PVA film. Interestingly, the quantity, $n_1\Delta G_1$ for both excipient films displayed a monotonous decrease with increasing water sorption. Although minor inflections were observed, the decrease was almost linear. Consequently, the assumption of inertness of the excipient during the sorption process is certainly not valid. It has been suggested that this perturbation of the film surface becomes very significant after specific sites of adsorption have been saturated (5). It is also believed that in region A, the film surface is actually restructured owing to the

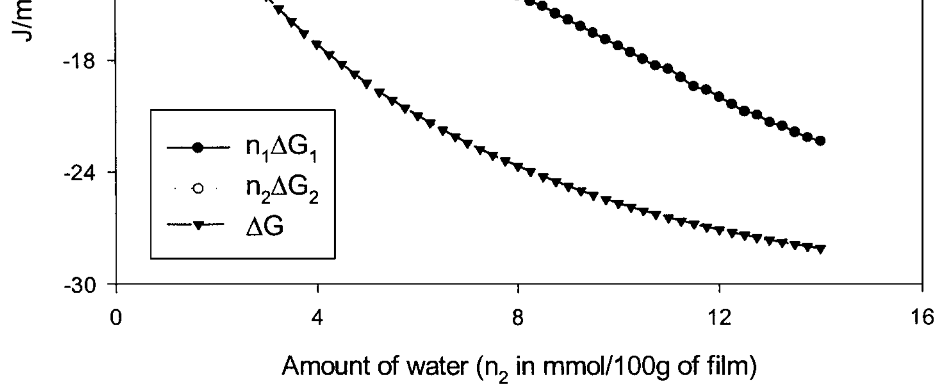

Figure 5. Integral free energy of adsorption (ΔG) and weighted relative partial molal free energies of excipient film ($n_1\Delta G_1$) and water ($n_2\Delta G_2$) for water-GB thin film system at $T = 303$ K.

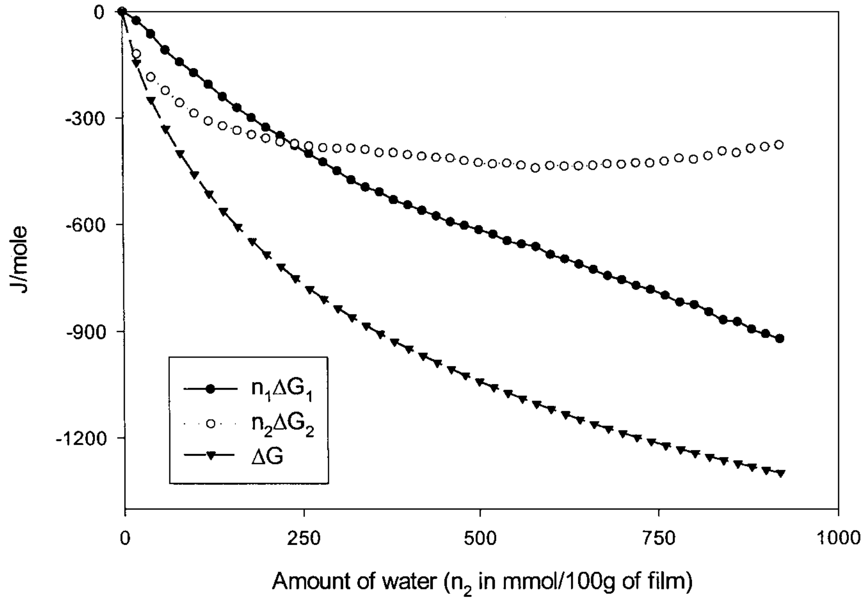

Figure 6. Integral free energy of adsorption (ΔG) and weighted relative partial molal free energies of excipient film ($n_1\Delta G_1$) and water ($n_2\Delta G_2$) for water-PVA thin film system at $T = 303$ K.

interaction with water and this altered surface serves as the substrate for subsequent adsorption. Surprisingly, the integral free-energy function (ΔG) is deceptively smooth and follows a monotonic decline. This observation emphasizes the need to examine the relative contributions of water and the excipient film and proves them to be more informative. The behavior described here was observed consistently for GB and PVA films under all conditions of study.

It is evident from Figures 1 and 2 that both GB and PVA films exhibit hysteresis during desorption. Assuming that the adsorbed and desorbed states reflect different equilibrium positions, the partial molal free energy of water (adsorbate) in the adsorbed and desorbed states may be examined. As noted above, $\Delta G_{2\text{h}}$ is the excess partial molal free energy of water owing to hysteresis phenomena. Actually, $\Delta G_{2\text{h}}$ is the partial molal free energy of water using the sorption part of the isotherm as the standard state. Figures 7 and 8 show the $\Delta G_{2\text{h}}$ values computed for GB and PVA thin films at varying temperatures, respectively. $\Delta G_{2\text{h}}$ values for GB film increase rapidly up to 8 mmol water/100 g of film. Afterward, the rate of approach to $\Delta G_{2\text{h}} = 0$ slows significantly. Similar behavior was noticed for PVA thin film with the inflection point being approximately at 150 mmol water/100 g of film. At $T = 313$ K, there was practically no hysteresis observed for the PVA film. When $\Delta G_{2\text{h}}$ values for GB and PVA films were plotted at $T = 303$ K to examine the effect of film thickness, substantial differences were observed, although the general behavior remained as described above.

Isoteric Heats of Adsorption

Figures 9 and 10, respectively, show ΔH_2 for GB and PVA thin films at different temperatures. At $T = 303$ K for the GB film, five exothermic maxima (at $n_2 \cong 0.75, 1.25, 1.75, 2.25$, and 3.25 mmol/100 g of film) were observed. However at $T = 313$ K, only three exothermic maxima (at $n_2 \cong 0.25, 5.50$, and 7.25 mmol/100 g of film) were noticed highlighting the differences in ΔH_2 profiles at different temperatures. The ΔH_2 function flattens out after $n_2 \cong 4$ mmol/100 g of film at $T = 303$ K, whereas the same shows an increasing trend at amount of water above $n_2 \cong 8$ mmol/100 g of film at $T = 313$ K. These exothermic maxima denote the completion of a tightly bounded monolayer, followed by additional intermediate layers. In the region where ΔH_2 shows an increasing trend after the last exothermic maxima, water molecules progressively assume a more liquid-like structure (i.e., bulk water).

From the studies of Texter et al., the energy values at exothermic maxima can provide additional details of the nature of water interaction (6). The first exothermic maxima of approximately 20 kJ/mol (64 kJ/mol when

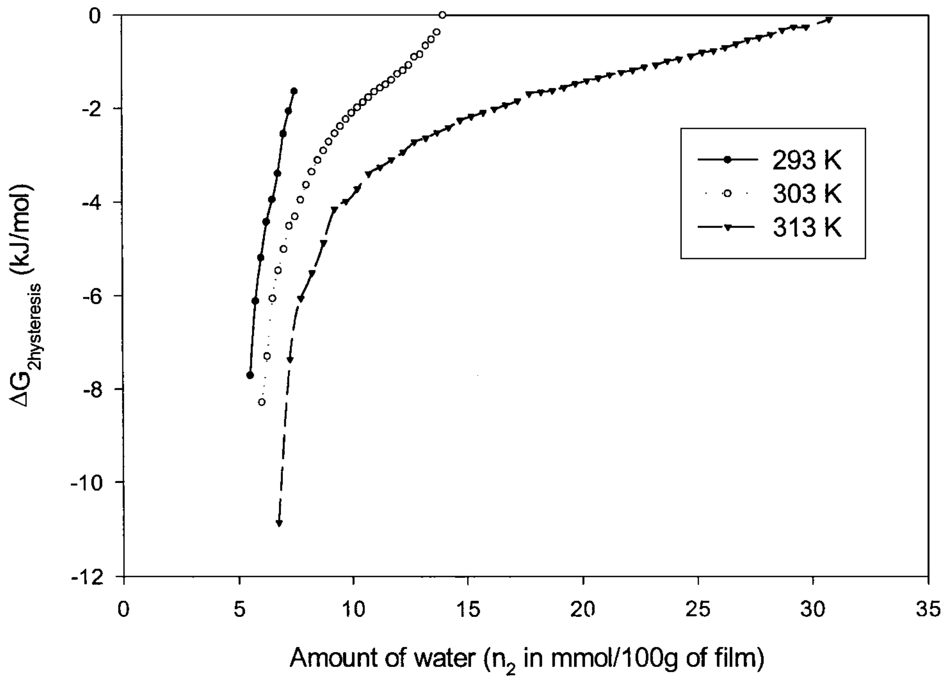

Figure 7. Relative partial molal free energy of hysteresis for adsorbed water on GB thin film at various temperatures.

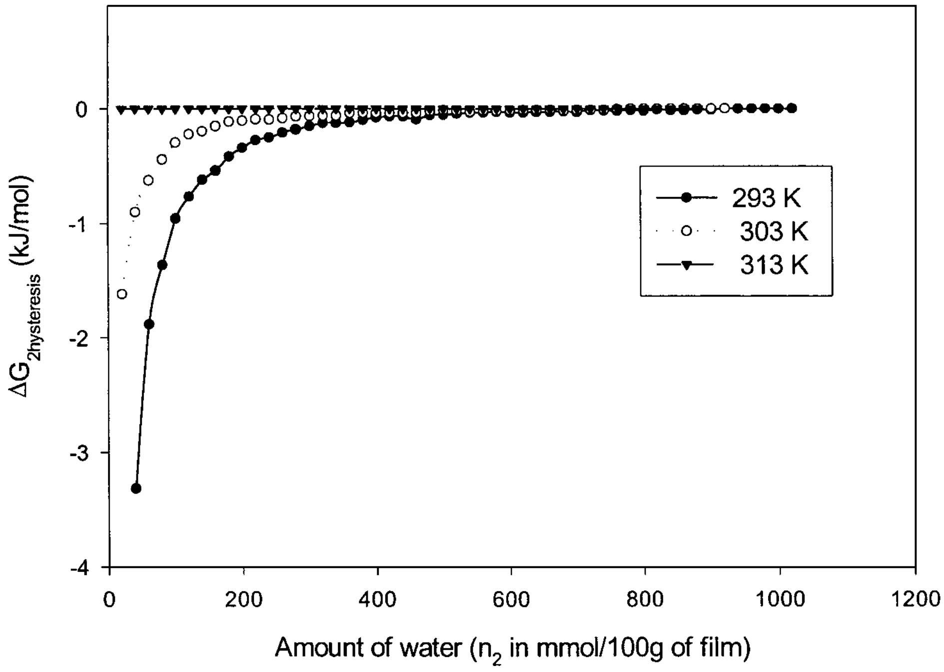

Figure 8. Relative partial molal free energy of hysteresis for adsorbed water on PVA thin film at various temperatures.

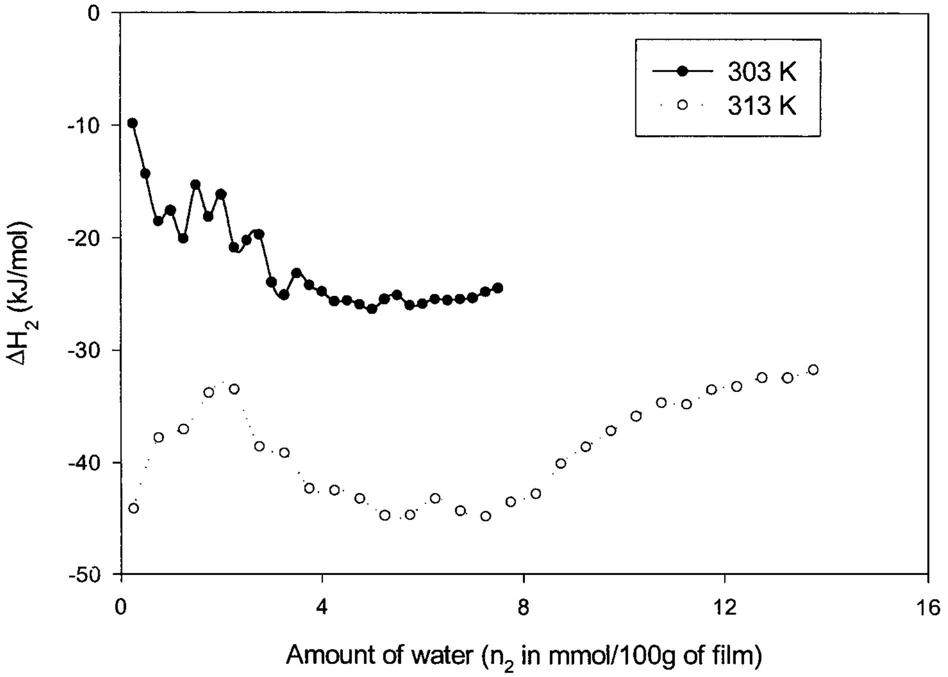

Figure 9. Relative partial molal enthalpy of adsorbed water on GB thin film at various temperatures.

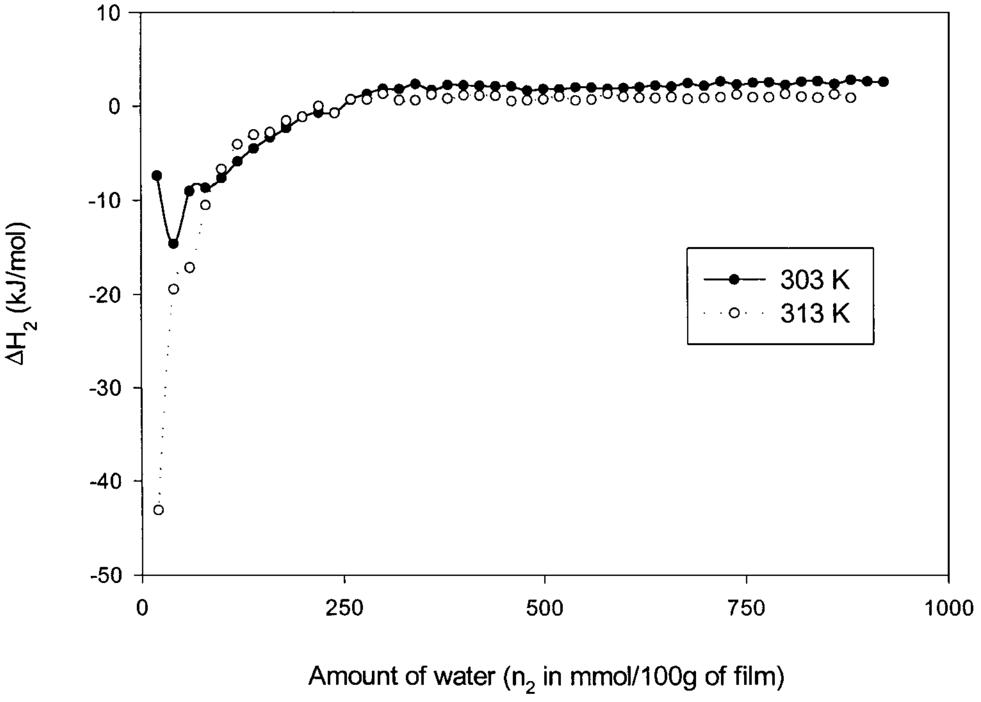

Figure 10. Relative partial molal enthalpy of adsorbed water on PVA thin film at various temperatures.

water vapor is the reference) indicates that each water molecule is involved in two hydrogen bonds. Similarly at $T = 313$ K, an energy value of 90 kJ/mol suggests the formation of three hydrogen bonds per water molecule. Examination of ΔH_2 profiles for PVA thin films showed similar behavior except for the differences in energy values at exothermic maxima. At $T = 303$ K, a maxima of 60 kJ/mol suggests the formation of two hydrogen bonds per water molecule, and at $T = 313$ K, 90 kJ/mol denotes three hydrogen bonds per water molecule. It must be noted that the values of the exothermic maxima are in agreement with the reported range of 60 to 90 kJ/mol believed to indicate chemisorption. This observation corroborates our earlier hypothesis of chemisorption through formation of irreversible hydrogen bonds with the excipient films.

In addition to the enthalpy changes of water, it is also useful to investigate the functions ΔH, $n_1\Delta H_1$, and $n_2\Delta H_2$. Figure 11 presents these functions for the GB thin film at $T = 303$ K. As in case of free-energy changes, the ΔH function is smooth and shows a linear increase, whereas $n_1\Delta H_1$ and $n_2\Delta H_2$ functions are more informative owing to the inflection points (although minor). The enthalpy function of water progressively decreases, whereas the same for the excipient film steadily increases. Similar behavior was also observed at $T = 313$ K. Similar plots of ΔH, $n_1\Delta H_1$, and $n_2\Delta H_2$ for PVA thin film at $T = 303$ K shown in Figure 12 are quite different. The ΔH function increases up to $n_2 = 250$ mmol/100 g of film and then decreases slowly. The $n_2\Delta H_2$ function rapidly attains a minima followed by a progressive increase, whereas $n_1\Delta H_1$ curve reaches a maxima from which a rapid decline is observed. These functions also behaved in the same manner at $T = 313$ K.

Entropy Changes

Figures 13 and 14, respectively, show the entropy variation for water (ΔS_2) for GB and PVA thin films. Interestingly, the entropy profiles are very similar to the enthalpy profiles discussed above. This similarity arises from the fact that ΔG_2, as discussed above, shows dramatic changes only in the lower coverage regions and then flattens out. Combining this observation with the formula used for ΔS_2 computation, differences are evident only in the lower coverage areas, with the shapes of the curves remaining similar. The initial rapid decrease in entropy indicates the lack of mobility as water molecules adsorb on to the film surface in a tightly bound manner. As additional water is sorbed,

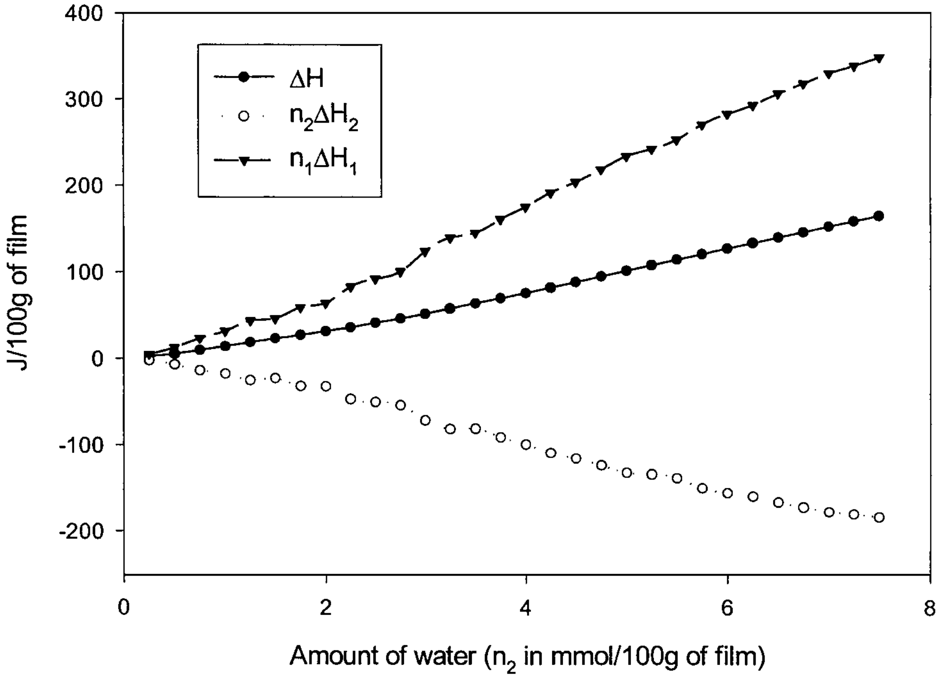

Figure 11. Integral enthalpy of adsorption (ΔH) and weighted relative partial molal enthalpies of excipient film ($n_1\Delta H_1$) and water ($n_2\Delta H_2$) for water-GB thin film system at $T = 303$ K.

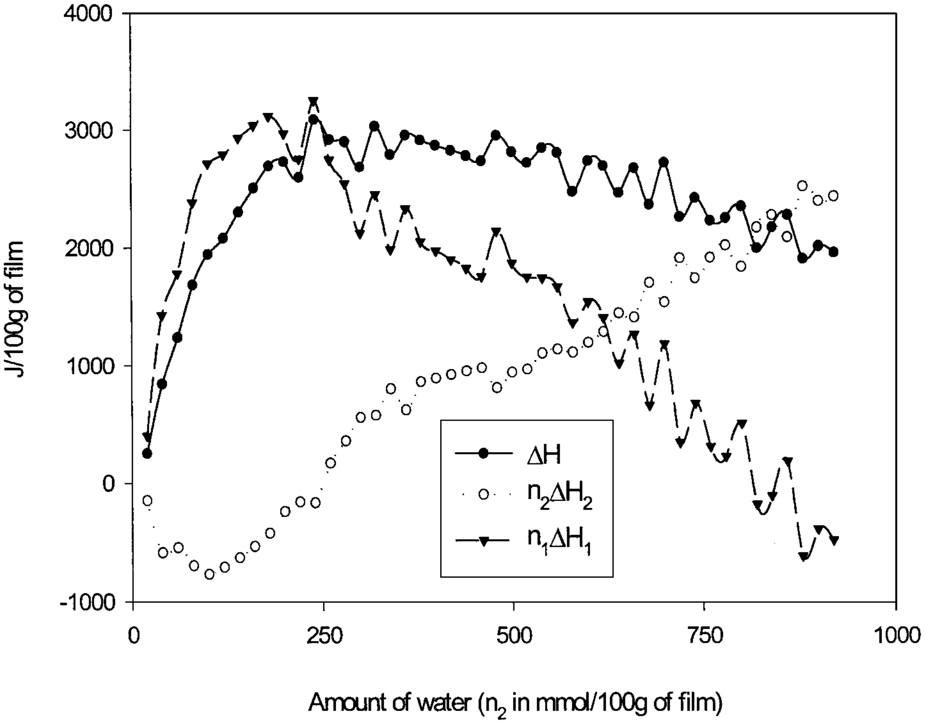

Figure 12. Integral enthalpy of adsorption (ΔH) and weighted relative partial molal enthalpies of excipient film ($n_1\Delta H_1$) and water ($n_2\Delta H_2$) for water-PVA thin film system at $T = 303$ K.

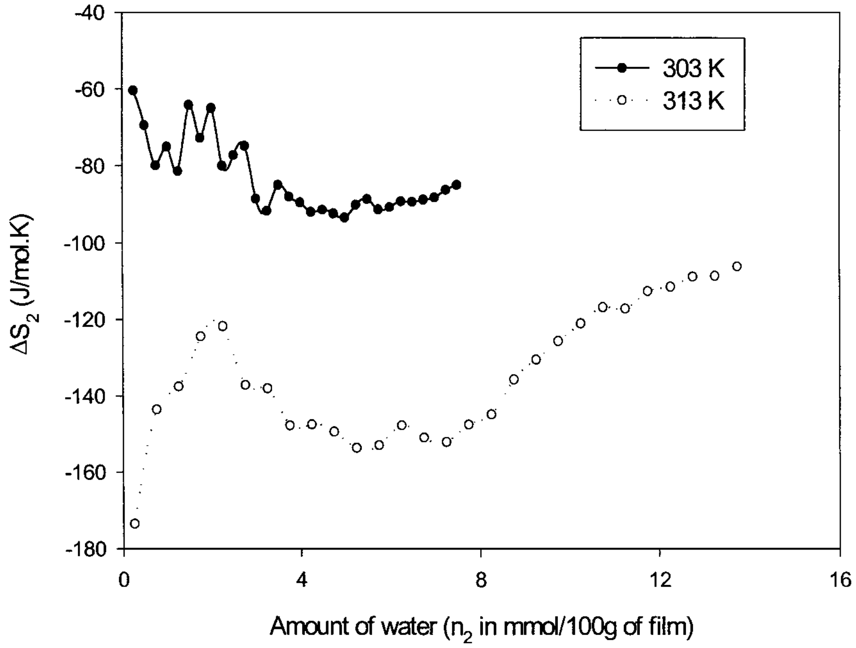

Figure 13. Relative partial molal entropy of adsorbed water on GB thin film at various temperatures.

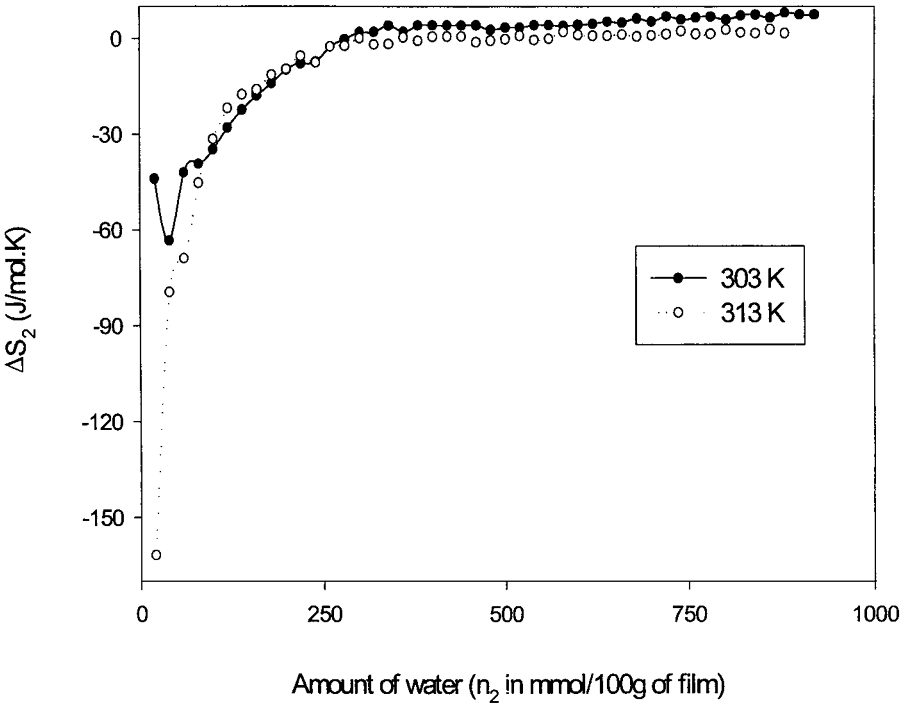

Figure 14. Relative partial molal entropy of adsorbed water on PVA thin film at various temperatures.

the disorder and mobility increases because of the formation of clusters of water molecules around the sorbed water. At greater water content, the formation of two- or three-dimensional condensed surface phases is observed, requiring that water molecules lose part of their translational entropy owing to lateral hydrogen bonding (5).

Examination of $n_1 \Delta S_1$, $n_2 \Delta S_2$, and ΔS was also performed. As discussed, these functions were entirely consistent with the profiles of $n_1 \Delta H_1$, $n_2 \Delta H_2$, and ΔH described above. For the GB film, the $n_2 \Delta S_2$ function showed a monotonic decline, whereas $n_1 \Delta S_1$ and ΔS showed a monotonic increase at both temperatures. In case of PVA thin film, $n_1 \Delta S_1$ and ΔS showed initial increase and then remained constant, whereas $n_2 \Delta S_2$ decreased initially followed by a progressive increase at both temperatures.

Behavior of Microrate Constants

In an earlier report, sorption and desorption microrate constants for both excipient films at various temperatures were estimated. From the results of this analysis, the desorption microrate constants are not true estimates as the excipient films undergo a change owing to hydrogen bonding with the water molecules, and on completion of drying, equilibrium state is not achieved. Hence, the variation of sorption microrate constants with temperature has only been examined here. Only PVA thin film data were used because the GB film data showed wide variation. Figure 15 shows the plots of $\ln(k_1)$ versus water activity at three different temperatures. It is interesting to note that these plots are linear, suggesting an exponential-type relationship between sorption microrate constants and water activity. On linear regression analysis, the fits were excellent ($R^2 > 0.97$ in all cases), and the estimated slopes were very similar (2.12 at $T = 313$ K, 2.43 at $T = 303$ K, and 2.49 at $T = 293$ K). These results suggest the utility of these relationships in predicting sorption microrate constants at varying water activity and temperature.

Comparative Evaluation

A comparative evaluation of the results obtained by application of theoretical models and thermodynamic analysis was performed to understand the nature of information elicited from each method of analysis. The

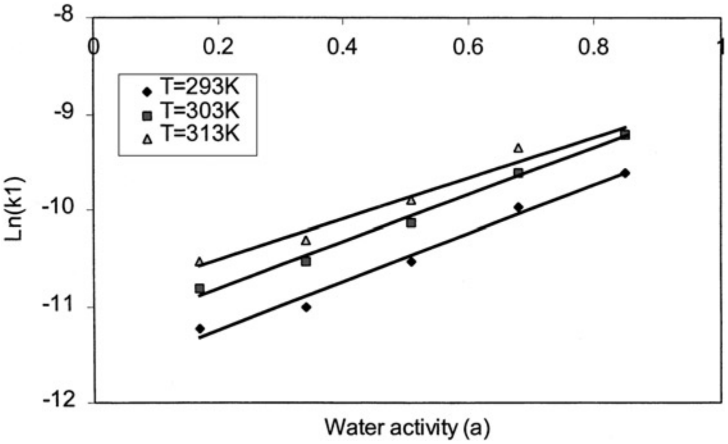

Figure 15. Variation of sorption microrate constants (k_1) with water activity for water-PVA thin film system at different temperature (solid lines are best-fit lines from linear regression).

successful fit of GAB model to sorption data suggested the existence of water in three different states, and this observation has been corroborated by the results of the thermodynamic study. However, there was very poor agreement between the monolayer values (V_m) computed through the use of GAB model and thermodynamic analysis. The observation of type 3 isotherms suggesting the heat of sorption of water in the first layer to be less than that in intermediate layers has been verified through the computation of isoteric heats of adsorption for both excipients.

Whereas the theoretical models assumed inertness of the excipient films in the sorption process, the results from the thermodynamic study have proven this assumption to be invalid. The postulate of hydrogen bonding between water molecules and excipient films to explain hysteresis on drying has been confirmed. Further, the energy values corresponding to the exothermic maxima (in ΔH_2 curves) facilitated the determination of the number of hydrogen bonds formed per water molecule. Theoretical models are useful from an analytical and predictive/modeling perspective (quantitative aspects), and thermodynamic analysis allows clarification of mechanistic details (qualitative aspects) in studying water interaction with excipient film systems.

CONCLUSIONS

The results from both studies clearly show that for comprehensive elucidation of water interaction phenomena with excipient films, it is necessary to use both application of theoretical models and thermodynamic analysis. It can be inferred that the application of theoretical models facilitates comprehension of quantitative aspects and that thermodynamic analysis provides qualitative aspects of water sorption phenomena. Results from both studies confirm that sorbed water exists in three different states: one tightly bound layer, additional less tightly bound layers, and bulk water. This study has confirmed that owing to irreversible hydrogen bonding between water and the excipient films, hysteresis is observed on isothermal drying. Relative partial molal free energies of the adsorbent (excipient films) have shown the assumption of inertness of adsorbent in the adsorption process to be incorrect. It has also been found that sorption microrate constants increased exponentially with water activity for the PVA thin film at all temperatures studied.

ACKNOWLEDGMENT

The generous financial support and access to laboratory and library facilities of SmithKline Beecham Corporation are most gratefully acknowledged.

REFERENCES

1. Achanta, A.S.; Adusumilli, P.S.; James, K.W.; Rhodes, C.T. Hot Melt Coating: Water Sorption Behavior of Excipient Films. Drug Dev. Ind. Pharm. **2001**, *27*, 1–14.

2. Copeland, L.E.; Young, T.F. A Thermodynamic Theory of Adsorption. Adv. Chem. Series **1961**, *33*, 348–355.
3. Tabibi, S.E.; Hollenbeck, R.G. Interaction of Water Vapor and Compressible Sugar. Int. J. Pharm. **1984**, *18*, 169–183.
4. Hollenbeck, R.G.; Peck, G.E.; Kildsig, D.O. Application of Immersional Calorimetry to Investigation of Solid-Liquid Interactions: Microcrystalline Cellulose-water System. J. Pharm. Sci. **1978**, *67*, 1599–1606.
5. Tabibi, S.E. Ph.D. Thesis, Water Vapor Adsorption by Compressible Sugar and Its Effect on Powder Compressibility, University of Maryland (1982).
6. Texter, J.; Klier, K.; Zettlemoyer, A.C. Water at Surfaces. In *Progress in Surface and Membrane Science*. Vol. 12, Cadenhead, P.A., Danielli, J.K., Eds.; Academic Press: New York, 1978, pp. 327–403.