Evaluation of the Moisture Sorption Behaviour of Several Excipients by BET, GAB and Microcalorimetric Approaches

Robert Roškar* and Vojko Kmetec

Faculty of Pharmacy, University of Ljubljana; Aškerčeva 7, 1000 Ljubljana, Slovenia.
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Moisture content of solid-state pharmaceutical products is one of the main factors that affect drug stability, therefore suitable sorption studies need to be performed to assure drug quality throughout their shelf life. The Brunauer–Emmett–Teller (BET) and the Guggenheim–Anderson–de Boer (GAB) models are usually used for this purpose. Using gravimetrically obtained data, both methods were applied in the present work to evaluate the sorption characteristics of several excipients. Microcalorimetric analysis was also performed in order to evaluate the interaction between water and the substances. The results of these experiments show excellent agreement between data and the BET model up to 55% RH and the GAB model over the entire humidity range, confirmed by high values of the statistical determination coefficients. Furthermore, microcalorimetric measurements suggested that the hygroscopicity of solid materials could be estimated approximately using this approach.

Key words water sorption; BET model; GAB model; microcalorimetry

Moisture content of solid dosage forms is one of the main factors that affect stability. The interaction of pharmaceutical solids with water can affect their chemical stability as well as their physical and mechanical properties. The influence of moisture on solid-state stability has therefore been extensively documented.[1,2] It is important now to understand and to anticipate the behaviour of a product exposed to a variety of environmental conditions (*e.g.* relative humidity) in order to recommend appropriate storage conditions for maintaining the quality of a drug throughout its proposed shelf life.

Determination of a moisture sorption isotherm is the general approach for characterizing the relationship between water and solids. The Brunauer–Emmett–Teller (BET) model[3] is the most widely used method for predicting moisture sorption by solids, especially for systems exhibiting type II adsorption behaviour. In some cases it is also suitable for describing isotherms type I, III and IV.[4] An important application of the BET isotherm is the evaluation of solid material surface area.[5] In general, the BET model describes the isotherms well up to a relative humidity of 50%, depending on the material and the type of sorption isotherm. The range is limited because the model cannot describe properly the water sorption in multilayers. In order to analyze the sorption isotherm over a wider range of relative humidities, a Guggenheim–Anderson–de Boer (GAB) model was developed by Guggenheim,[6] Anderson[7] and de Boer[8] based on some modified assumptions of the BET model. These assumptions are: the presence of an intermediate adsorbed layer having different adsorption and liquefaction heats and also the presence of a finite number of adsorption layers. However, the GAB equation also provides the monolayer sorption values and could be used for solid surface area determinations, at the same time covering a broader range of humidity conditions.[9]

Both methods have become very popular in food technology where the theory of mono and multilayer adsorption is applied to the sorption of water by a wide variety of dehydrated foods. Here the monolayer value is considered to represent the optimal moisture content for the preservation of these food products.[10—13] Due to the above mentioned reasons the GAB isotherm has been recommended as the funda-

mental equation for water sorption by foods.[14]

With regard to pharmaceutical additives, there is not much information in the literature except for cellulose, starch and their derivatives,[15—18] so the main objective of our work was to evaluate the sorption behaviour of several pharmaceutically important excipients. Both approaches to the study of moisture sorption behaviour are presented, with the aim of finding the most suitable model for forecasting the sorption behaviour of studied compound. Additionally, isothermal microcalorimetry was used to evaluate the interaction of water with the excipients, based on the ability of this technique to detect energy changes accompanying sorption processes.[19—21]

Experimental

Materials Six excipients—microcrystalline cellulose (Avicel PH 102, FMC), crospovidone (Kollidone CL, BASF), copolividonum (Kollidone VA 64, BASF), magnesium stearate (Magnesii stearas, ACEF), colloidal silica (Aerosil 200, Degussa) and lactose monohydrate (Tablettose 70, Meggle) were employed. Each of the materials was subjected to the moisture sorption study and to thermal analysis.

Water Vapour Sorption Study Equilibrium water adsorption was measured gravimetrically. Five hundreds milligram of previously dried material (in the oven at 100 °C for 4 h) were weighed into Petri dishes and placed in a climatic chamber (VC 4034, Vötsch Industrietechnik). The chamber was set at 20% RH and maintained at 25 °C. The samples were withdrawn at one day intervals, weighed and replaced in the chamber. The RH of the chamber was then raised to an appropriate higher level. This procedure was repeated four to six times within the range of 20 to 98% relative humidity. The moisture content was determined on a dry weight basis using an analytical balance (AG245, Mettler Toledo) of sensitivity 0.01 mg. Experimental data are presented as the average moisture content of three samples.

Determination of BET and GAB Equation Parameters The BET and GAB equation parameters were derived according to Eqs. 1 and 2, respectively:

$$W = \frac{W_m C p / p_0}{(1 - p/p_0)(1 - p/p_0 + C p/p_0)} \tag{1}$$

$$W = \frac{W_m C K p / p_0}{(1 - K p/p_0)(1 - K p/p_0 + C K p/p_0)} \tag{2}$$

where W is the weight of adsorbed water, W_m the weight of water forming a monolayer, C the sorption constant, p/p_0 the relative humidity and K the additional constant for the GAB equation.

The constants from Eqs. 1 and 2 were obtained by an iterative technique

which utilizes the non-linear regression routine provided by statistical software SPSS. The suitability of the fitted model to experimental data was assessed by calculating the determination coefficient (R^2). Experimental points up to 55% relative humidity were used for calculating the BET parameters and data from the entire humidity range were used in the case of the GAB equation.

Microcalorimetry   The calorimeter used in these studies was a MicroDSC III (Setaram) operating in the isothermal mode at 20 °C. Mixing batch vessels with two distinct chambers were used, where the upper chamber was filled with distilled water ($100\,\mu l$) while the previously dried sample of excipient (6—7 mg) was weighed into the lower part. An empty vessel was used as reference. A 10 min equilibration time was allowed before data were collect using the built in Setsoft software package. When the calorimetric signal was well stabilized (15 min), water was introduced into the lower chamber. A calorimetric run was carried out until the signal line stabilized once again; the whole experiment lasted not more than 1.5 h. Every excipient was analyzed three times.

Results and Discussion

The evaluation of water sorption profiles of pharmaceutical ingredients is of utmost importance for a suitable formulation of solid dosage forms. Chemical stability and physical properties of the drug can be changed if too much water is bound due to water sorption ability of the drug constituents. There is a limited number of sorption data for pharmaceutical materials except for starch and cellulose derivatives that exhibit a type II-like isotherm, which can be treated by the BET equation. The BET (Eq. 1) and its extended form, the GAB equation (Eq. 2), were applied to several pharmaceutical substances whose water sorption was studied over the range of 20 to 98% RH. The results of these analyses (Figs. 1—3) were fitted excellently by the BET model up to 55% RH and by the GAB model over the entire humidity range.

The moisture content in the monolayer (W_m), sorption constants (C and K), together with the determination coefficients (R^2) measuring the suitability of the applied model, are listed in Table 1.

The parameters of both equations have been statistically adjusted in the process of finding the best fit of calculated curves to the experimental points. It was found that, in this process, W_m was more influential than other constants. Additionally, in the GAB model the values of constant K were crucial to the adjustments in the upper range of RH, yet with only a small loss of fitting in the lower range. In our study the values of W_m obtained by the two methods are similar, as shown in Table 1, the difference being mainly due to the additional constant K in the GAB equation. For Avicel PH 102,
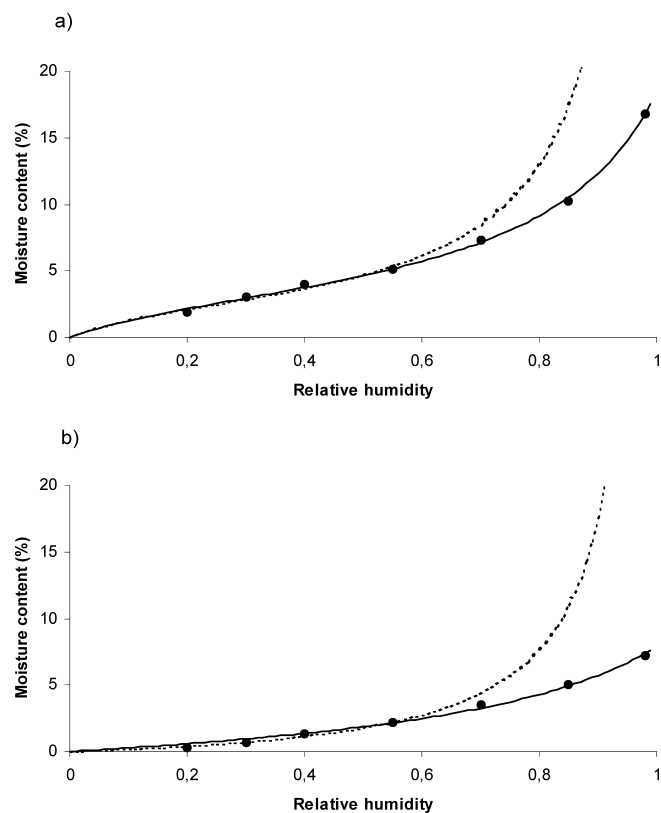

Fig. 1.   Moisture Sorption Isotherms of (a) Avicel PH 102 and (b) Magnesium Stearate Fitted by the BET (Dotted Line) and GAB (Solid Line) Models to the Experimental Data (●)
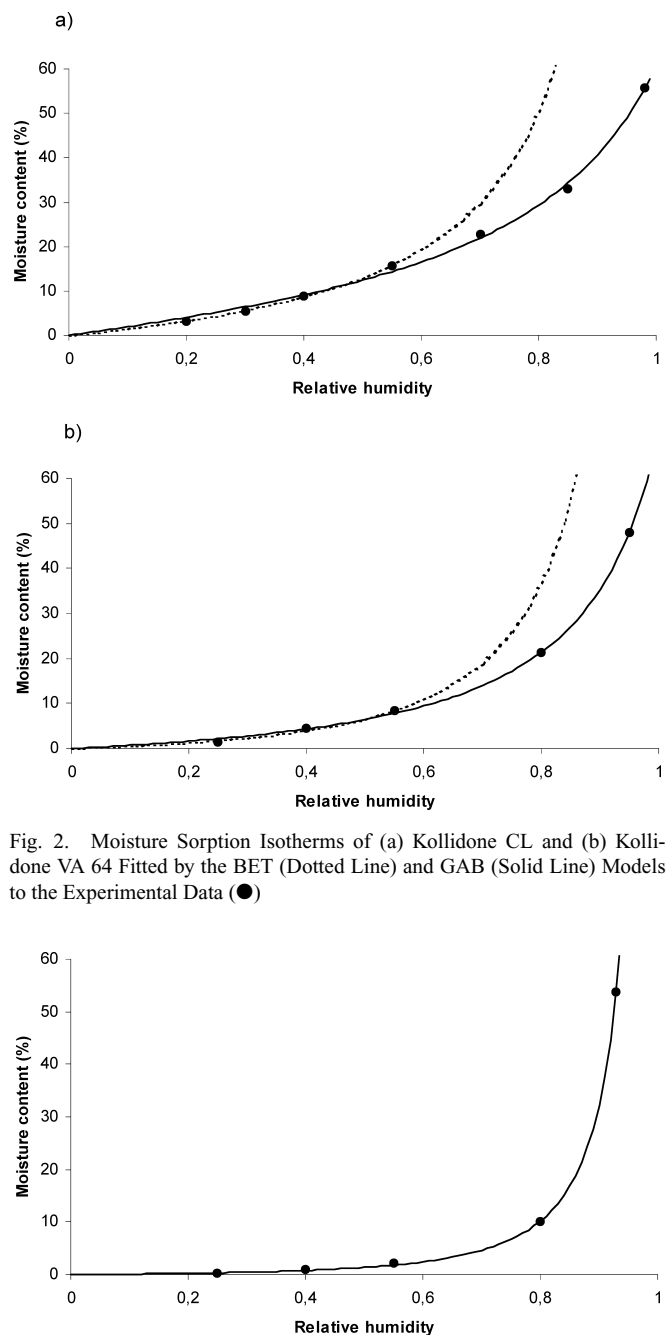

Fig. 2.   Moisture Sorption Isotherms of (a) Kollidone CL and (b) Kollidone VA 64 Fitted by the BET (Dotted Line) and GAB (Solid Line) Models to the Experimental Data (●)
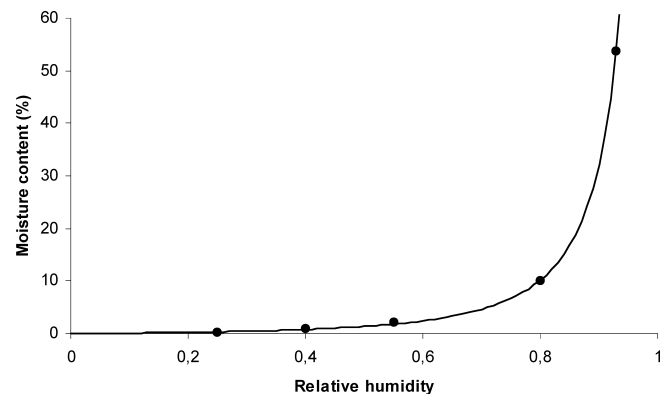

Fig. 3.   Moisture Sorption Isotherm of Aerosil, for Which the BET and the GAB Equations Give the Same Fit to the Experimental Data (●)

which is known to exhibit a type II isotherm, the W_m values obtained in our experiment are similar to those found in the literature.[15—18] High values of W_m obtained in these studies indicate that more than one layer of water molecules is sorbed on compounds at declared experimental conditions. Since higher values of the constant C reflect the suitability of the model used,[4,22] the lower values of C obtained in the case of all excipients, except Avicel PH 102, mean that their isotherms fit more to a type III isotherm category. As a consequence, also the variability of parameters obtained is moderately high (see standard errors in Table 1) causing the calculated W_m to deviate from the actual monolayer.

Excellent agreement between the experimental data and the simulated curves, confirmed by high determination coefficients (Table 1), proved the suitability of the BET model up to approximately 55% RH and the GAB equation over the entire whole humidity range for the excipients studied. With $K=1$ in the case of Aerosil, the GAB equation is reduced to the original BET equation, which describes correctly its sorption behaviour, although in the literature even the Langmuir equation has been used for this substance.[23] Lactose monohydrate is not included in Table 1 as it has not been treated in the same way as other substances due to its non-hygroscopic nature, demonstrated by the absence of water sorp-

Table 1. The Fitted Parameters According to BET and GAB Model Together with the Determination Coefficients (R^2) and Standard Errors (S.E.)

Excipient	BET equation parameters			GAB equation parameters			
	W_m (S.E.)	C (S.E.)	R^2	W_m (S.E.)	C (S.E.)	k (S.E.)	R^2
Avicel PH 102	0.027 (0.002)	6.81 (3.22)	0.9849	0.034 (0.002)	5.64 (1.34)	0.82 (0.01)	0.9987
Kollidone CL	0.124 (0.004)	1.09 (0.06)	0.9997	0.146 (0.030)	1.61 (0.54)	0.79 (0.03)	0.9975
Kollidone VA64	0.124 (0.073)	0.36 (0.29)	0.9914	0.100 (0.028)	0.72 (0.30)	0.88 (0.03)	0.9994
Mg stearate	0.020 (0.005)	0.82 (0.33)	0.9902	0.029 (0.014)	1.26 (3.06)	0.72 (0.07)	0.9952
Aerosil	0.060 (0.045)	0.13 (0.11)	0.9999	0.060 (0.045)	0.13 (0.11)	1 (0.02)	0.9999

Table 2. Moisture Content of Excipients under Different Conditions

Excipient	Moisture content (%)				Hygroscopicity class[b]
	64% RH		83% RH		
	Obtained[a]	Literature[b]	Obtained[a]	Literature[b]	
Avicel PH 102	6.2	6.6	9.9	9.1	II
Kollidone CL	18.5	22.2	32.2	29.6	IV
Kollidone VA64	11.0	ND	24.5	ND	IV[c]
Mg stearate	2.9	3.3	4.9	5.0	I
Aerosil	3.1	2.6	13.5	4.8	II[c]
Lactose	0	0.2	0	0.2	I

a) Moisture content predicted by the GAB model.   b) Data from ref. 24; ND, no available data.   c) Classification based on our results.
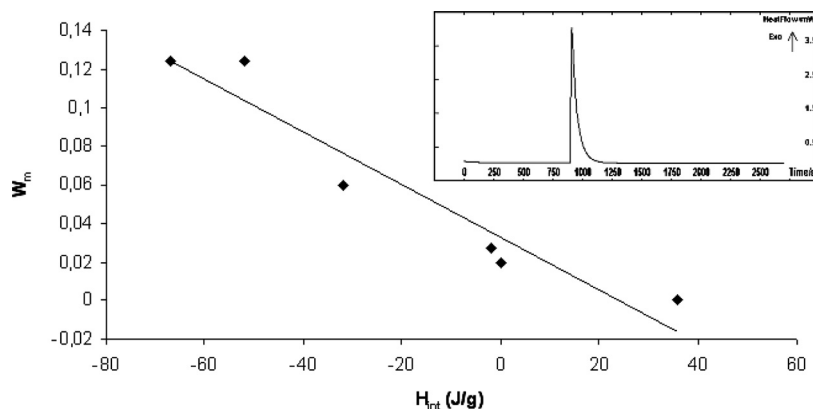

Fig. 4. The Heat Flow Signal of Aerosil at 20 °C after the Addition of Water (Upper Window) and Correlation between the Adsorption Parameters (W_m) and the Enthalpies of Interaction with Water (H_{int}) for the Excipients (Lower Window)

In the case of lactose we assumed $W_m = 0$.

tion over the entire humidity range.

In addition to sorption profiles of studied excipients, their higroscopicities were estimated according to the generally accepted classification into four hygroscopicity classes.[24] Results of these experiments are presented in Table 2 for two humidity conditions together with some reference values from the literature revealing generally good agreement with our estimates. The only difference was in Aerosil which in our case belongs into hygroscopicity class II, rather than class I.

The hygroscopic nature of the substances has been further investigated by microcalorimetric analysis, measuring the interaction of dried material with excess water. A typical thermogram of an excipient obtained after the addition of water (Fig. 4; upper window) exhibits a sharp exothermic enthalpy peak. Due to the non-specificity of microcalorimetric analysis the enthalpy peak obtained is actually the result of several simultaneous processes of interaction with water-adsorption, wetting responses, dissolution phenomena, *etc.*[20] Comparison of enthalpies (H_{int}) obtained from such measurements with previously determined sorption parameters (W_m), showed a strong negative correlation, especially for less hygroscopic materials (class I and II) (Fig. 4; lower window), supporting the hygroscopicity classification of the materials. Despite moderately high variability of the data, due mainly to reasons given above and to the small amounts of excipient used in the microcalorimetric analyzer, the sorption characteristics of substances can be tentatively predicted using this approach.

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