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DISTRIBUTION OF WATER IN SOLID PHARMACEUTICAL SYSTEMS

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ABSTRACT

Knowledge of the amount of moisture associated with particular components of a solid dosage form, as well as its state, are essential for the pharmaceutical formulator in attaining a system with optimal physical/chemical properties. Moisture is introduced into ultimately closed pharmaceutical systems either associated with the materials or in the headspace as relative humidity. This moisture will distribute (i.e., reequilibrate) between the various components and the headspace to attain a final water activity, a_w (~relative humidity/100) in the vapor phase. The Sorption-Desorption Moisture Transfer (SDMT) model allows *a priori* prediction of this thermodynamic variable for systems in which uptake isotherms and dry masses for individual components, temperature, headspace volume and initial total system moisture content are known. Final component moisture contents are then obtained from the individual materials' respective isotherms. Practical applications of the SDMT model include the rational determination of: initial LOD values of the formulation and capsule to avoid capsule brittleness problems, an adequate headspace volume above nonhydrating crystalline substances to protect against deliquescence, and the appropriate amount of desiccant for a solid product.

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 single solid at a particular relative humidity and temperature depends on its chemical affinity for the solid and the number of available sites of interaction. In multicomponent systems (i.e. consisting of individual solids in the formulation, container, cotton, desiccant, etc.) where each material introduced into the system has a different moisture content and thermodynamic water activity, moisture transfer will occur from component to component via the vapor phase to attain the most thermodynamically favored state. This phenomenon has been recognized and presented in the pharmaceutical literature by several workers (1-6) studying moisture transfer to/from gelatin capsules and various active and inactive ingredients. It is also the underlying basis for inclusion of desiccant materials in solid pharmaceutical products.

Many pharmaceutical properties of solids and solid dosage forms are intimately dependent on the amount of moisture sorbed, as well as its degree of binding.

Hence, knowledge of whether moisture will sorb or desorb from a particular component of the formulation (or system) is essential for the pharmaceutical formulator. The present work addresses the underlying thermodynamic basis for moisture transfer, as well as the use of water sorption/desorption isotherms to describe the transfer of moisture and predict the final moisture contents for individual components in a system.

The potential value of the approach to be described is that it conveniently allows one to predict such factors as: the direction and extent of any water transfer to and from gelatin capsules and active ingredients, the amount of desiccant needed to maintain a given relative humidity in a closed container, the headspace volume which might be used to reduce water sorbed to an active ingredient, and the effect of storage temperature and temperature cycling on the moisture content of various chemically unstable ingredients.

THEORETICAL

The Sorption-Desorption Moisture Transfer (SDMT) model (7,8) 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 headspace 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.

Consider a closed system into which two solids, A and B, have been placed (the proposed method can and

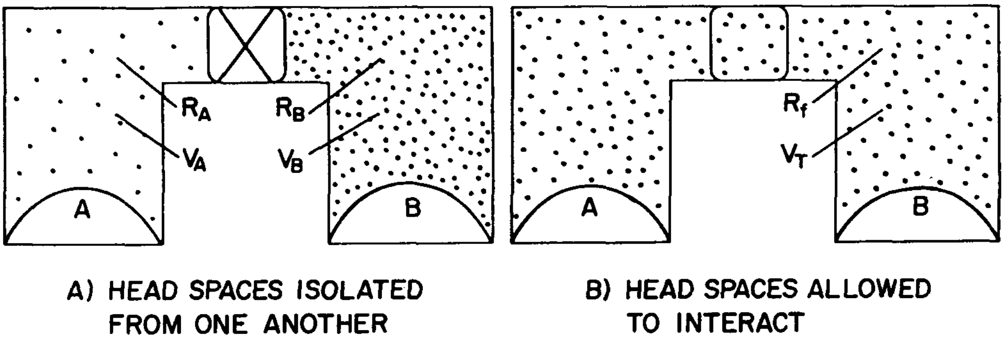

FIGURE 1

Schematic representation of moisture transfer between two solids.

will be extended to more than two components, but for mathematical simplicity only two components will be used for the present discussion). One may conceptualize each solid, as shown in Figure 1a, to initially contain a given amount of associated moisture corresponding to relative humidities, R_A and R_B, and headspace volumes, V_A and V_B. Figure 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 headspace volume, V_T, will result in a new final relative humidity, R_f. In the situation described in Figure 1, where initially $R_B > R_A$, one 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 (9-12). The most useful approach in

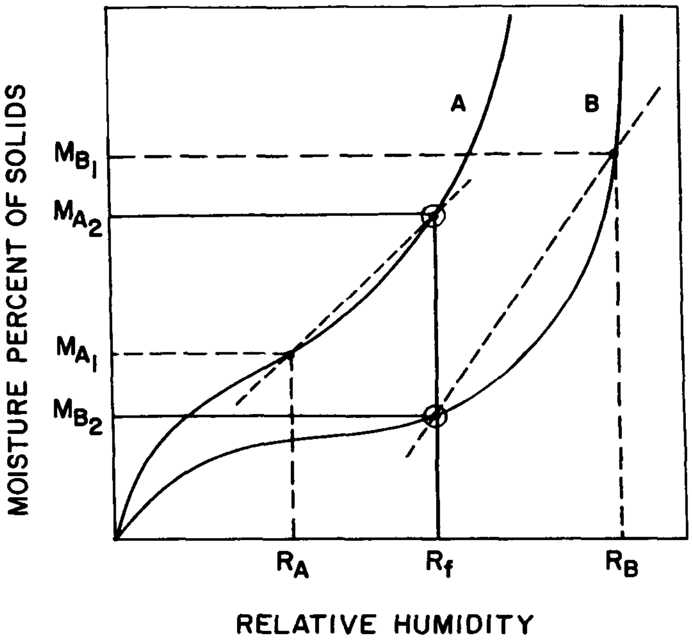

FIGURE 2

Salwin and Slawson's (13,14) graphical representation of moisture transfer during equilibration.

terms of application to pharmaceutical systems, and one upon which the present work is based, was reported by Salwin and Slawson (13) and Salwin (14) who were interested in the transfer of moisture in "dehydrated" foods used by the Armed Forces. Figure 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 moisture contents of M_{A1} and M_{B1} (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_{A2} and M_{B2}, 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 Figure 2). The slopes of these lines are given by:

$$S_A = \frac{M_{A2} - M_{A1}}{R_f - R_A} \qquad S_B = \frac{M_{B2} - M_{B1}}{R_f - R_B} \qquad (1)$$

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 Figure 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:

$$R_f = \frac{R_A S_A W_A + R_B S_B W_B}{S_A W_A + S_B W_B} \qquad (2)$$

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 equation 1. A better estimate of R_f was then calculated from equation 2 using these slope values. This iterative cycling was continued until the final value of R_f was determined. There is no limit to the number of components which can be analyzed in this way.

Although this technique was fairly successful when tested with various food products in a very limited range of relative humidities, 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 SDMT model (7) follows the Salwin-Slawson approach in principle, but 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 mechanism(s) of sorption (15-17). Previous work (18, 19) with a wide range of pharmaceutical excipients has shown that three-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 (20), Anderson (21), and deBoer (22), and termed the GAB equation by van den Berg (23), fits data very well over the entire range of relative humidities:

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

where W is the weight of vapor per weight of dry solid sorbed onto a solid at a particular relative pressure (P/P_o), 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. Important to emphasize here is that the approach to be developed can use any isotherm equation. In fact, the Langmuir equation will be utilized for describing one of the components included in a mixture study to be presented later. For purposes of deriving the general expression, however, only the GAB equation will be utilized. To account for water in the vapor state, the ideal gas law, depicted as IGL, is used.

Referring to Figure 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 headspace volume, V_A, as given by the ideal gas law. When written out in its entirety, equation 4 takes the form:

$$M_A = W_A \left(\frac{W_{mA} C_{gA} K_A (P/P_o)_A}{[1-K_A(P/P_o)_A][1-K_A(P/P_o)_A + C_{gA} K_A (P/P_o)_A]} \right) + \frac{P_o V_A (P/P_o)_A (18)}{RT} \tag{5}$$

where W_m, C_g, and K have been described previously, $(P/P_o)_A$ = $R_A/100$ = the initial relative water vapor pressure, P_o = 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 grams. A similar equation can be written for the total amount of water in chamber B. M_T, the total moisture in the system, is then obtained by summing M_A and M_B.

Upon exposure of V_A to V_B, moisture transfer will occur. Since M_T is known and V_A and V_B can be summed to give V_T, the total headspace volume for the two chambers, equation 6 can be used to describe the system once moisture transfer has occurred and a new "equilibrium" state has been attained.

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

Equation 6 written in its entirety takes the form:

$$M_T = W_A \left(\frac{W_{mA}\ C_{gA}\ K_A(P/P_o)}{[1-K_A(P/P_o)][1-K_A(P/P_o) + C_{gA}\ K_A(P/P_o)]} \right) + W_B \left(\frac{W_{mB}\ C_{gB}\ K_B(P/P_o)}{[1-K_B(P/P_o)][1-K_B(P/P_o) + C_{gB}\ K_B(P/P_o)]} \right) + \frac{P_o V_T (P/P_o)(18)}{RT} \tag{7}$$

where (P/P_o) is now the final relative water vapor pressure in the equilibrated system following exposure of the two chambers to one another. Rearranging equation 7, a fifth order polynomial in (P/P_o) is obtained:

$$(P/P_o)^5 + C_1(P/P_o)^4 + C_2(P/P_o)^3 + C_3(P/P_o)^2 + C_4(P/P_o) - C_5 = 0 \tag{8}$$

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

To solve equation 7 or 8, the real root between $(P/P_o) = 0$ and $(P/P_o) = 1$ must be found. Either approximation techniques such as Newton's method or iterative techniques, employing a least squares regression routine on a computer, can be used.

To summarize, the SDMT model will allow *a priori* prediction of the final relative pressure for a closed system in which the initial moisture contents, dry weights, and sorption/desorption isotherms for each solid, headspace volumes and temperature are known. Final moisture contents can then readily be obtained from the sorption/desorption isotherms for the respective components.

EXPERIMENTAL

Figure 3 shows a schematic representation and details of a glass vacuum rack used for moisture transfer and sorption studies. Details are described elsewhere (18). In essence, this apparatus permitted: (1) gravimetric determination of sorption/desorption isotherms using an electrobalance, (2) monitoring of moisture transfer by measurement of water vapor pressure using a pressure transducer, (3) headspace volume determinations using helium gas expansions, and (4) temperature control.

Sorption and desorption isotherms were obtained independent of any moisture transfer studies. Isotherms were measured by one of two techniques: *in vacuo* using the apparatus described above, or using desiccators. Both techniques employed saturated salt solutions to control the relative humidity.

Moisture transfer studies were conducted *in vacuo*, where the water vapor pressure was monitored via a pressure transducer. Headspace volumes were determined by helium gas expansion techniques. Moisture contents of solids were obtained gravimetrically and/or by

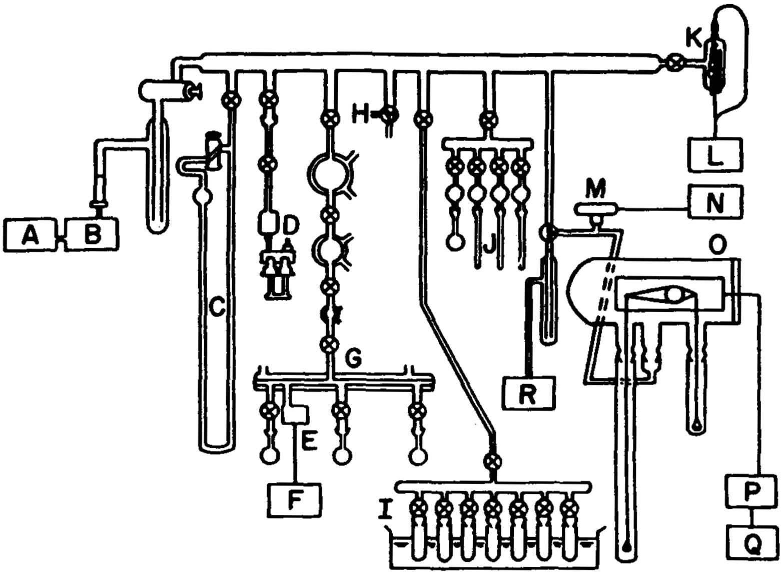

FIGURE 3

Water Sorption Apparatus (18) Components: A-Forepump #1; B-Oil Diffusion Pump; C-Oil Manometer; D-Surface Area Equilibration Port; E-Pressure Transducer; F-Electronic Manometer; G-Volumetric Sorption Apparatus; H-Connection to Pure Helium Gas; I-Relative Humidity Chambers; J-NMR Equilibration Ports; K-Ionization Gauge; L-Ionization Gauge Controller; M-Convectron Gauge; N-Convectron Gauge Controller; O-Electrobalance; P-Electrobalance Control Unit; Q-Recorder; R-Forepump #2.

pressure measurement and subsequent calculation using the respective GAB constants. Total moisture content was obtained by summing the initial moisture contents in the individual cell compartments.

TABLE 1

Various Constants Obtained from Sorption/Desorption Isotherms (7, 18)

GAB Constants

Component	Mode	Temp(°C)	W_m*	C_G	K
Microcrystalline	Sorption	23	0.0299	55.7	0.870
Cellulose	Desorption	23	0.0429	24.7	0.820
Corn Starch	Sorption	23	0.0753	67.0	0.804
	Desorption	23	0.114	26.9	0.641
Gelatin	Sorption	23	0.169	3.47	0.650
Capsules	Desorption	23	0.186	22.3	0.377

Langmuir Constants

Component	Mode	Temp (°C)	W_m*	C_L
Silica Gel	Sorption	23	0.572	1.78

*units = grams of water per gram of dry sample

RESULTS

Table 1 lists the GAB constants for microcrystalline cellulose (MCC) and cornstarch (CS), as well as the Langmuir constants for silica gel, obtained from the respective sorption/desorption isotherms. The Langmuir model was used to describe the silica gel isotherm due to its inherent hyperbolic shape. Only sorption values are presented for silica gel since its purpose in these studies was as a desiccant.

Tables 2 through 5 give predicted versus 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 2-6.

Note in Table 2 where 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 versus experimental results for a ternary mixture of mirocrystalline 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. Here, a fourth term was added to the right side of equation 7:

$$W_C \left(\frac{W_{mc}\, C_{LC}\, (P/P_o)}{1 + C_{LC}\, (P/P_o)} \right) \tag{9}$$

where W_C is the dry weight of silica gel.

In general, the predicted versus experimental moisture contents determined for each component for the

TABLE 2

Predicted versus Experimental Moisture Transfer between Two Samples of Microcrystalline Cellulose (7)

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	Pred	Exp	Pred	Exp	Pred	Exp
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 = 3.3855 g
Microcrystalline cellulose-2 = 5.2133 g

Temperature: 23°C

TABLE 3

Predicted versus Experimental Moisture Transfer between Microcrystalline Cellulose and Corn Starch (7)

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	Pred	Exp	Pred	Exp	Pred	Exp
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 versus Experimental Moisture Transfer between Microcrystalline Cellulose and Corn Starch (7)

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	Pred	Exp	Pred	Exp	Pred	Exp
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 versus Experimental Moisture Transfer between Microcrystalline Cellulose and Gelatin Capsules (7)

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	Pred	Exp	Pred	Exp	Pred	Exp
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

TABLE 6

Predicted versus Experimental Moisture Transfer Among Microcrystalline Cellulose, Gelatin Capsules and Silica Gel (7)

Initial

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

Final

%RH of Final Mixture		MCC $\% H_2O$ based on		Gelatin Caps $\% H_2O$ based on		Silica Gel $\% H_2O$ based on	
Pred	Exp	Pred	Exp	Pred	Exp	Pred	Exp
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 = 5.2000 g
Gelatin Capsules = 2.4698 g
Silica Gel = 2.0934 g
Temperature: 23°C

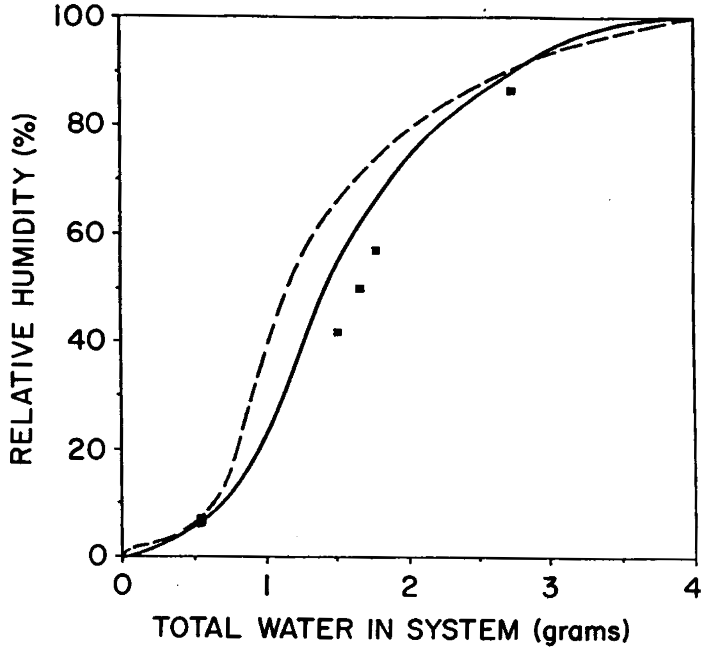

FIGURE 4

Moisture transfer between microcrystalline cellulose and corn starch where corn starch desorbs (7): data points determined experimentally;------Salwin-Slawson prediction;———SDMT model prediction.

various combinations of solids are in good agreement except for some systems which had been initially equilibrated at opposite extreme relative humidities, i.e., 0% and greater than 95% RH. The extent of agreement between experiment and calculation is graphically demonstrated in Figure 4 for combinations of microcrystalline cellulose and corn starch. Comparisons are also made with the approach used by Salwin and Slawson 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 equation 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 three-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 conformational change (19). Associated also with this latter fact is some uncertainty because of the complex sorption/desorption hysteresis often seen with such systems. A more detailed analysis of hysteresis phenomena is presented in reference 7.

DISCUSSION

The utility of the SDMT model is best demonstrated by considering several practical applications familiar to the pharmaceutical formulator.

First, consider the problem of hard gelatin capsule brittleness. Figure 5 shows that gelatin capsules exhibit brittleness at room temperature when the environment to which they are exposed falls to less than about 40% relative humidity. This corresponds to about 10% moisture content of the capsules (24).

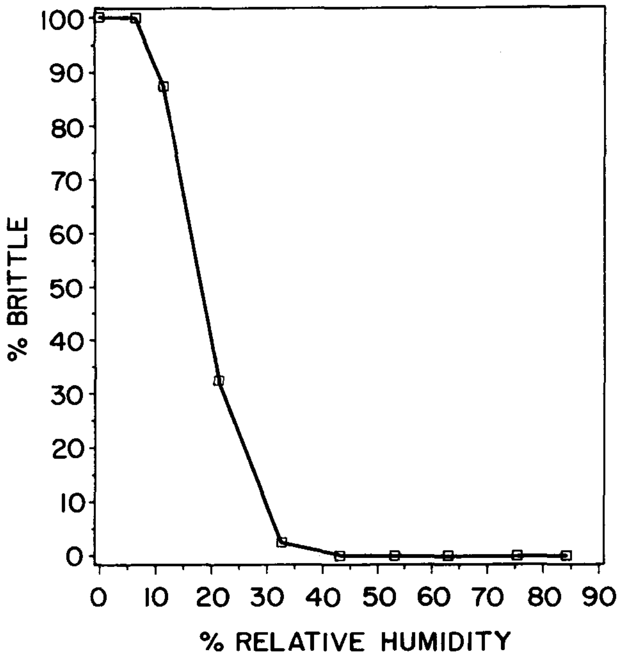

FIGURE 5

Empty gelatin capsule brittleness (24).

Hence, filling overdried granulation into gelatin capsules with an initial moisture content only slightly in excess of 10% will lead to moisture transfer from the capsule to the granulation and consequently, brittle capsules.

Figure 6 shows water sorption isotherms for gelatin capsules and Mexitil® (24). Since moisture was assumed to transfer from the capsules to the Mexitil® formulation as a whole, and not to an individual component(s) of the formulation, a single isotherm was generated for Mexitil®. The respective GAB constants are also included in Figure 6.

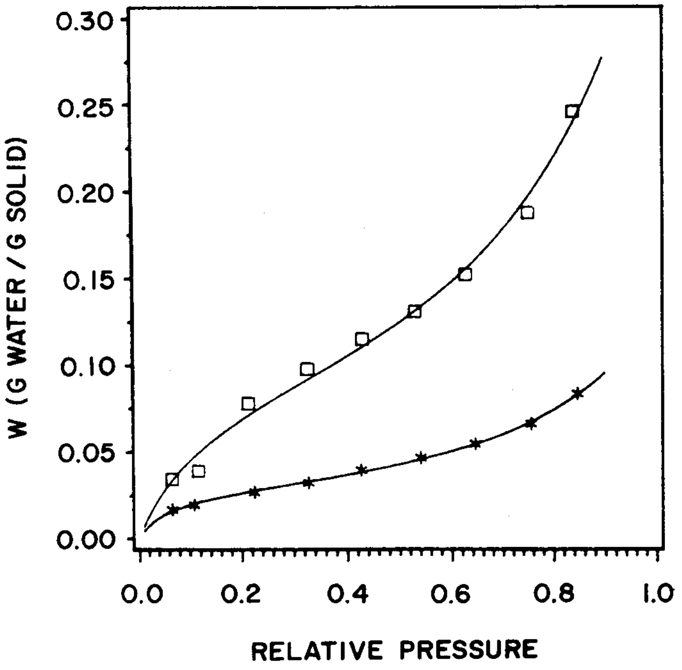

FIGURE 6

Water uptake isotherms and GAB fits for Mexitil® (*) and gelatin capsules (□)(24). GAB Values-Mexitil®: $W_m = 0.0274$, $C_g = 21.2$, $K = 0.800$; Gelatin Capsules: $W_m = 0.0874$, $C_g = 10.6$, $K = 0.775$.

With the above information and estimates of the initial moisture contents for the formulation and the empty gelatin capsules, one can employ the SDMT model to predict the final relative pressure for a given system and relate this to brittleness via Figure 5.

Table 7 presents results of a moisture distribution study for gelatin capsules initially equilibrated at a given relative humidity and Mexitil® independently equilibrated at another relative

TABLE 7

Predicted Versus Experimental Moisture Transfer Between Mexitil® and Gelatin Capsules

Initial					Final					
Gelatin Capsules		Mexitil®					Moisture Content (g/g)			
					%RH		Gelatin Capsules		Mexitil®	
%RH	Moisture Content (g/g)	%RH	Moisture Content (g/g)	M_T (g H_2O)	Exp	Pred	Exp	Pred	Exp	Pred
37.0	0.0992	11.0	0.0202	0.445	21.4	21.0	0.0710	0.0702	0.0269	0.0267
38.4	0.102	23.3	0.0279	0.149	29.0	29.9	0.0850	0.0866	0.0308	0.0313
44.7	0.114	7.3	0.0165	0.439	18.4	20.5	0.0649	0.0692	0.0252	0.0264
47.2	0.118	33.1	0.0329	0.624	37.0	39.4	0.0992	0.104	0.0350	0.0363
44.8	0.114	44.8	0.0393	0.680	44.7	44.8	0.113	0.114	0.0393	0.0393
56.2	0.138	0.0	0.000	0.0951	11.1	13.3	0.0477	0.0534	0.0202	0.0219
55.8	0.137	12.2	0.0212	0.151	27.5	32.9	0.0823	0.0919	0.0301	0.0328
55.6	0.137	24.2	0.0284	0.170	33.7	39.8	0.0933	0.104	0.0332	0.0365
56.2	0.138	33.0	0.0329	0.183	38.4	44.5	0.102	0.113	0.0357	0.0392
55.3	0.136	44.7	0.0392	0.731	47.2	49.4	0.118	0.123	0.0408	0.0422
55.1	0.135	55.1	0.0462	0.803	55.3	55.1	0.136	0.135	0.0463	0.0461

Experiments - 1, 3, 4, 5, 10, 11 used samples with capsule masses of 2.34 g and Mexitil® masses of 10.48 g. Initial Capsule Headspace Volume = 61.07 ml. Initial Mexitil® Headspace volume = 116.32 ml.

Experiments - 2, 6, 7, 8, 9 used samples with capsule masses of 0.68 g and Mexitil® masses of 2.65 g. Initial Capsule Headspace Volume = 62.82 ml, Initial Mexitil® Headspace volume = 121.62 ml. (Exception: Initial Mexitil® Headspace Volume in experiment 2 = 709.70 ml) humidity. Values calculated for the equilibrium relative humidity using the SDMT model are also presented, as are moisture contents for each material calculated using the GAB equation. In addition, Table 7 shows the effect of varying the masses of gelatin capsules and Mexitil®, as well as varying the headspace volumes. In all cases, agreement between theory and experimental results is very good, again demonstrating the utility of the SDMT model for predicting the final relative humidity for this system.

Analysis of these results (Table 7) in view of Figure 5, where brittleness is apparent at relative humidities below 40%, suggests that Mexitil® granulation should be equilibrated at a relative humidity of at least 40% to avoid brittleness if the capsule initially contains 12% moisture. For the mass ratios of the capsule and Mexitil® chosen in this study, this corresponds to a minimum initial LOD value of 3.7% for the Mexitil®. However, it must be emphasized that the minimum acceptable granulation LOD value is quite dependent on the initial capsule LOD.

Additional support for this approach is evident from Figure 7 where the brittleness of filled Mexitil® capsules is plotted against relative humidity of equilibration. Note the similarity between Figures 5 and 7 that contrast empty and filled gelatin capsules.

As a second example, 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

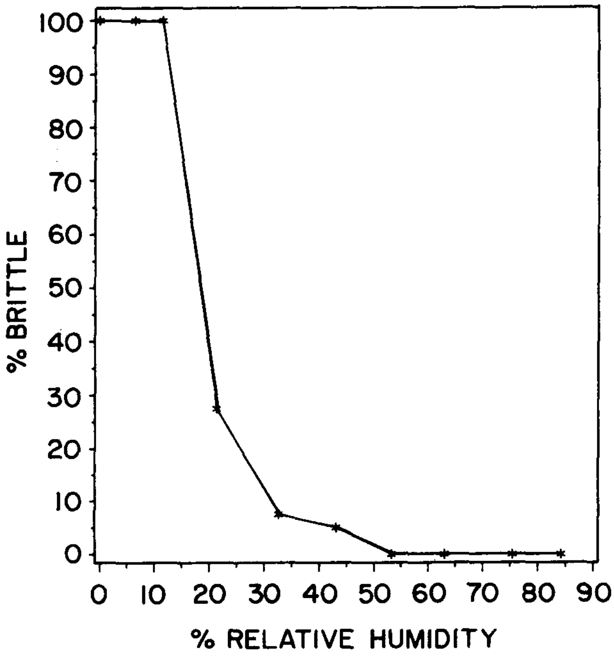

FIGURE 7

Mexitil® 250 mg capsule brittleness (24).

from the GAB equation as described earlier in this paper.

	W_m	C_g	K
Component A	0.0000072	34.3	0.840
Component B	0.0000241	29.7	0.739

and the following relative humidities at saturation and 20°C:

Component A $RH_o = 75\%$
Component B $RH_o = 84\%$

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 (25) and Kontny and Zografi (26). Thus, if the relative humidity of the container goes above 63%, deliquescence will occur (27). 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 a given headspace. During processing, let us assume further that a total water content of 8.5×10^{-5} grams 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 headspace volume (or vial size) be maintained such that the relative humidity is below 63%?

Using equation 7 it is possible to solve for the term V_T, the total headspace volume, at various values of P/P_O. Table 8 gives the final calculated equilibrium relative humidity results for various headspace volumes, showing clearly that a vial providing a headspace volume of at least 7 ml is necessary to maintain an acceptable relative humidity below 63%.

The SDMT model can also be utilized to rationally select the appropriate amount of desiccant that should be included in a closed product container to maintain a given relative humidity (28). Consider a system consisting of a formulation containing aspirin (and

TABLE 8

Calculated Final Relative Humidities as a Function of Headspace Volume for 0.95 g of Component A and 0.05 g of Component B with 85 μg Total Water.

Headspace Volume (ml)	Final Relative Humidity (%)
3	94
4	85
5	75
6	66
7	58
10	42
15	29
20	22

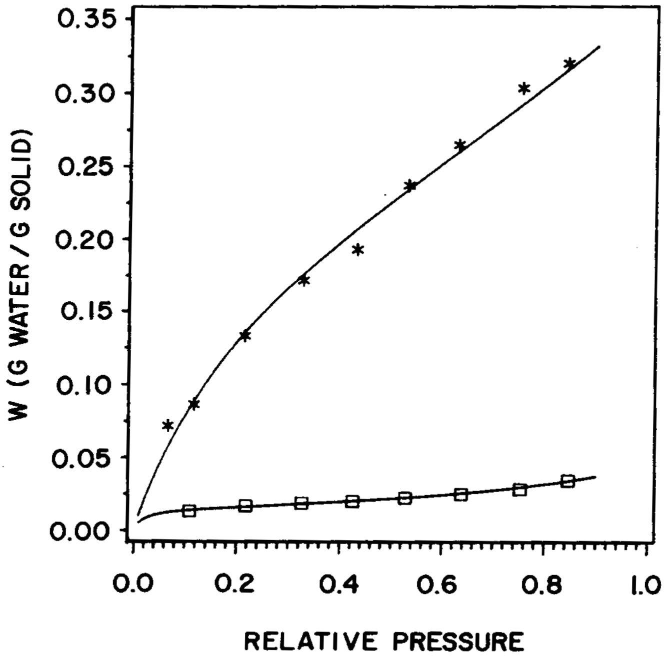

FIGURE 8

Water uptake isotherms and GAB fits for an aspirin formulation (□) and silica gel (*). GAB Values-ASA: W_m = 0.0149, C_g = 71.0, K = 0.671; Silica Gel: W_m = 0.256, C_g = 10.3, K = 0.387.

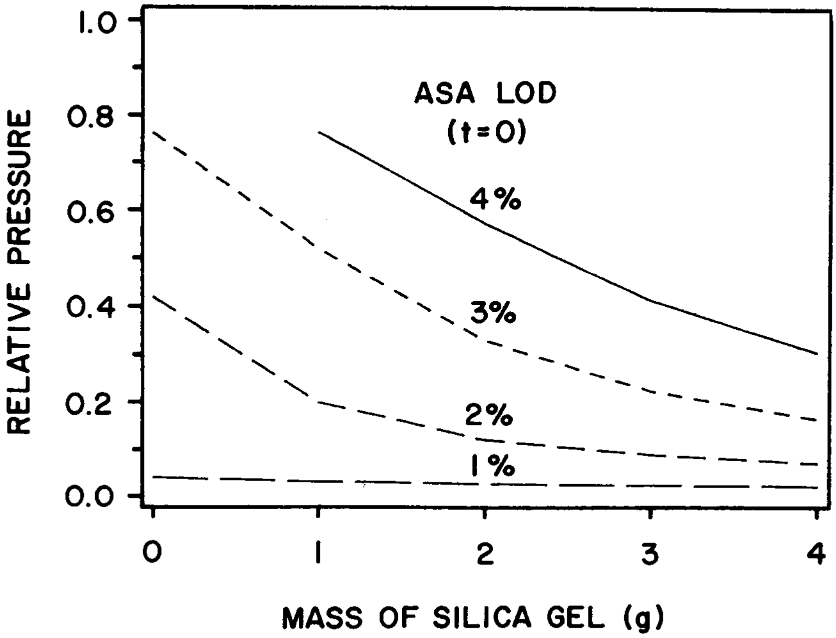

FIGURE 9

SDMT-predicted relative pressure vs. mass of desiccant for aspirin formulation/silica gel. Initial silica gel LOD = 0%.

other common excipients) and silica gel as a desiccant. Figure 8 shows the uptake isotherms for these materials, including their respective GAB values.

Assuming 50 tablets (600 mg total each) in a container with a headspace volume of 30 ml, one can simulate final relative pressures inside the container for various masses of silica gel of varying initial moisture contents. Figures 9-11 depict this for initial silica gel moisture contents of 0%, 10% and 20%, respectively, and varying initial moisture contents for the aspirin formulation. It is obvious

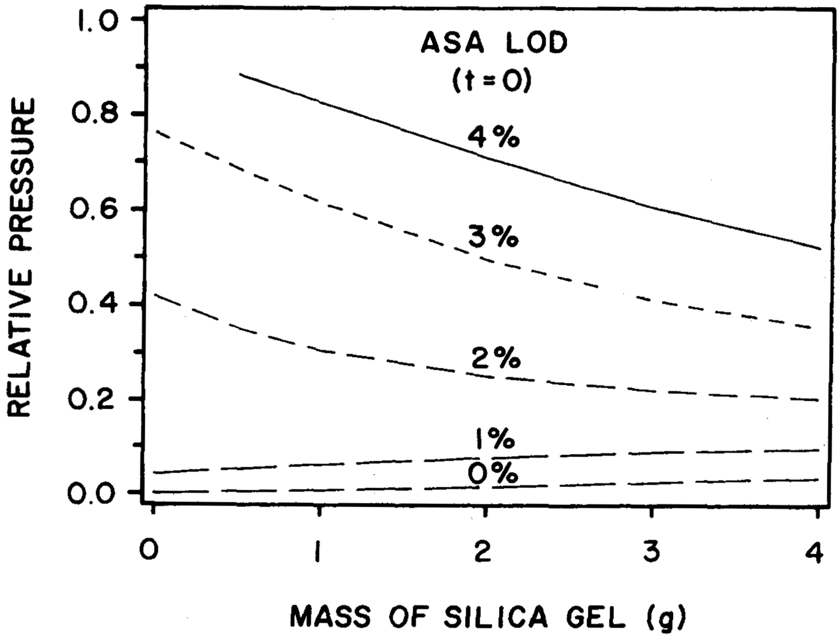

FIGURE 10

SDMT-predicted relative pressure vs. mass of desiccant for aspirin formulation/silica gel. Initial silica gel LOD = 10%.

that the final relative pressure in the system is markedly dependent on the initial moisture content of the formulation, as well as the mass and initial moisture content of silica gel employed.

This has considerable impact on the stability (physical and/or chemical) profile of a product affected by moisture. For discussion purposes, assume one wants to maintain the relative humidity inside the container at 25%. Here it is obvious from Figures 9-11 that the initial moisture contents of the solid formulation and the silica gel influence to a great

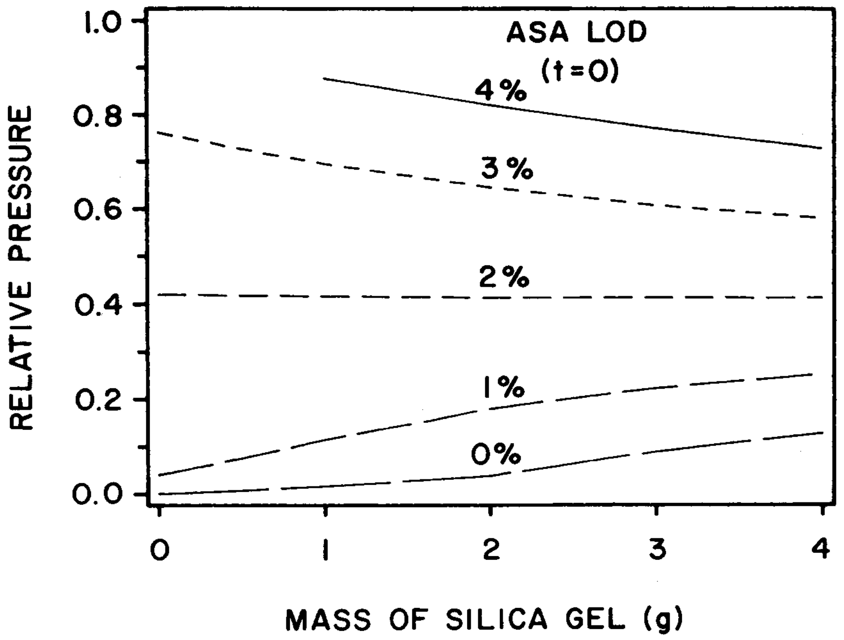

FIGURE 11

SDMT-predicted relative pressure vs. mass of desiccant for aspirin formulation/silica gel. Initial silica gel LOD = 20%.

extent the final relative humidity. For certain sets of initial conditions (high moisture contents for both the aspirin formulation and the silica gel), it is not possible to attain an RH of 25% without using impractical amounts of desiccant. This strongly supports the need for moisture content specifications as well as in process moisture content determinations of these components.

The discussion to this point has only addressed the case of a closed system. However, it is well known that moisture does indeed enter into containers through the cap seal and via permeation through the container material itself. Provided one had an estimate of the rate at which water enters a container, this could readily be added as another term to obtain M_T at a given time by simply multiplying this rate by the time point(s) of interest and proceeding as described previously. However, the rate of moisture penetration into a container is not constant. Rather, it is a complex function that is dependent on many variables, including the relative humidity inside and outside the container. Assuming a constant external relative humidity, one must determine the factors which influence the time dependence of attaining a given internal relative humidity. Not only will the parameters discussed in the SDMT model be important, but diffusional considerations must be incorporated as well. This topic is under investigation at the present time.

CONCLUSIONS

In summary, the Sorption/Desorption Moisture Transfer (SDMT) model has been developed to provide the pharmaceutical formulator with a tool for following and providing a better understanding of moisture transfer phenomena that are critical to development activities. In essence, the SDMT model allows *a priori* calculation of the final relative water vapor pressure inside a closed container and subsequent calculation of individual component moisture contents. Utilization of the model requires water sorption-desorption isotherms for the materials present, their dry weights and initial moisture contents, headspace volume(s) and temperature.

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