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Prediction of moisture transfer in mixtures of solids: transfer via the vapor phase

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Summary

A mathematical method has been developed and tested to predict the final relative water vapor pressure in a closed system for a multicomponent mixture of solids knowing the initial water content for each component. From the final relative pressure and individual sorption–desorption isotherms, it is then possible to estimate the extent to which moisture redistributes via the vapor phase among the various components. The model utilizes any equation which describes the moisture sorption–desorption isotherm of each component over the entire range of relative pressures and includes as variables the initial dry weight and moisture content of each component, head space volume, and temperature. Experimental studies were carried out in a vacuum rack assembly linking various solids via the vapor state and measuring relative pressures of water vapor before and after redistribution using a sensitive pressure transducer at a known temperature and head space volume. Both the mathematical simulations and experiments were carried out with various combinations of corn starch, microcrystalline cellulose, gelatin capsules, and silica gel. Pharmaceutical situations where such information might be useful are discussed.

Introduction

The interaction of water with pharmaceutical solids occurs in virtually all stages of manufacture, from synthesis of raw materials to storage of the final dosage form. The amount of water associated with a solid at a particular relative humidity and temperature depends on its chemical affinity for the solid and the number of available sites of interaction. This study addresses the situation where various solids, each with an initial moisture content, are mixed together into a solid dosage form and stored in a closed container at a given temperature and head space volume. In the situation to be considered, it is assumed that the system is completely closed, i.e., the total moisture present is constant, and that moisture transfer only occurs via the vapor phase. Several studies in the pharmaceutical field (Strickland and Moss, 1962; Ito et al., 1969; Bond et al., 1970; Bell et al., 1973; York, 1981; Serajuddin et al., 1986) have recognized that moisture transfer can occur in this manner between components used in solid dosage forms, e.g., gelatin capsules and various active and inactive ingredients.

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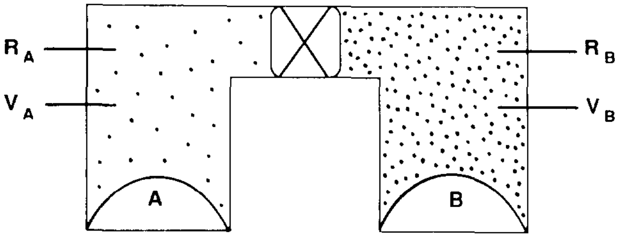
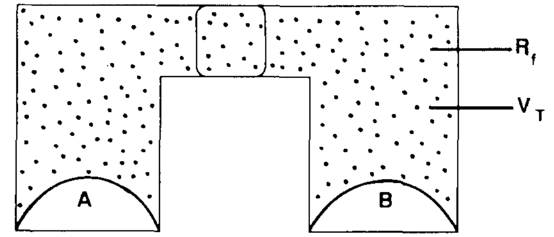
In this paper we present a mathematical method of predicting a priori the amount of water associated with each component in a mixture given the initial moisture content of each solid, their dry weights, head space volumes, temperature, and any equation which can describe the individual sorption or desorption isotherms for the solid. The potential value of this approach is that it conveniently allows one to predict such factors as: the amount of desiccant needed to maintain a given relative humidity in the container, the head space volume which might be used to reduce water sorbed to an active ingredient, the direction and extent of any water transfer to and from gelatin capsules and active ingredients, and the effect of storage temperature and temperature cycling on the moisture content of various chemically unstable ingredients.



a) head spaces isolated from one another



b) head spaces allowed to interact

Fig. 1. Schematic representation of component moisture transfer between solids.

Theory

Consider a closed system into which two solids, A and B, have been placed (the proposed method can and will be extended to more than two components, but for mathematical simplicity only two components will be used for the present discussion). We may conceptualize each solid, as shown in Fig. 1a, to initially contain a given amount of associated moisture corresponding to relative humidities, R_A and R_B, and head space volumes, V_A and V_B. Fig. 1b represents the situation where the two solids are now both exposed to the total water vapor present and where water is free to desorb from one solid and sorb onto the other. At equilibrium the transfer of water vapor into the new total head space volume, V_T, will result in a new final relative humidity, R_f. In the situation described in Fig. 1, where initially $R_B > R_A$, we would expect water molecules from solid B to desorb into the vapor phase with subsequent sorption to solid A.

A few studies have appeared in the food science literature attempting to address this problem quantitatively (Chuang and Toledo, 1976; Chirife, 1978; Lang and Steinberg, 1980, 1981a and b; Hong et al., 1986). The most useful approach in terms of application to pharmaceutical systems, and one upon which the present work is based, was reported by Salwin and Slawson (1959) and Salwin (1962) who were interested in the transfer of moisture in "dehydrated" foods used by the Armed Forces. Fig. 2 depicts hypothetical sorption isotherms for solids A and B. Components A and B are stored initially at relative humidities, R_A and R_B, respectively, and therefore have a moisture content of M_{A_1} and M_{B_1} (expressed as percent of dry solid weight). Once the components are exposed to one another, a final equilibrium relative humidity, R_f, results somewhere between R_A and R_B. The moisture associated with each solid is now M_{A_2} and M_{B_2}, with a gain in the moisture content of solid A and a loss in moisture for solid B. To simplify the analysis, it was assumed by Salwin and Slawson that the change in moisture content for A and B is linear with respect to relative humidity (depicted as dotted lines in Fig. 2). The slopes of these lines are given by:

$$S_A = \frac{M_{A_2} - M_{A_1}}{R_f - R_A} \qquad S_B = \frac{M_{B_2} - M_{B_1}}{R_f - R_B} \qquad (1)$$

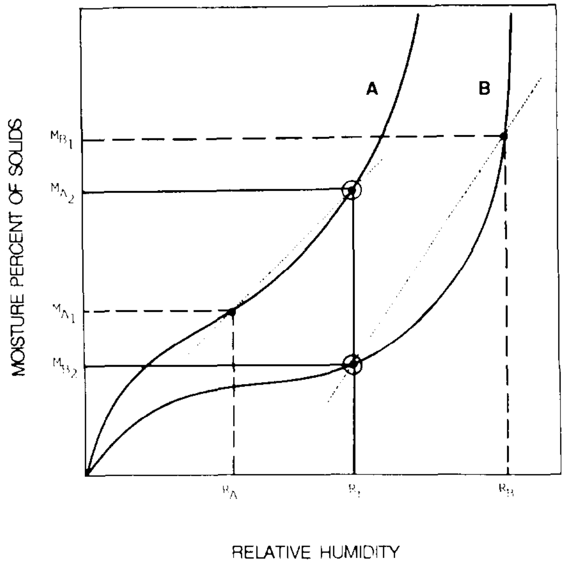


Fig. 2. Salwin and Slawson's graphical representation of changes in moisture during equilibration (Salwin and Slawson, 1959).

The correctness of this assumption will obviously depend on the shape of the isotherm in the range of moisture content change. Ordinarily such plots as depicted in Fig. 2 are not linear in the regions of interest. Making this assumption, however, assuming the total weight of water to be constant, and neglecting the content of water in the vapor phase, they developed a final equation for a two-component system whereby:

$$R_f = \frac{R_A S_A W_A + R_B S_B W_B}{S_A W_A + S_B W_B} \tag{2}$$

where W_A and W_B are the dry weights of each solid and S_A and S_B are the slopes of the change in moisture content with relative humidity. Although R_A and R_B, and M_A and M_B were obtained directly from the isotherms of each material, the various slope terms had to be estimated using some value for R_f. This was done by making a preliminary estimate of R_f somewhere between R_A and R_B and using this to calculate the slope values of S_A and S_B from Eqn. 1. A better estimate of R_f was then calculated from Eqn. 2 using these slope values. This iterative cycling was continued until the final value of R_f was determined. No limit was placed on the number of components which could be analyzed in this way.

Although this technique was fairly successful when tested with various food products in a very limited range of relative humidites, there are several possible drawbacks and disadvantages to the method. First, is the assumption of slope linearity between the initial and final relative humidities. Although this assumption may be valid when moisture transfer occurs over a narrow range in the isotherm (as was the case in Salwin and Slawson's work), a high degree of error may result if the moisture transfer is over a wide range, especially where curvature in the isotherm exists. Second, unless the desorption isotherm is identical to the sorption isotherm, i.e., no hysteresis, it is not entirely correct to use only the sorption branch of the isotherm, since at least one component must experience desorption in the moisture transfer process. Lastly, although the amount of moisture in the vapor state is probably negligible for mixtures where components have high moisture contents as described by Salwin and Slawson, it may have a profound effect with components of very low moisture contents (e.g., crystalline drugs containing very small amounts of adsorbed water). For general applicability, therefore, it is desirable to account for this vapor state moisture.

The present approach, which we call the sorption–desorption moisture transfer (SDMT) model, follows the Salwin–Slawson approach in principle, but it uses constants from equations which mathematically describe the entire sorption–desorption isotherm and also takes into account the amount of moisture in the vapor state. Any number of equations could be used to describe water sorption–desorption isotherms, depending on the nature of the solid and the mechanisms of sorption (Venkateswaren, 1970; Caurie, 1981; Van den Berg and Bruin, 1981). Previous work in this laboratory (Kontny, 1985; Zografi and Kontny, 1986) with a wide range of pharmaceutical excipients has shown that 3-parameter extensions of the BET equation can describe essentially the entire isotherm. In particular with excipients derived from starch and cellulose, it has been shown that the following equation, independently developed by Guggenheim (1966), Anderson (1946), and De-

Boer (1968), and termed the GAB equation by Van den Berg (1981), fits data very well over the entire range of relative humidities:

$$W = \{W_m C_g K(P/P_0)\}\{[1 - K(P/P_0)] \times [1 - K(P/P_0) + C_g K(P/P_0)]\}^{-1} \tag{3}$$

where W is the weight of vapor per weight of dry solid sorbed onto a solid at a particular relative pressure (P/P_0), W_m is the weight of vapor per weight of dry solid assumed to be associated with all primary binding sites, and C_g and K are constants related to the free energy of sorption. We emphasize here that the approach to be developed can use any isotherm equation, and indeed in the results and discussion section we will use the Langmuir equation for one of the components included in a mixture being studied. For purposes of deriving the general expression, however, only the GAB equation will be utilized. To account for water in the vapor state, we use the ideal gas law, depicted as IGL.

Referring to Fig. 1, the total moisture in chamber A is the sum of the moisture associated with the solid component A and with the vapor state in the volume V_A. This can be described by the equation:

$$M_A = W_A GAB_A + IGL_A \tag{4}$$

where M_A = the total mass of moisture in chamber A, W_A = the dry weight of component A, GAB_A = the mass of moisture associated with component A as given by the GAB equation for A at its initial relative humidity R_A, and IGL_A = the mass of moisture in the head space volume, V_A, as given by the ideal gas law. When written out in its entirety, equation 4 takes the form:

$$\begin{aligned} M_A = W_A\Big(&\{W_{m_A} C_{g_A} K_A(P/P_0)_A\}\{[1 - K_A(P/P_0)_A] \\ &\times [1 - K_A(P/P_0)_A + C_{g_A} K_A(P/P_0)_A]\}^{-1}\Big) \\ &+ \frac{P_0 V_A (P/P_0)_A \times 18}{RT} \end{aligned} \tag{5}$$

where W_m, C_g, and K have been described previously, $(P/P_0)_A = R_A/100$ = the initial relative water vapor pressure, P_0 = the pressure of pure water vapor at temperature T, and R = the gas constant. The second term on the right side of equation 5 has been multiplied by 18, the molecular weight of water, to obtain the amount of water vapor in g. A similar equation can be written for the total amount of water in chamber B.

Once the total amounts of moisture have been determined for each individual chamber, the total moisture in the system, M_T, can be expressed by:

$$M_T = W_A GAB_A + W_B GAB_B + IGL_{V_T} \tag{6}$$

where the ideal gas law term is now written for the total head space volume, V_T, for the two chambers. Eqn. 6 written in its entirety takes the form:

$$\begin{aligned} M_T = W_A\Big(&\{W_{m_A} C_{g_A} K_A(P/P_0)\}\{[1 - K_A(P/P_0)] \\ &\times [1 - K_A(P/P_0) + C_{g_A} K_A(P/P_0)]\}^{-1}\Big) \\ &+ W_B\Big(\{W_{m_B} C_{g_B} K_B(P/P_0)\}\{[1 - K_B(P/P_0) \\ &\times [1 - K_B(P/P_0) + C_{g_B} K_B(P/P_0)]\}^{-1}\Big) \\ &+ \frac{P_0 V_T (P/P_0) \times 18}{RT} \end{aligned} \tag{7}$$

where (P/P_0) is now the final relative water vapor pressure in the equilibrated system following exposure of the two chambers to one another. Rearranging equation 7 and setting (P/P_0) equal to x, a fifth-root polynomial equation is obtained.

$$x^5 + C_1 x^4 + C_2 x^3 + C_3 x^2 + C_4 x - C_5 = 0 \tag{8}$$

where C_1, C_2, C_3, C_4, and C_5 are constants. The constant terms, made up of parameters from Eqn. 7, are given in Appendix 1.

To solve Eqns. 7 or 8, the real root between $(P/P_0) = 0$ and $(P/P_0) = 1$ must be found. Approximation techniques, such as Newton's method, can be used, though these approaches become excessively rigorous with more than two components, i.e., for each additional component added in the moisture transfer process, an increase of two additional roots results in Eqn. 8. Although it is mathematically possible to determine the constant values for a higher-order system, the computation involved makes these methods somewhat impractical.

An iterative technique, therefore, was used with systems having more than two components to circumvent the necessity of converting Eqn. 7 into the classical polynominal notation as given by Eqn. 8. Since M_T remains constant in a closed system, an estimate for the relative water vapor pressure, $(P/P_0)_{est}$, in Eqn. 7 can be used to determine M_T^{calc}, a calculated total moisture content in the system if the relative water vapor pressure equals $(P/P_0)_{est}$. If $M_T^{calc} > M_T$, then a lower estimate must be chosen for $(P/P_0)_{est}$. If $M_T^{calc} < M_T$, then a higher estimate must be chosen for $(P/P_0)_{est}$. If $M_T^{calc} = M_T$, then $(P/P_0)_{est}$ is the predicted final relative water vapor pressure in the system following moisture transfer.

Materials and Methods

The following solids were used as sample components for experimental determinations of moisture transfer: microcrystalline cellulose [1], corn starch [2], gelatin capsules [3], and silica gel [4]. Before use all components were stored under ambient conditions. Water vapor was provided by using saturated solutions of various water-soluble salts. A schematic representation and details of the vacuum glass rack used for moisture transfer and sorption experiments has been reported previously (Kontny et al., 1987). Sorption–desorption isotherms were obtained gravimetrically for all components using a Cahn model RG-2002 electrobalance (Ventron Corporation). The apparatus used to measure moisture transfer is detailed in Fig. 3. The volumes labeled V_1–V_4 were used to simulate varying head spaces which might be found above a dosage form in a pharmaceutical container. These volumes were experimentally determined using helium gas expansion. Helium gas expansion was likewise used to determine the head space volumes in each sample cell. All of the glass components in Fig. 3 were maintained at 23 ± 0.1° C with circulating water in a room also maintained at a temperature of 23 ± 1° C. This minimized possible effects of temperature variation due to the unthermostated portions of the apparatus.

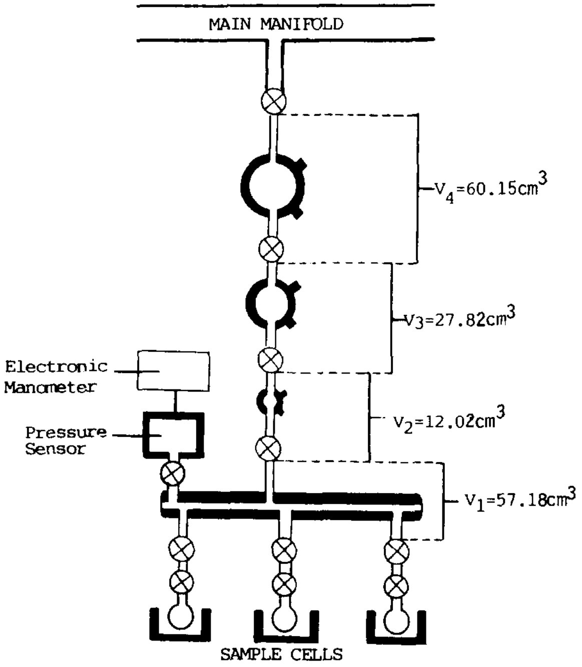


Fig. 3. Moisture transfer compartments. ⊗ denotes stopcock locations; shaded areas indicate water-jacketed vessels.

In order to perform the moisture transfer studies, it was necessary to obtain the dry weight of each sample. A specially designed sample cell, attached to the moisture transfer apparatus (Fig. 3), was constructed so that each sample could be dried under vacuum conditions with heat, then reweighed by removing the cell from the vacuum glass rack without exposure of the sample to atmospheric conditions. After reweighing, the cell could be reattached to the glass rack for the moisture transfer experiments.

Once the cells were reattached to the moisture transfer apparatus, the samples were individually exposed to various relative humidities using ther-

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[1] Avicel PH101, FMC Corporation.

[2] Argo, Best Foods.

[3] Size no. 3, Eli Lilly Company.

[4] 6–12 mesh, Fisher Scientific Company.

mostated saturated salt solutions, attached to another portion of the vacuum glass rack, via the main manifold. Equilibration was allowed to occur overnight or longer, and the equilibrium water vapor pressure was measured directly using a Barocel type 600 pressure sensor (sensitivity = 0.001 Torr, Datametrics, Dresser Industries). Once all sample cells were equilibrated to the desired relative humidities, stopcocks above each cell were opened, allowing the head spaces of each cell to interact. Equilibration often required several days.

To proceed with this proposed model, Eqn. 5 was first used to calculate the initial amount of water in each sample cell. In this equation the GAB constants for the sorption branch of the isotherm were used since experimentally the components were dried before allowing initial moisture to equilibrate in the cell. A total moisture content, M_T, in the system was then obtained by summing the initial moisture contents in the individual cells. By placing this value of M_T into Eqn. 7, then all terms were known except the final relative water vapor pressure (P/P_0). It should be noted that in Eqn. 7, since one of the components will experience desorption, the GAB constants for the desorption branch of the isotherm were used for this component.

Results and Discussion

Moisture isotherms were obtained gravimetrically for gelatin capsules and silica gel at 23°C. The gravimetric moisture isotherms for microcrystalline cellulose and corn starch used in this study were taken from previous studies (Kontny, 1985). The data for all components except silica gel produced sigmoidal-shaped functions which were fitted to the GAB equation; silica gel yielded a hyperbolic function which was fitted to the Langmuir equation:

$$W = \frac{W_m C_L (P/P_0)}{1 + C_L (P/P_0)} \tag{9}$$

where W, W_m, and (P/P_0) have been described previously in the GAB model and C_L is the Langmuir constant. Table 1 lists the GAB constants, obtained by computer fitting as described previously (Kontny, 1985), and the Langmuir constants, obtained by linear regression. Only sorption values are presented for silica gel since in these studies it acted as a desiccant.

Tables 2–5 give predicted vs experimental results for various binary combinations of microcrystalline cellulose, corn starch, and gelatin capsules. The percent water associated with each component before and after moisture transfer was estimated from initial and final percent relative humidities, predicted from the model and determined experimentally. The term percent water, used throughout this paper, is actually 100 (g water per g dry solid), but it is retained as percent water because of common usage and space considerations in Tables 2–5. Note in Table 2 where

TABLE 1

Various constants obtained from sorption-desorption isotherms

	Mode	Temp (°C)	W_m [a]	C_g	K
GAB Constants					
Microcrystalline cellulose [b]	Sorption	23	0.0299	55.7	0.870
	Desorption	23	0.0429	24.7	0.820
Corn starch [b]	Sorption	23	0.0753	67.0	0.804
	Desorption	23	0.114	26.9	0.641
Gelatin capsules [c]	Sorption	23	0.169	3.47	0.650
	Desorption	23	0.186	22.3	0.377
Langmuir constants					
Silica gel [c]	Sorption	23	0.572	1.78	

[a] g water/g dry sample.
[b] Kontny, 1985.
[c] Present work.

TABLE 2

Predicted vs experimental moisture transfer between two samples of microcrystalline cellulose

Initial				Final					
MCC-1		MCC-2		% RH of final mixture		MCC-1 % H_2O based on		MCC-2 % H_2O based on	
% RH	% H_2O	% RH	% H_2O	Predicted	Exptl.	Predicted	Exptl.	Predicted	Exptl.
10.6	2.8	50.3	5.2	25.2	31.6	3.6	3.9	4.7	5.2
31.6	3.9	65.1	6.8	44.3	49.2	4.7	5.1	6.3	6.8

Total head space volume: 182.9 ml. Dry weights: microcrystalline cellulose-1 = 3.3855g; microcrystalline cellulose-2 = 5.2133 g. Temperature: 23° C.

both sample cells contained microcrystalline cellulose, that although the percent relative humidity of the final mixture is the same for each sample, the percent water differs. This is so because sample 1 (MCC-1) experienced sorption while sample 2 (MCC-2) experienced desorption during the transfer process and the two isotherms are not identical because of hysteresis. Table 6 gives the predicted vs experimental results for a ternary mixture of microcrystalline cellulose, gelatin capsules, and silica gel. Since silica gel was found to follow the Langmuir equation, it was necessary to modify equation 7 to include this third solid component. A fourth term was added to the right side of Eqn. 7:

$$W_c\left(\frac{W_{m_c}C_{L_c}(P/P_0)}{1+C_{L_c}(P/P_0)}\right) \tag{10}$$

where W_c is the dry weight of silica gel.

TABLE 3

Predicted vs experimental moisture transfer between microcrystalline cellulose and corn starch

Initial				Final					
MCC		Corn starch		% RH of final mixture		MCC % H_2O based on		Corn starch % H_2O based on	
% RH	% H_2O	% RH	% H_2O	Predicted	Exptl.	Predicted	Exptl.	Predicted	Exptl.
99.9	22.9	~ 0	~ 0	0.8	5.1	0.6	2.3	2.3	5.8
~ 0	~ 0	97.8	35.0	96.0	78.6	18.1	9.4	29.0	22.2
34.1	4.1	62.3	14.9	45.6	48.9	4.8	5.1	14.8	15.4

Total head space volume: 180.9 ml. Dry weights: microcrystalline cellulose, 1.5292 g; Corn starch, 14.8028 g. Temperature: 23° C.

TABLE 4

Predicted vs experimental moisture transfer between microcrystalline cellulose and corn starch

Initial				Final					
MCC		Corn starch		% RH of final mixture		MCC % H_2O based on		Corn starch % H_2O based on	
% RH	% H_2O	% RH	% H_2O	Predicted	Exptl.	Predicted	Exptl.	Predicted	Exptl.
96.0	18.1	~ 0	~ 0	88.3	38.7	15.3	5.8	25.8	10.6
38.7	4.4	61.2	14.6	40.0	46.3	4.4	4.9	13.8	14.9
72.7	8.1	32.3	9.8	56.6	63.4	7.6	8.6	13.6	15.1
~ 0	~ 0	95.2	31.9	8.6	25.8	2.6	3.6	7.4	11.5

Total head space volume: 179.4 ml. Dry weights: microcrystalline cellulose, 14.3760 g. Corn starch, 1.5408 g. Temperature: 23° C.

TABLE 5

Predicted vs experimental moisture transfer between microcrystalline cellulose and gelatin capsules

Initial				Final					
MCC		Gelatin capsules		% RH of Final mixture		MCC % H_2O based on		Gelatin capsules % H_2O based on	
% RH	% H_2O	% RH	% H_2O	Predicted	Exptl.	Predicted	Exptl.	Predicted	Exptl.
95.1	17.2	~ 0	~ 0	74.8	72.1	10.8	10.2	25.2	24.0
~ 0	~ 0	72.1	24.0	16.1	15.3	3.1	3.1	11.7	11.4
53.0	5.4	80.2	27.9	66.3	63.8	7.0	6.6	21.9	21.5
~ 0	~ 0	99.7	41.5	54.0	34.7	5.5	4.1	19.9	16.5

Total head space volume: 184.6 ml. Dry weights: Microcrystalline cellulose, 7.0041 g. Gelatin capsules, 1.7848 g. Temperature: 23° C.

In general, the predicted vs experimental moisture contents determined for each component for the various combinations of solids are in good agreement except for some systems which had been initially equilibrated at opposite extreme relative humidities (RH), i.e., 0% and greater than 95% RH. The extent of agreement between experiment and calculation is graphically demonstrated in Fig. 4 for combinations of microcrystalline cellulose and corn starch. Comparisons are also made with the approach used by Salwin and Slawson (1959) where it can be seen that considerable improvement results, particularly at intermediate relative humidities. This is most likely due to the use of desorption data in the present study which differ most from sorption data in this intermediate region, and to the avoidance of assuming a linear slope as in Eqn. 1.

The significant error obtained when samples were initially equilibrated at extreme relative humidities is not surprising since at both very low and very high relative humidities there is the greatest chance for experimental error in determining the amount of sorbed or desorbed moisture and in fitting 3-parameter equations such as the GAB equation. This is particularly true for situations where the absorption of water into the solid polymeric structure causes some degree of polymeric conformation change (Zografi and Kontny, 1986). Associated also with this latter fact

TABLE 6

Predicted vs experimental moisture transfer among microcrystalline cellulose, gelatin capsules and silica gel

MCC		Gelatin caps.		Silica gel	
% RH	% H_2O	% RH	% H_2O	% RH	% H_2O
64.3	6.7	64.3	20.7	~ 0	~ 0
75.5	8.6	75.5	25.6	~ 0	~ 0
78.3	9.3	78.3	26.9	~ 0	~ 0
84.5	11.2	84.5	30.3	~ 0	~ 0

% RH of final mixture		MCC % H_2O based on		Gelatin caps % H_2O based on		Silica gel % H_2O based on	
Predicted	Exptl.	Predicted	Exptl.	Predicted	Exptl.	Predicted	Exptl.
20.5	24.8	4.3	4.6	13.1	14.3	15.3	17.6
31.6	31.5	5.2	5.2	15.9	15.8	20.6	20.6
35.5	41.2	5.5	6.0	16.6	17.7	22.2	24.2
47.0	41.8	6.6	6.1	18.7	17.8	26.1	24.4

Total head space volume: 257.4 ml. Dry weights: microcrystalline cellulose, 5.5200 g; gelatin capsules, 2.4698 g; silica gel, 2.0934 g. Temperature. 23° C. Top part, initial values; bottom part, final values.

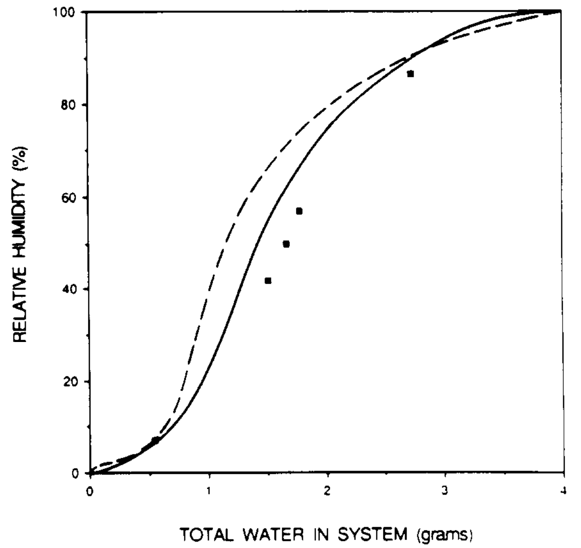

Fig. 4. Moisture transfer between microcrystalline cellulose and corn starch where corn starch desorbs: ■, data points experimentally determined; — — —, Salwin-Slawson prediction; ———, SDMT model prediction.

is some uncertainty because of the complex sorption–desorption hysteresis often seen with such systems.

Fig. 5 shows the hysteresis loop as that area between the main branches of the sorption (curve A) and desorption (curve B) isotherms. In most practical circumstances, sorption will not reach the highest point, but will instead reach some intermediate relative pressure, $(P/P_0)_i$, giving rise to a desorption curve differing to some degree from the main desorption curve. The precise desorption curve beginning at $(P/P_0)_i$ may assume one of several possible unique appearances (curves C and D). It should be apparent, therefore, that desorption commencing from an intermediate point along the sorption curve cannot be exactly represented by the equation for the main desorption curve. The error associated with this behavior should become more pronounced with components exhibiting higher degrees of hysteresis. Fig. 6 shows a typical set of results for desorption mini-isotherms obtained for gelatin capsules, which exhibited the greatest amount of hysteresis. The good agreement between calculated and experimental values for systems involving gelatin capsules indicates that this may not be a serious effect or that other opposing factors tend to compensate in the final results. However, this point should still be kept in mind.

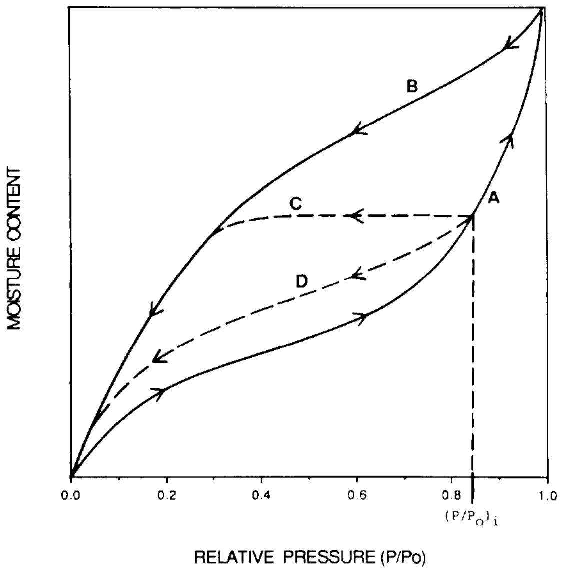

Fig. 5. Graphical representation of desorption beginning at an intermediate point along the sorption isotherm.

It may be of interest to provide an example of how the SDMT model might be used in one particular practical situation where head space volume is an important factor. Consider a mixture of two water-soluble solids, component A and component B, each of which has the ability to only take up very small amounts of moisture below their points of deliquescence. Let us assume the following constants and RH at saturation (RH_0) at 20 °C; from the GAB equation as described earlier in this paper:

	W_m	C_g	K	RH_0
Component A	0.00131	21.6	0.868	75%
Component B	0.000229	34.4	0.777	84%

When the solids are mixed together the equilibrium relative humidity above a saturated solution of both of these solids falls to 63%, i.e., the product of 0.75 and 0.84 multiplied by 100, as shown previously by Ross (1975) and Kontny and Zografi (1985). Thus, if the relative humidity of the container goes above 63%, deliquescence will occur (Van Campen et al., 1983a, b, c; Kontny

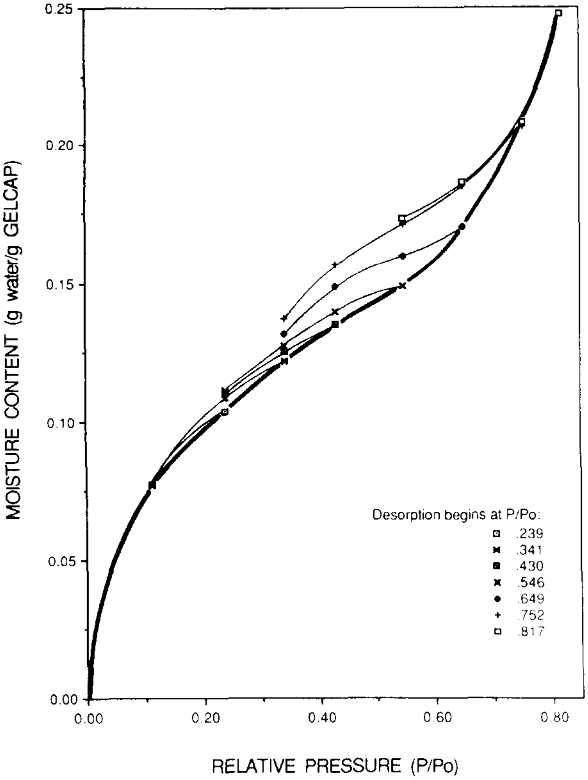

Fig. 6. Desorption mini-isotherms for gelatin capsules. Desorption beginning at intermediate points along the main sorption isotherm (bold line). Lines drawn for convenience of the reader.

and Zografi, 1985). In order to maintain acceptable stability in a dosage form containing these components, therefore, the equilibrium relative humidity must be kept below 63%.

Let us assume that a dosage form containing 0.95 g of component A and 0.05 g of component B is placed in a glass vial with an estimated 5 ml head space. During processing, let us assume further that a total water content of 2.81×10^{-3} g became associated with the solids and was enclosed in the vial. This might occur, for example, by desorption of moisture from a steam-autoclaved rubber stopper after sealing of the vial. What relative humidity in the vial is produced by this system at 20 °C and to what size must the head space volume (or vial size) be maintained such that the relative humidity is below 63%?

Using Eqn. 7 it is possible to solve for the term V_T, the total head space volume, at various values of P/P_0. Table 7 gives the final equilibrium relative humidity results for various head space volumes, showing clearly that a vial providing a head space in excess of 13 ml is necessary to maintain an acceptable relative humidity below 63%.

TABLE 7

Head space volume vs. final equilibrium relative humidity

Head space volume (ml)	Final equilibrium relative humidity
5	65.0
10	63.6
12	63.2
13	63.0
14	62.8
15	62.7
20	61.7

See text for details. The values are predicted using the SDMT model.

Another practical example of moisture transfer in a system containing a capsule formulation and gelatin capsules has been studied successfully by Kontny and Mulski, using this SDMT model, and will be reported shortly. A further application of the SDMT model might be in analyzing storage temperature variability. Given the temperature dependence of the sorption-desorption isotherms for the various ingredients in the product, for example, it should be possible to predict the effect of cycling the storage temperature on water distribution in any system.

Conclusions

The SDMT model has been used to predict the relative humidity in a closed container for mixtures of solids, knowing the dry weight of solids, the total moisture present, the head space volume, the temperature, and equations which describe the entire sorption–desorption isotherm. The importance of using desorption isotherms for situations where a solid might be expected to lose some of its moisture was demonstrated.

Experimental studies were carried out with various combinations of microcrystalline cellulose, corn starch, gelatin capsules, and silica gel in 2- and 3-component mixtures with very good general agreement with the SDMT model. Factors tending to reduce the success in prediction for some situations were discussed.

Although this work primarily used the GAB equation to describe the moisture isotherms, this is not a limitation of the model. The iterative process used for the predictive calculation is flexible enough to allow the incorporation of any equation which describes a moisture isotherm.

The SDMT model has the significant advantage over previous work in that simulations are possible for multiple-component systems. In this way a priori predictions can be obtained for approximate final equilibrium moisture conditions, thus minimizing unnecessary preliminary experimentation. An example of how head space volume might be optimized to reduce water sorption on solids was presented.

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Appendix 1. Constant terms for Eqn. 8

$$C_1 = \frac{1}{K_B(C_{g_B}-1)} - \frac{1}{K_B} + \frac{1}{K_A(C_{g_A}-1)} - \frac{1}{K_A} - \frac{M_T RT}{VP_0(18)}$$

$$C_2 = \frac{1}{K_A(C_{g_A}-1)}\left[\frac{1}{K_B(C_{g_B}-1)} - \frac{1}{K_A} - \frac{1}{K_B}\right] - \frac{1}{K_B(C_{g_B}-1)}\left[\frac{1}{K_B} + \frac{1}{K_A}\right] + \frac{1}{K_A K_B}$$
$$- \frac{RT}{VP_0(18)}\left[\frac{W_A W_{m_A} C_{g_A}}{K_A(C_{g_A}-1)} + \frac{W_B W_{m_B} C_{g_B}}{K_B(C_{g_B}-1)}\right]$$
$$+ \frac{M_T RT}{VP_0(18)}\left[\frac{1}{K_B}\left(1 - \frac{1}{(C_{g_B}-1)}\right) + \frac{1}{K_A}\left(1 - \frac{1}{(C_{g_A}-1)}\right)\right]$$

$$C_3 = \frac{VP_0(18)}{RT}\left[K_A(C_{g_A}-2) + K_B(C_{g_B}-2)\right] + W_A W_{m_A} C_{g_A} K_A K_B (C_{g_B}-2) + W_B W_{m_B} C_{g_B} K_A K_B (C_{g_A}-2)$$
$$+ \left\{M_T\left[K_A(C_{g_A}-1)(K_A + K_B(2 - C_{g_B})) + K_B(K_A + K_B)(C_{g_B}-1) - K_A K_B\right]\right\}$$
$$\times \left\{(K_A K_B)^2 (C_{g_A}-1)(C_{g_B}-1)\frac{VP_0 \times 18}{RT}\right\}^{-1}$$

$$C_4 = \left\{\frac{VP_0(18)}{RT} + W_A W_{m_A} C_{g_A} K_A + W_B W_{m_B} C_{g_B} K_B + M_T\left[K_A(2 - C_{g_A}) + K_B(2 - C_{g_B})\right]\right\}$$
$$\times \left\{(K_A K_B)^2 (C_{g_A}-1)(C_{g_B}-1)\frac{VP_0 \times 18}{RT}\right\}^{-1}$$

$$C_5 = \frac{M_T RT}{(K_A K_B)^2 (C_{g_A}-1)(C_{g_B}-1) VP_0 \times 18}$$

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