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Physical Characteristics of Solids

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1. STATES OF MATTER: CRYSTALLINITY AND AMORPHICITY

Prior to discussing the stability of drugs in the solid state, it is necessary to outline some characteristics of solids. A detailed discussion of the state of matter in regards to solids is outside the scope of this book. Suffice it here to say that solids may be characterized by being (a) crystalline or (b) amorphous. Crystalline solids are associated with a lattice, and amorphous solids are solids that are not crystalline. Some of the characteristics (those that apply to stability) of these two categories will be discussed in the immediate following.

There are seven crystal systems and two types of amorphates.

2. POLYMORPHISM

Inorganic (particularly ionic) solids usually are associated with one and only one crystal system. Well-known to all is that sodium chloride is cubic.

Organic solids, however, depending on how they are recrystallized, may occur in several different crystal modifications (polymorphs). There are two types of polymorphism, enantiotropes and monotropes. They are distinguished by their vapor pressure diagrams as shown in Figs. 1 and 2.

The situation referred to in Fig. 1 is one where there is a transition temperature, and DSC traces in such cases often have the appearance of either Fig. 2 or 3.

It is seen in Fig. 2 that two common situations may occur: first, the transformation may take place, so that there is an endotherm for the transformation followed by an endotherm for the melting. The melting point of form II (the room-temperature labile form) is recorded in this case as is the transition temperature.

The other possibility is that the transition is passed by, giving the melting point of the (now unstable) form I (lower trace). This forms an unstable melt, and often form II precipitates out, giving the exotherm shown in the lower graph followed by endotherm for the melting point of form II.

In some cases the exotherm is missing, and in such cases the melting endotherm of form II is also missing, i.e., the trace simply looks like the trace of melting of form

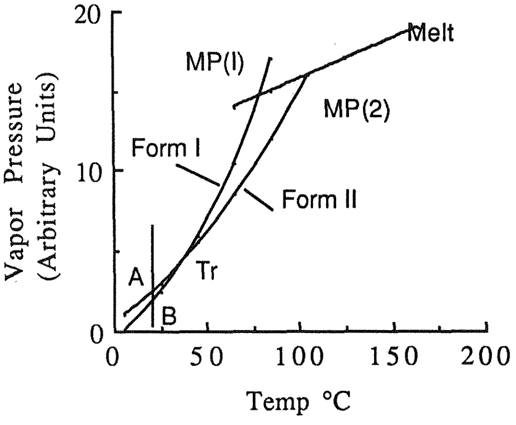

Fig. 1 Vapor pressure diagram of an enantiotropic pair.

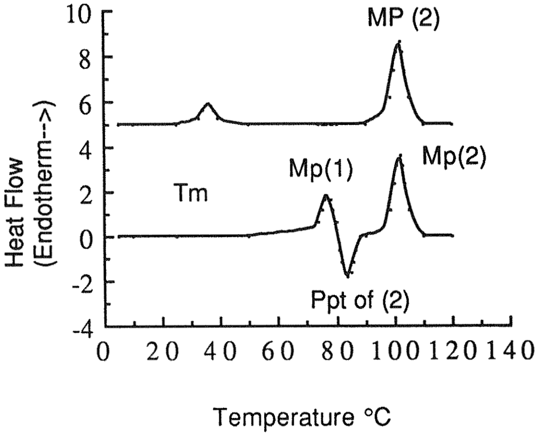

Fig. 2 Possible DSC traces resulting from heating of the room-temperature stable form of an enantiotropic pair.

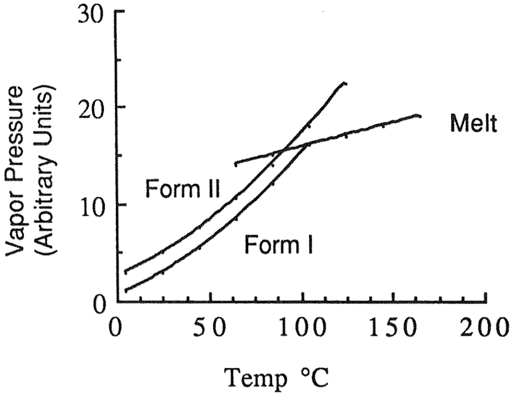

Fig. 3 Graph of vapor pressures for a monotropic pair.

I, as if no other form existed (similar to the bottom trace in Fig. 4). In such a case, if the compound is stable, it may be recooled, and the down direction melting point can be (and most often is) that of form II.

The other case is where one form (form II) is metastable throughout the melting range. This is exemplified in Fig. 3.

The DSC trace of such a pair may take one of several forms. The stable form will simply show up as a trace with one endotherm (the melting point of the stable form). Traces of the metastable form may either show up this way or as the lower trace in Fig. 4 .

As mentioned, if the compound is stable to melting, it is advisable to recool the mass and record the melting point on the down trace. Most often, however, decomposition of the solid and melt preclude conclusions from cooling curves.

The most powerful tool in polymorphic investigations, where it comes to determining whether two samples are of identical or different crystal systems, is

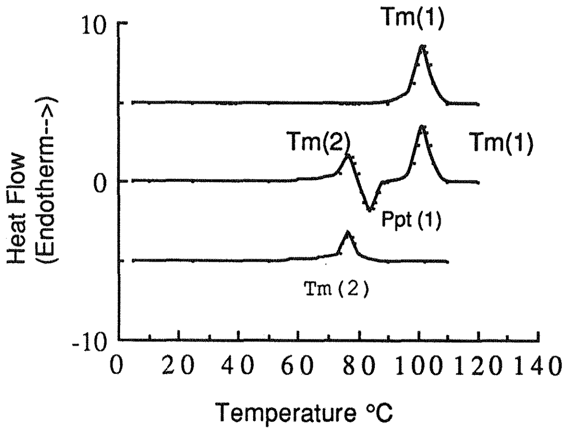

Fig. 4 Some possible DSC traces of the heating of polymorphs that are monotropic. The top trace is the heating of the stable polymorph in Fig. 3, and the two lower traces are the heating of the metastable polymorph, which may either simply melt (lower trace) or, as shown in the middle trace, melt and precipitate (exotherm) as the stable form I and then (second endotherm) remelt.

x-ray diffraction. Spacings in a crystal are related to the angle of the incoming beam (ϕ) by Bragg's law, which states that $2d\sin(\phi) = -k\lambda$, where λ is the wavelength of the x-rays used. The intensities are often used to monitor the amount of one form in another, or the amount present after a given time, t, when a conversion is taking place. An example of this is the work by Franchini and Carstensen on ranitidine (1994) where correlation was found between the content of form I in form II by the intensity at a 2ϕ value where form I did not "absorb" and where form II had a peak. Care should be taken in the interpretation of peak heights (or areas under the peak), since orientational factors can affect this. Orientation will, however, not affect the position of the peak.

It should be pointed out that in the strictest sense (Carstensen and Franchini, 1995, Martínez-Oharriz et al., 1994), there can only be true monotropism if the heats of solution are identical (and have the same temperature dependence). It is, therefore, advisable to perform heats of solution, calorimetrically, as was done for ranitidine by Franchini and Carstensen (1994) and for diffusinal by Martínez-Oharriz et al. (1993). If the heat of solution of the metastable polymorph in the pair is higher than that of the stable, the two curves may intersect at a temperature lower than the lowest temperature investigated. Of course, if this intercept is below absolute zero, then monotropism still prevails. If the heat of solution of the metastable polymoprh in the pair is lower than that of the stable one, then the two curves may intersect above the melting point, and in that case monotropism also prevails.

In the case of ranitidine, the two forms have identical solubilities (within experimental error), and what is denoted form I has a lower melting point. If the heats of solution are truly identical, this would then imply that form I is metastable over the entire temperature range and that it is a monotropic pair.

It follows from thermodynamics that the change in Gibb's energy by a path from metastable to stable form, ΔG, is given by

$$\Delta G = -RT \ln\left[\frac{P_{\text{metastable}}}{P_{\text{stable}}}\right] \tag{8.1}$$

It is negative, so the form with the highest vapor pressure at a given temperature is the least stable (metastable) compound. The term metastability (rather than instability) is used because under advantageous conditions the metastable compound may be "stable", i.e., not change for years or even decades.

3. SOLUBILITIES OF POLYMORPHS

It can be shown via Henry's law that solubilities are (approximately) linearly related to vapor pressures (actually activities as solubility are linearly related to fugacities). The graphs in Figs. 1 and 2 then become as shown in Figs. 5 and 6.

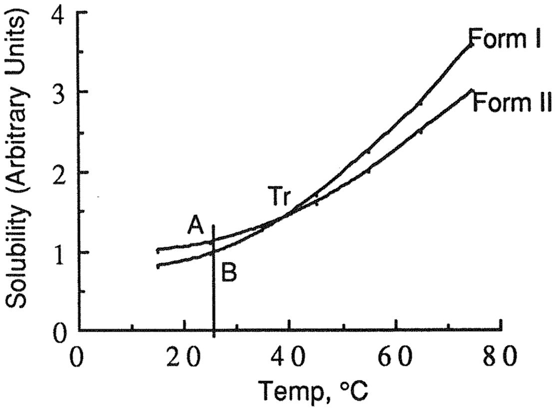

Fig. 5 Solubilities (in mass of solute per mass of solvent) of an enantiotropic pair.

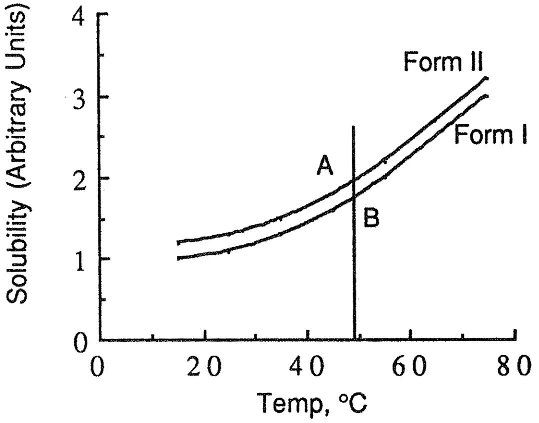

Fig. 6 Solubilities (e.g., in mass of solute per mass of solvent) of a monotropic pair.

If the Henry's law argument is applied to Eq. (8.1), then

$$\Delta G = -RT \ln\left[\frac{S_{\text{metastable}}}{S_{\text{stable}}}\right] \tag{8.2}$$

where S denotes solubility, R the gas constant, and T absolute temperature.

There are cases where the solubilities are close to one another over the entire temperature range, and in such cases it may be difficult to separate the two polymorphs in the final purification (recrystallization, reprecipitation), and there are cases where companies have been forced to suggest specifications that stipulate a minimum and a maximum of one polymorph in relation to another.

Increased solubility increases dissolution rates, and herein lay the initial interest in polymorphism in pharmacy. Shefter and Higuchi (1963) have shown the effect of solvates and hydrates on dissolution rates of several drug substances.

Pfeiffer et al. (1970) determined the solubility of cephaloglycin and cephalexin in binary mixtures and established that, depending on the composition of the medium, one or another polymorph would be stable (Fig. 7).

Poole and Bahal (1968) showed the differences in dissolution rates of anhydrous and dihydrate forms of ampicillin. The anhydrous form is amorphous, and hence would have a higher apparent solubility and hence a faster dissolution. Poole and Bahal (1970) have used Van't Hoff plots to show the conversion temperature between the anhydrous and dihydrate forms of an aminoalicyclic penicillin.

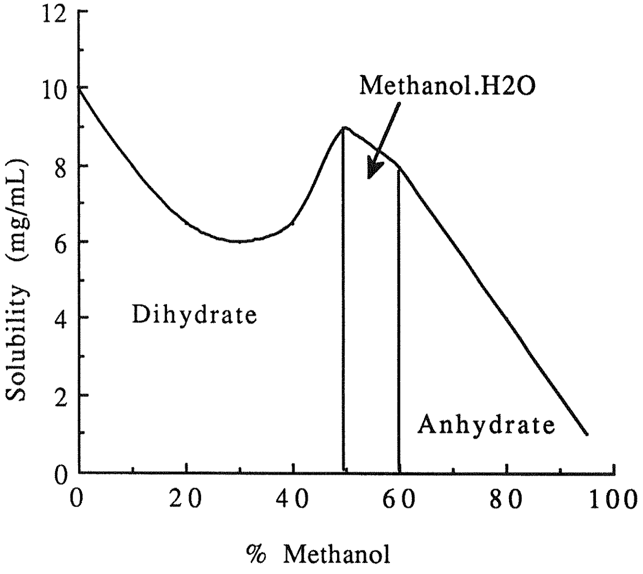

Fig. 7 The areas indicate the solid phase in which the solution is in equilibrium. (Graph constructed from data by Pfeiffer et al., 1970.)

4. RATES OF CONVERSION IN MOIST STORAGE

Good stability of a metastable compound can be achieved by (a) low temperature, (b) coarse crystals, and (c) dry storage. The moisture is the most significant contributor to conversion.

Moisture will condense onto the surface of the metastable form (II), which will then saturate the moisture layer to form a solution which is supersaturated in (I). This will eventually nucleate, and all of the II will convert to I.

The conversion rate is therefore a function of the nucleation rate in "solution," and it is well known (Mullin, 1961) that the nucleation rate, J, is inversely proportional to the viscosity of the solution and also to the supersaturation ratio, ΔS by the relation

$$J = A \exp\left[\frac{-q}{T^3 \ln \Delta S}\right] \tag{8.3}$$

For very soluble compounds, ΔS will be a very small number, and the tendency for one polymorph to change into another will be very small. An example of this is ranitidine.

5. EQUILIBRIUM MOISTURE CONTENT OF SOLIDS AND HYGROSCOPICITY

Hygroscopicity is the potential for moisture uptake that a solid will exert in combination with the rate with which this will happen. The condition of the atmosphere is an important factor as well, so a short, concise definition of hygroscopicity is not possible.

If a solid is placed in a room, moisture will condense onto it. If this moisture is simply a limited amount of adsorbed moisture, the substance is not hygroscopic under those conditions. These conditions exist if the water vapor pressure in the surrounding atmosphere is lower than the water vapor pressure over a saturated solution of the solid in question.

Often, however, the water vapor pressure in the atmosphere, P_a, is lower than that of the saturated solution, P_p. Then there will be a thermodynamic tendency for water to condense upon the solid. This is depicted in Fig. 8.

From a thermodynamic point of view, the situation shown dictates that moisture keeps on adsorbing until all solid has dissolved, and then continues until the solution is sufficiently dilute to have a vapor pressure of P_a. In this respect the moisture uptake curve differs from that of surface adsorption (polymers, and situations at atmospheric pressures below P_s), because these have asymptote at much lower levels.

The rate and extent of which moisture can condense on solids is usually collected under the term "hygroscopicity." In recent years a series of articles dealing with this phenomenon (e.g., Van Campen et al., 1980) have appeared in the pharmaceutical literature dealing with this subject. The purpose here is to derive a rational equation for the rate with which moisture is adsorbed onto a water-soluble solid.

As mentioned, if a solid is placed in an atmosphere that has a vapor pressure, P_a, higher than the vapor pressure, P_s, of the saturated solution of the compound,

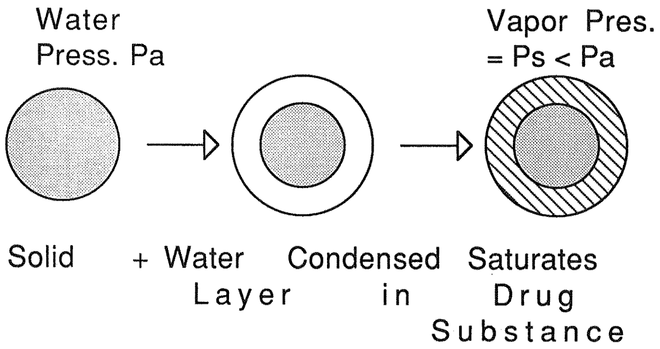

Fig. 8 Mechanism of moisture condensation.

the condensed water will dissolve solid. It will be assumed below that the sorbed solution is saturated at all times. The question is what sort of curve might be expected for the extent of moisture uptake with time (the moisture uptake rate curve, the MUR curve).

Assume that, at time t, a certain amount of moisture, w, has been adsorbed by a particular solid particle weighing m grams and of diameter, d_0, where the subscript denotes the condition prior to moisture adsorption. At time t, moisture will have adsorbed, some solid will have dissolved, and the diameter, d, of the solid itself will have decreased from its original value. The diameter of the ensemble, D, is the sum of the diameter of the remaining solid and the thickness, h, of the moisture layer.

It is assumed in the following that one gram of solid is studied and that the sample is monodisperse. Such a sample would consist of N particles, where

$$Nm = \frac{N\rho\pi d_0^3}{6} = 1 \tag{8.4}$$

The amount of solid present at time t is given by the original amount less the amount dissolved. If there are W grams of water adsorbed by one gram of solid (i.e. w gram dissolved per particle), then

$$N\left(\frac{\rho\pi}{6}\right)d^3 = N(m - wS) = 1 - WS \tag{8.5}$$

or

$$d^3 = \frac{1 - WS}{N(\rho\pi/6)} \tag{8.6}$$

The volume of liquid adsorbed by one solid particle has a volume of the total particle minus the solid particle, i.e.,

$$\begin{aligned} \frac{w}{\rho^*} &= \left(\frac{\pi}{6}\right)D^3 - \left(\frac{\pi}{6}\right)d^3 \\ &= \left(\frac{\pi}{6}\right)D^3 - \frac{\pi/6(1 - WS)}{N(\rho\pi/6)} \end{aligned} \tag{8.7}$$

where ρ^* is the density of the adsorbed liquid. Since it is assumed that it is always saturated, it is time-independent, and under ideal conditions it would be

$$\rho^* = (1 - x_s)\rho_0 + x_s\rho \tag{8.8}$$

where $1 - x_s$ and x_s are the volume fractions of liquid and solid, respectively, in the ensemble particle, and ρ_0 and ρ are the respective densities. It follows from Eq. (8.7) that the amount of moisture adsorbed per gram can be expressed in terms of diameters as

$$\mathrm{W} = \rho^* N\left(\frac{\pi}{6}\right)D^3 - \frac{\rho^*(1 - WS)}{\rho} = QD^3 - F + FSW \tag{8.9}$$

where

$$F = \frac{\rho^*}{\rho} \tag{8.10}$$

$$Q = \rho^* N\frac{\pi}{6} \tag{8.11}$$

Equation (8.9) may be written

$$F + (1 - FS)W = QD^3 \tag{8.12}$$

or

$$D = \left\{\frac{F + (1 - FS)W}{Q}\right\}^{1/3} \tag{8.13}$$

The area, a, of the particle (solid plus liquid) is, hence,

$$a = \pi\left\{\frac{F + (1 - FS)W}{Q}\right\}^{2/3} = B[E + W]^{2/3} \tag{8.14}$$

where

$$\mathrm{B} = \pi\left[\frac{1 - FS}{Q}\right]^{2/3} \tag{8.15}$$

$$\mathrm{E} = \left\{\frac{FQ}{1 - FS}\right\}^{2/3} \tag{8.16}$$

The rate of condensation (dW/dt) is proportional to the pressure gradient, i.e., the difference between the water vapor pressure, P, in the atmosphere and the vapor pressure, P_s, over a saturated solution. At a given atmospheric milieu, this gradient is a constant.

It is also proportional to the surface area, a, by a mass transfer coefficient, k, so that we may write

$$\frac{dW}{dt} = ka(P_a - P_s) = k(P_a - P_s)B[E + W]^{2/3} \tag{8.17}$$

where Eq. (8.14) has been used for the last step. This may be written

$$\frac{dW}{[E + W]^{2/3}} = 3G\,dt \tag{8.18}$$

where

$$3G = k(P - P_s)B \tag{8.19}$$

Eq. (8.18) integrates to

$$[E + W]^{1/3} = Gt + [E]^{2/3} \tag{8.20}$$

where the initial conditions, $W = 0$ at $t = 0$, have been imposed. Equation (8.20) can be solved by iteration.

As an example of this, VanCampen et al. (1980) studied the moisture pickup in a vacuum system by using a Cahn balance and exposing the evacuated head space to relative humidities created by salt baths. They also reported moisture uptake rates of choline chloride at room temperature and different relative humidities using a desiccator method. An example of their results obtained by the latter method is shown in Fig. 9.

Jakobsen et al. (1997) have employed a highly sensitive microcalorimeter to evaluate the hygroscopicity of hydrophilic drug substances, such as flupentixol dihydrochloride (solubility>1 g/mL) as well as hydrophobic substances (such as

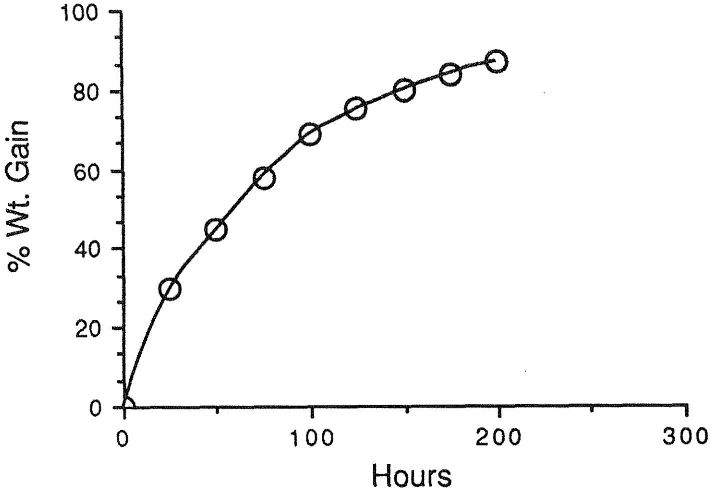

Fig. 9 Data for choline chloride moisture adsorption at 100% RH. (Drawn from data published by VanCampen et al., 1980.)

ertindole, solubility 10 μg/mL). Pinderre et al. (1997) have described coating powders with Eudragit to protect them against moisture uptake and have evaluated the coatings by way of moisture uptake rates.

6. CRITICAL MOISTURE CONTENT

There are humidities below which a solid will not adsorb (considerable amounts of) moisture, i.e., not form a "bulk-sorbed" layer. These are dictated by the solubility of the compound, as will be seen below.

Suppose a solid is placed in a room of a given RH, as shown in Fig. 10. If the RH were 30%, then it might pick up moisture at a given rate, at 50% RH at a higher rate, and at 80% RH at an even higher rate.

The rate with which it picks up moisture is determined by weighing the sample at given intervals, as demonstrated in Table 1. It is noted that there is a linear section of the curve (up to 6 days), as shown in Fig. 11 and 12. The slope of this linear segment is the moisture uptake rate (MUR). The actual uptake rates (determined from the linear portions) are shown in Table 2.

The uptake rates can simply be obtained by weighing the sample after a given time (6 days), but in such a case it is assumed that the moisture uptake is still in the linear phase. If, e.g., the weight gain is 5 mg per 10 g sample in 6 days, then the MUR is 5/10/6 = 0.083 mg/g/day.

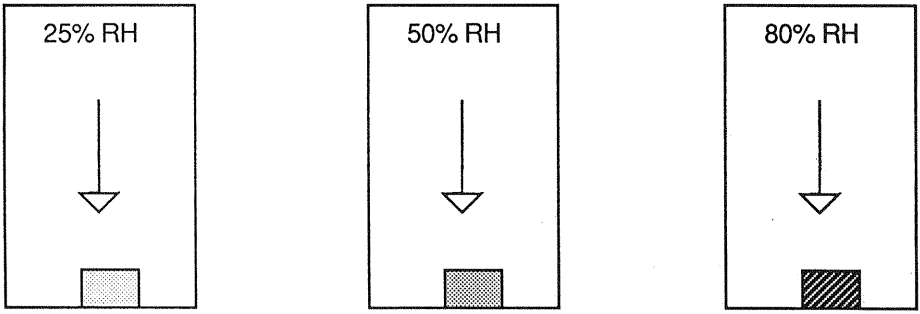

Fig. 10 Mechanism of moisture uptake.

Table 1 Moisture Uptake of a Water-Soluble Compound at 50% RH

Days stored at 50% RH	Moisture pickup (mg/g)
2	0.5
6	1.5
18	2.25
36	3.4
100	3.0
144	4.2
288	4.3

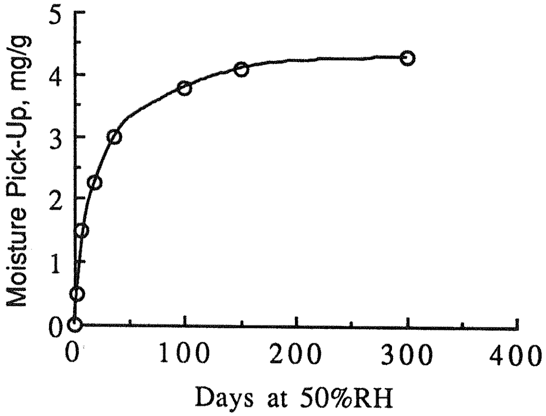

Fig. 11 Moisture uptake data from Table 1.

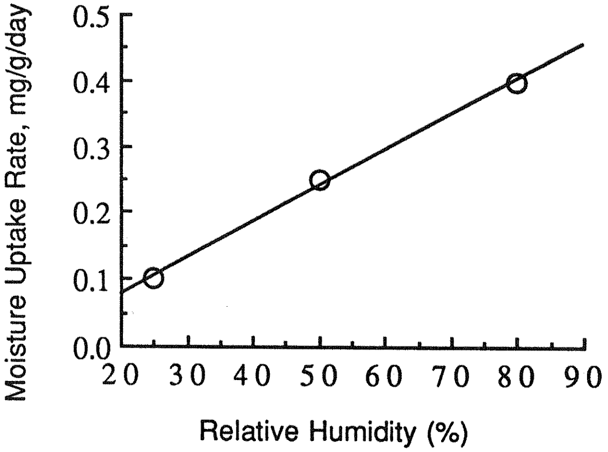

Fig. 12 Moisture uptake rate as a function of RH. Least squares fit is $y = -0.06264 + 0.006374x$, with $R^2 = 0.999$.

Table 2 Moisture Uptake Rate of Water-Soluble Compound

% RH	mg/g/day
25	0.1
50	0.25
80	0.45

If the MUR values are plotted versus RH, then a straight line results (Fig. 11). The curve intercepts the x-axis at 20% RH. This means that the compound can be stored without moisture pickup in atmospheres of less than 20% RH. In some cases the compound will dry out under such conditions (e.g., a hydrate), but in general

Table 3 Characteristics of Disodium Hydrogen Phosphate

Type	% Moisture in solid		P(H_2O) (mm Hg)	Water activity (RH/100)
Anhydrous	0			
		Pair	9	0.38
Dihydrate	20			
		Pair	14	0.58
Heptahydrate	47			
		Pair	18	0.75
Dodecahydrate	60			
		Pair	22	0.92
Satd. solution (100 g water/4.5 g salt)				

the useful information reached from such a graph is the maximum RH that is satisfactory for storage of the products. 20% RH happens to be the relative humidity over a saturated solution of the compound (or over a salt pair, as will be discussed presently).

For inorganic compounds and hydrates, the curves are stepwise curves. For instance, for disodium hydrogen phosphate, the following situation exists: the compound can form three hydrates (2, 7, and 12) aside from being anhydrous. The percent of moisture in, e.g., the dihydrate, is calculated as follows: disodium hydrogen phosphate has a molecular weight of 142. The dihydrate hence has a molecular weight of $142 + 36 = 178$. Hence the moisture percentage is

$$100 \times \frac{36}{178} = 20\%$$

The moisture contents for the remaining hydrates are shown in Table 3.

7. EQUILIBRIUM MOISTURE CURVES FOR SALT HYDRATES

The previous section dealt with the *rate* with which moisture is taken up. As shown in Fig. 11, at longer time periods, the moisture level (the weight of the sample) will taper off and plateau at an equilibrium value. This equilibrium value is also a function of RH, and there are two types of curves that occur when equilibrium values are plotted against RH: salt pairs and continuous adsorption. The former will be discussed first.

It is seen in the table that the RH of the atmosphere above a mixture of anhydrous disodium hydrogen phosphate and the dihydrate is 9 mm Hg or $100(9/24) = 38\%$ RH. It is noted that any mixture of the anhydrous salt and the dihydrate will given this relative humidity. Hence disodium hydrogen phosphate containing from 0 to 20% moisture will have above it an atmosphere of 38% RH. Similarly, as shown in Table 3, the heptahydrate contains 47% moisture, and mixtures of di- and heptahydrate give rise to water vapor pressures of 14 mm Hg (58% RH). Proceeding in this fashion, a graph as shown in Fig. 13 results.

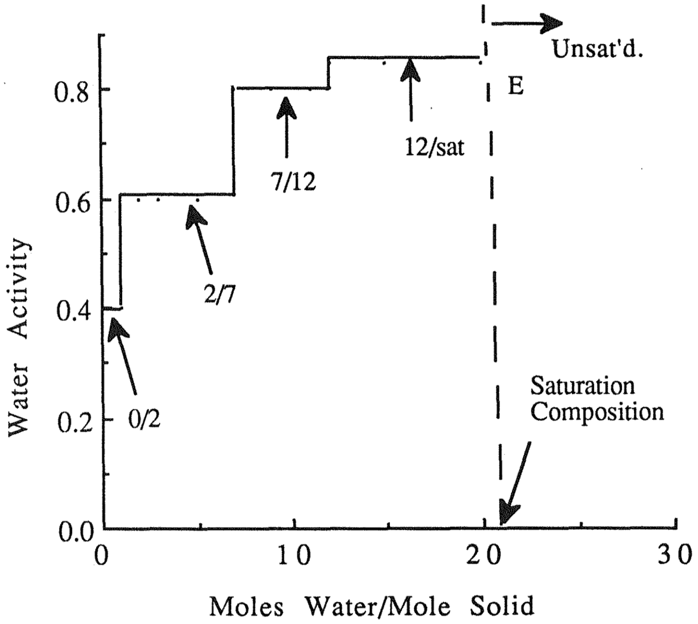

Fig. 13 Vapor pressure diagram of salt forming a dihydrate, a heptahydrate, and a dodecahydrate.

Two further points need to be mentioned. (a) If disodium hydrogen phosphate is stored at a relative humidity between 38 and 58% RH, it will not pick up moisture. Once the relative humidity is raised to (slightly above) 58%, then it will start picking up moisture until it has completely converted into the heptahydrate. (b) If the relative humidity is raised to (slightly above) 92% RH, then the dodecahydrate is converted to saturated solution. At higher RH values, the equilibrium will be dictated by the water vapor pressure over the now unsaturated solution.

At 100% RH the system in equilibrium is infinite dilution (pure water), and if a diagram such as this (and the following diagram for organic macromolecules) is carried out to 100% RH, then a sharply increasing curve should result at very high RH. The diagram in Fig. 12 is at a given temperature. Figure 13 shows a diagram of a dihydrate at different temperatures. At the temperature T_3, the line for the salt pair has caught up with that of the saturated solution. Essentially this means that the enthalpy of hydration for the solid is higher than the heat of vaporization of water from the saturated solution, since both have Clausius–Clapeyron type vapor pressures. Above T_3, therefore, the salt would have a higher vapor pressure than the saturated solution, but this is thermodynamically untenable, and T_3 is simply the highest temperature (and a triple point) where the dihydrate exists.

For a monohydrate as depicted in Fig. 14, the moisture content of the "salt hydrate" will increase drastically when the water vapor pressure is higher than that depicted by point H. Moisture keeps on condensing and converting the monohydrate to saturated solution, and this will continue until all is dissolved. After that the vapor pressure will increase so that it is always in equilibrium with the concentration in the (now) unsaturated solution.

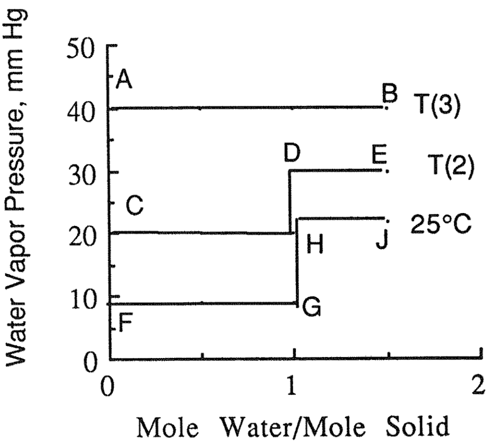

Fig. 14 Single salt pair (monohydrate) vapor pressures as a function of temperature. The line at point A has been drawn a mite to the left for graphical clarity. It occurs at 1 mole of water/mole of solid.

In general for an x-hydrate with a saturation concentration of $1/(x+y)$ moles of salt per mole of water, the reaction on the constant pressure isotherm is

$$B \cdot xH_2O + yH_2O \rightarrow B \text{ dissolved in } (x+y) \text{ moles of } H_2O \tag{8.21}$$

The solubility of B in water is $1/(x+y)$.

Beyond the solubility concentration, there will be a total of z moles of water and 1 mole of solid, so that the mole fraction of water will be $z/(1+z)$. The vapor pressure of the now unsaturated solution would be given by Raoult's law, i.e., $a = P/P_0 = z/(1+z)$, or, since a here is plotted versus z, it would be given by

$$z = \frac{a}{1-a} \tag{8.21a}$$

However, many authors plot a versus z.

Example 8.1.

The diagram in Fig. 15 is a vapor diagram of a drug substance that forms a pentahydrate. Comment on the following statements: (a) The pentahydrate is stable between 10 and 45%. (b) If the hydrate is exposed to a relative humidity of 81%, then it will lose water and become anhydrous. (c) It neither loses nor picks up moisture at 81%. (d) It gains moisture and forms a saturated solution.

Answer.

(a) and (d) are correct, but (d) is strictly correct only for 80% RH. (It will form a very slightly undersaturated solution.)

As an example of research on hydrate forms, it should be mentioned that Allen et al. (1978) have shown that erythromycin exists in crystalline form as an anhydrate, a

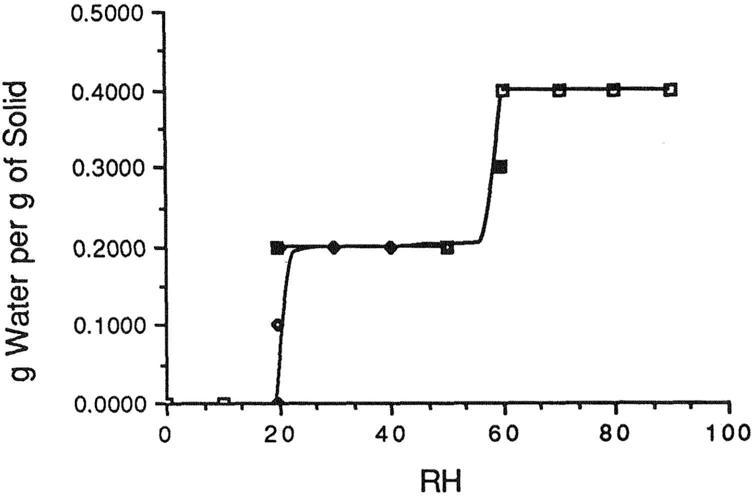

Fig. 15 Vapor phase diagram of an organic substance that forms a pentahydrate at 25°C (MW 360 + 90).

monohydrate, and a dihydrate. Shefter and Kmack (1967) showed that the dehydration kinetics of theophylline hydrate were first order.

Hemihydrates also exist. Wu et al. (1996) have reported on an anhydrous and a hemihydrate form of brequinar sodium. Both have fairly comparable solubilities. Loosely bound water is also present in the structure, and this is lost (in thermograms) at 90°C, and the water of hydration is released at about 175°C.

It should be mentioned that in some cases "bound" moisture is indeed held very tightly. Magnesium chloride tetrachloride is an example. Heating this substance to 80–100°C will remove two of the molecules of water. But further heating results in the removal of 2 moles of hydrochloric acid, leaving magnesium hydroxide behind.

8. MOISTURE EQUILIBRIUM CURVES OF A SMOOTH NATURE

There are substances such as gelatin and corn starch that give rise to moisture equilibrium curves of the type shown in Fig. 16. These are referred to as BET moisture isotherms.

As a dry sample is exposed to increasingly higher vapor pressures, P_u (u stands for "up"), moisture contents x_u will be in equilibrium with the sample. If the experiment is terminated at a pressure of P^*, and the vapor pressures in the atmospheres decrease, then, e.g. at P_d (d stands for "down") the moisture content will be x_d, i.e., higher than during the up curve. The hysteresis loops shown in Fig. 15 are exaggerated for graphical clarity. Such curves can be shown to be variants of the BET equation or the GAB equation (Guggenheim, Anderson, and deBoer) (Guggenheim et al., 1968; Zografi and Kontny, 1986; Grandolfi, 1986). It is noted that y_d is not an equilibrium condition. Obviously

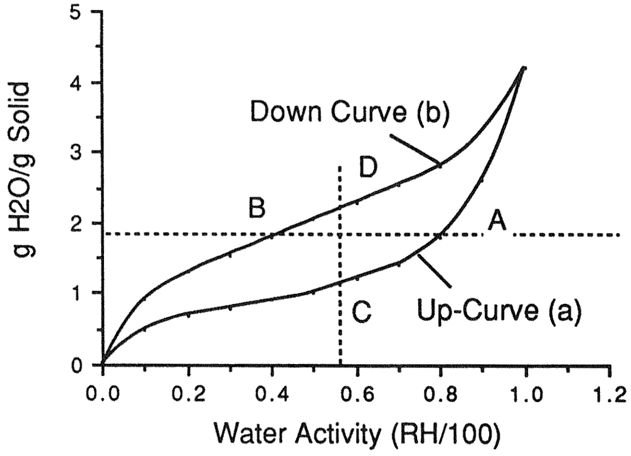

Fig. 16 BET up (adsorption) and down (desorption) moisture isotherm.

ΔG is negative in going from the down curve to the up curve, because

$$\Delta G = V \int_{P_u}^{P_d} V\,dP = V[P_u - P_d] < 0 \tag{8.22}$$

Several common tablet excipients give rise to Langmuir isotherms. An excipient study by Sangvekar (1974), when all the data are lumped together, gives an equation of the type

$$\frac{1}{y} = \frac{A}{P} + B \tag{8.23}$$

Usually, in pharmaceutical and engineering literature, the moisture equilibrium curves are shown in a sense opposite to that shown in Fig. 15, i.e.,

$$P = \phi(y) \tag{8.24}$$

The high RH tail of the curve is usually above 85% RH and therefore does not apply to most realistic pharmaceutical conditions, but it is applicable to one often-conducted test (40°C, 75%RH). Zografi and Kotny (1986) have described these types of moisture isotherms by either a BET equation or a GAB equation.

For routine isotherms, the high relative humidity tail is difficult to obtain with reasonable precision, and one approach (Carstensen, 1980) is to approximate them by Langmuir isotherms (i.e., not use the high-end portion).

9. AMORPHATES

Solids which are not crystalline are denoted amorphous. If one melts a (stable) solid and recools it, then it should crystallize when the melting point is arrived at.

This requires nucleation, and nucleation propensity is a function of the viscosity of the liquid in which it occurs. Materials that are viscous about their melting point are therefore prone to form supercooled solutions.

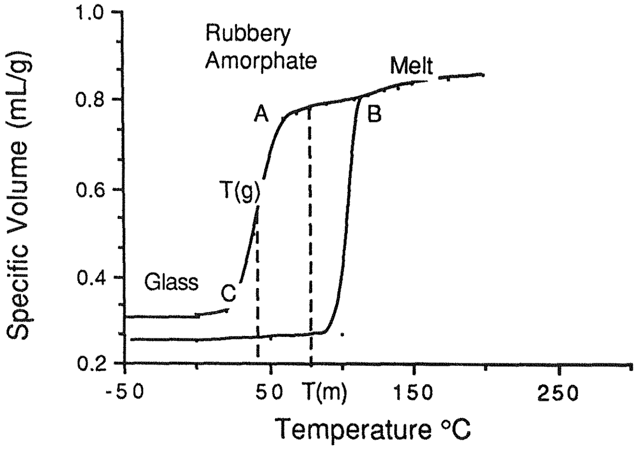

Fig. 17 Molecular volume as a function of temperature of a solid prone to forming an amorphate.

At a given high viscosity (attained at or below the melting point), the melt will have the appearance of a solid, and this is the type of material referred to as amorphous.

Right below the melting point, the molecules will have no specific orientation, and molecular movements will be random in direction and magnitude (within the limits of the system) as opposed to a crystalline material, where the molecules are arranged in lattices (ordered arrays), and where the orientation of each molecule is set.

At a temperature T_g, lower than the melting point, there will be a physical change in the amorphate. An example of this is shown in Fig. 17.

Between points A and B the properties of the amorphate are often like that of the melt. This is referred to as the "rubbery" state, and below C it is referred to as a glass.

10. WATER ABSORPTION "ISOTHERMS" INTO AMORPHATES

Amorphates are solids that are not crystalline. It is assumed at this point that the term "solid" is self-evident, although amorphates in the rubbery state (just below the melting point of the crystalline form of the compound) are actually highly viscous liquids. When exposed to humid atmospheres, they will pick up moisture in a fashion that is not like that of a BET isotherm (to be covered shortly). The moisture actually penetrates into the solid, which thus may be considered a "solution."

In an ideal situation, the water activity, a, will decrease linearly with $(1-x)$, where x is the mole fraction of solute. At a given point ($x=0.24$ in Fig. 17) the solution becomes saturated. (This concentration, of course, differs from compound to compound.) Beyond this concentration, the solution itself will be saturated, and the vapor pressure will not change with further addition of compound; rather, the composition will change, but the vapor pressure will stay constant. In this type of graph the coordinates are in the opposite direction of a usual isotherm.

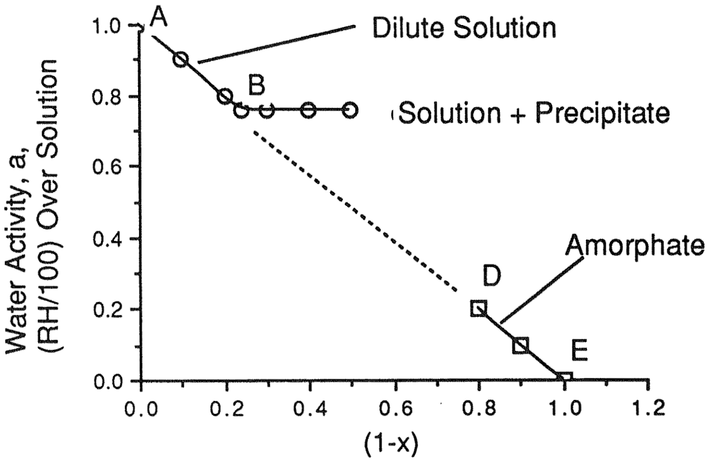

Fig. 18 Moisture isotherm for an amorphous solid. (Graph constructed from data published by Carstensen and VanScoik, (1990.)

If an amorphous form of the compound is produced and exposed to different relative humidities, then the "isotherm" is often quite linear, if the amount of water absorbed is expressed as a mole fraction (line DE in Fig. 18). As shown by Carstensen and VanScoik (1990) for amorphous sugar, this line is an extension of the solution vapor pressure line (AB in Fig. 18), and one may consider the moist amorphate as a highly concentrated, supersaturated "solution."

Due to the random arrangement and the mobility of the molecules in an amorphate as opposed to a crystalline modification, amorphates are usually less stable chemically than crystalline modifications (Carstensen et al., 1993).

Carstensen and VanScoik (1990) were the first to point out that for an amorphous substance, it is illogical to use the traditional moisture isotherms, because in this case it is probably not an adsorption, but rather an absorption, which is at play.

By exposing amorphous sucrose to various relative humidities, various moisture levels were reached. If these moisture levels were expressed as mole fractions of sucrose, then the vapor pressures fell in line with the vapor pressure curve of sucrose itself.

The fraction to the right of point B is the principle used for salt solutions to obtain constant relative humidity in desiccators. With electrolytes, the vapor pressure depression is larger (due to the 2- or 3-fold number of ionic particles, over that of the molarity of the salt), and the solubilities are often high, so that these are preferred for creating constant relative humidity in desiccators.

Zografi and Hancock (1993) have used this principle in their investigation of whether such an approach, i.e., solution theory, could be applied to macromolecules. To quote, "If one considers the absorption process to be completely analogous to the solution process, then it should be possible to use basic solution theories to model the data." Their data for PVP K30 are shown in Fig. 19.

First of all note that the "ideal solution" model advocated earlier is (probably) not applicable to macromolecules. (The concentrations, however, are not converted to mole fractions, but such a conversion would not make the plot linear.) The data

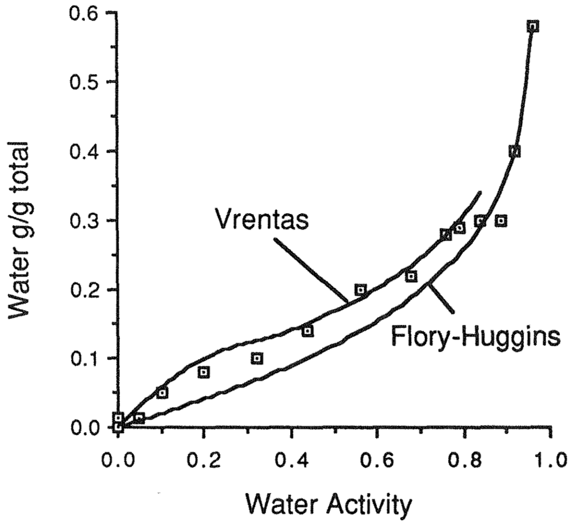

Fig. 19 Fit of vapor pressure data of aqueous solutions of PVP K30 at 30°C to the Flory–Huggins equation. The points are taken off Figs. 6 and 7 as accurately as possible, as is the trace of the Flory–Huggins equation. (Plot constructed from data published by Hancock and Zografi, 1993.)

obviously, fit the Vrentas equation better at low water activity, but the Flory–Huggins equation may be more applicable at high water activity. Data become slightly uncertain at such high humidities in any event.

It has been mentioned that one method of stabilizing a "solution" for marketing is to lyophilize it and thus increase its storage stability. Many lyophilizates are amorphous. The method for making a lyophilizate is first to make a solution, then to freeze it, and then to sublime off the moisture. In this process it is important that the solution stay sufficiently stable before and during freezing. Various lyoprotectants are used for such purposes, and Dekeyser et al. (1997), for instance, have shown that chymopapain is stabilized in the presence of different lyoprotectants such as maltodextrins.

Amorphates exhibit glass transition temperatures. These are a function of water content, as shown e.g. by Hancock and Dalton (1999) and in Table 4. These authors and others (e.g., Carstensen, 1995) compared moisture adsorption isotherms with the equations of Flory–Huggins, Vrentas, and Raoult.

Glass transition temperatures are always somewhat approximate. For instance, in contrast to the above, Hatley (1997) has reported the T_g of sucrose to be 64°C at 0.73% moisture.

11. MOISTURE EXCHANGE BETWEEN DOSAGE FORM INGREDIENTS

Gore and Ashwin (1967) were the first to report that for an excipient (in their case citric acid), "given a knowledge of the equilibrium moisture content for a particular moisture sensitive compound at the upper limit of its moisture specification, it would

Table 4 Glass Transition Temperatures of Water-Containing Sugar Amorphates

Water (%)	Lactose glass trans. temp. (°C)	Sucrose glass trans. temp. (°C)	Raffinose glass trans. temp. (°C)	Trehalose glass trans. temp. (°C)
0	112	74	103	115
1	102	60	92	101
2	94	50	83	90
3	85	32	75	80
4	80	<25	67	70
	71	<25	58	60

Source: Table constructed from data by Hancock and Dalton (1999).

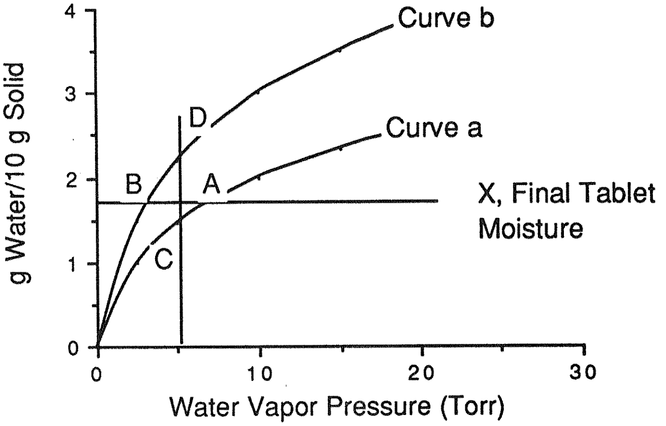

Fig. 20 Langmuir moisture isotherm presentation of initial part of a BET isotherm. From (Carstensen, 1980.)

be a simple matter to define moisture limits for citric acid in a particular formulation".

A solid dosage form (e.g., a tablet) is usually made to a given moisture content, e.g. (Fig. 20), 1.8 g per 100 g of solid. Since the drug and the excipients have different moisture isotherms, they will have different equilibrium RH values. There can, however, only be one RH condition in the pore space of the solid dosage form, so the result is that compound b will pick up moisture (move from B to D) and compound a will lose moisture (moving from A to C). The question is to estimate, quantitatively, where (at what RH) the line DC will be.

In Fig. 19, the two moisture equilibrium curves have (in an abbreviated fashion) been represented as Langmuir isotherms. This can be verified by inspection of Fig. 10, where lines OC and OB would both fairly well adhere to Eq. (8.25).

This may be used to estimate the moisture movement in a solid dosage form after it is manufactured. In consulting Fig. 20 and assuming that the up curve is that of drug (A) and the down curve that of excipient (B), there are m_A grams of A on an anhydrous basis, and A contains a fraction (on a dry basis) of q_A

moisture, i.e., a total of $m_A q_A$ grams of water. There are m_B grams of B on an anhydrous basis, and A contains a fraction (on a dry basis) of q_B moisture, i.e., a total of $m_B q_B$ grams of water.

The dry weight of the dosage form is therefore $m\mathrm{A} + m\mathrm{B}$, and as the dosage form (e.g., tablet) is made, it is made at a particular moisture content of a fraction (on a dry basis) of q moisture, i.e., a total of $mq = [m_B + m_A]q$ grams of water.

Since, as seen from the figure, the relative humidity (the vapor pressure, P) in the pore space must be one particular figure (P), it follows that A must give up moisture (from point A to point C) and B must take up moisture (from point B to point C).

The moisture isotherms are of the type

$$x(\mathrm{A}) = \frac{q_A m_A}{m_A} = q_A = Q_A P_A^{1/n_A} \tag{8.25}$$

and

$$x(\mathrm{B}) = \frac{q_B m_B}{m_B} = q_B = Q_B P_B^{1/n_B} \tag{8.26}$$

The values of n usually do not differ much (and the two isotherms can therefore be represented as only differing in the values of the Q's). It is noted that the areas have not been taken into account, and the isotherms apply to two samples of material. (To account for the area, plotting by BET would have to be done.)

Where a known amount of A, m_A, is mixed with a known amount of B, m_B, mass balance (assuming no loss of moisture) gives

$$x_C[m_A + m_B] = x_A m_A + x_B m_B \tag{8.27}$$

or

$$x_C = \frac{x_A m_A + x_B m_B}{m_A + m_B} \tag{8.28}$$

and the amount of moisture lost can then be gauged from

$$\text{moisture loss in A} = m_A(x_A + x_C) \tag{8.29}$$

and for B,

$$\text{moisture loss in B} = m_B(x_D - x_B) \tag{8.30}$$

Since x_C is known, P is then also known.

If for instance the two compounds are mixed together, moisture added (as in a granulation), and this then dried, then x_C is known. Mass balance about ACB in Fig. 20 then gives that the moisture loss experienced by A,

$$m_A(x_A - x_C) = m_A Q_A[P^{1/n} - P_C^{1/n}] \tag{8.31}$$

must equal the moisture gained by B, i.e.,

$$m_B(x_C - x_B) = m_B Q_B[P_C^{1/n} - P_B^{1/n}] \tag{8.32}$$

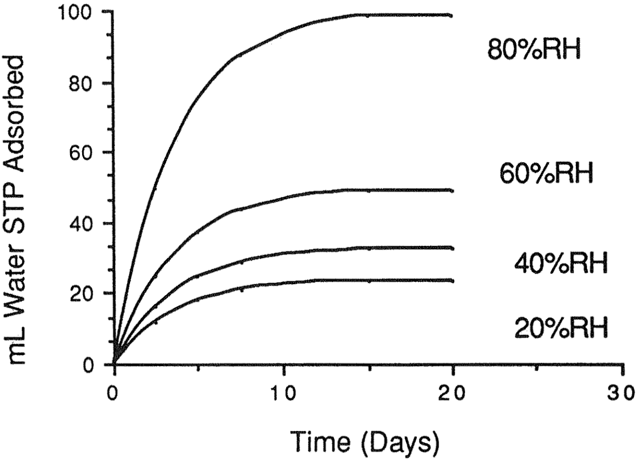

Fig. 21 Moisture uptake curves for a sample of silica gel at 20, 40, 60, and 80% RH.

All quantities are known, so that P [$= P_C = P_D$] can be calculated, i.e., both moisture losses and gains, and the final relative humidity can be calculated. In this latter case, the isotherms should be determined on samples that had been wetted and dried the same way the final mix had been wetted and dried (since the surface area changes).

12. EQUILIBRIUM MOISTURE CONTENTS FOR MACROMOLECULES

For an organic compound such as starch, a smooth equilibrium moisture curve will result. Here again there is a sharp upswing at very high relative humidities.

If experiments such as are exemplified in Table 1 and Fig. 11 are carried out on e.g. cornstarch, then curves of the *type* shown in Fig. 21 result. The figure shows moisture uptake rate curves at four different relative humidities: 20%, 40%, 60%, and 80%. When the moisture contents (x mg water/mg solid) of these levels are plotted as a function of relative vapor pressure, P/P^* (the relative humidity, divided by 100, the so-called water activity), then an isotherm results. This moisture isotherm has the shape shown in Fig. 16.

When $P/[x\{1-P\}]$ is plotted versus P, then a straight line results.

13. ADSORPTION ISOTHERMS OF SILICA

The curve in Fig. 21 eventually levels off. The equilibrium level is a function of the relative humidity at which the experiment is carried out. Table 5 shows an example of moisture uptake curves of a sample of silica, at various relative humidities. These levels are tabulated in the second column. It is customary in isotherm work to convert these adsorbed amounts to the volumes that would have been occupied at 0°C and 1 atm, and this can easily be done, e.g., for the first row. The number of moles is $n = (17.5 \times 10^{-3})/18 = 9.75 \times 10^{-4}$ moles. The volume of this at 25°C and 1 atm would be $V = nRT/P = 9.75 \times 10^{-4} \times 82 \times 298/1 = 23.8$ mL. These figures are shown in the third column and are denoted V.

Table 5 Data from Which Fig. 22 Was Constructed, and Conversion to BET Parameters

RH (%)	mg adsorbed	V (mL) (0°C, 1 atm)	RH/(V{100-RH})
20	17.5	23.8	0.01
40	23.9	32.5	0.021
60	36.1	49.2	0.030
80	72.6	98.9	0.040

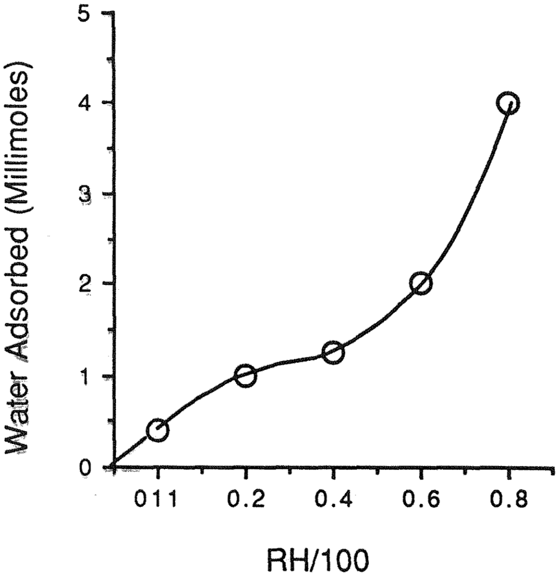

Fig. 22 The equilibrium levels in Fig. 20 plotted versus relative humidity.

The isotherms of this type are called BET isotherms. The data in the third column are shown in Fig. 22. It can be shown that such data follow the BET equation:

$$\frac{\mathrm{RH}}{V\{100-\mathrm{RH}\}} = \phi + \frac{1}{V_\mathrm{m}}\left[\frac{\mathrm{RH}}{100}\right] \tag{8.33}$$

Treatment by this equation is shown in Fig. 23. V_m is here the volume (0°C, 1 atm) of water that just constitutes one layer on the entire surface of the solid sample. RH/[V{100-RH}] has been calculated in the table (last column) and is plotted in Fig. 23 versus RH/100.

The slope of the line is $1/V_\mathrm{m}$, so

$$\frac{1}{V_\mathrm{m}} = 0.05 \qquad \text{or} \qquad V_\mathrm{m} = 20\,\mathrm{mL} \tag{8.34}$$

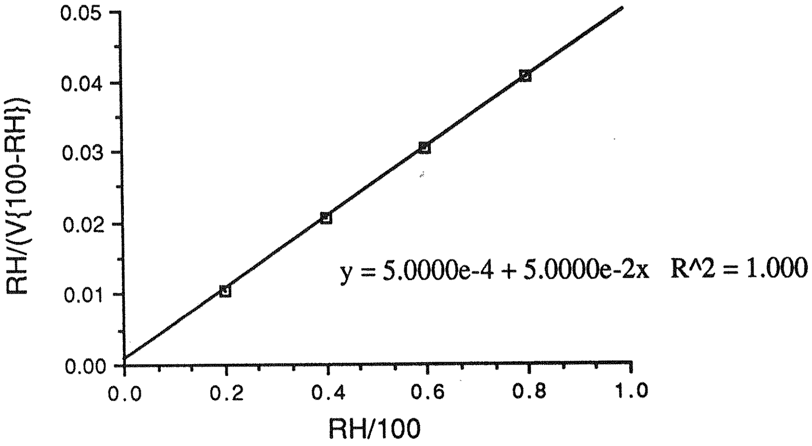

Fig. 23 Data from Table 5 treated by the BET equation.

This can be converted to moles (n) and then to molecules (N);

$$\begin{aligned} n_{\mathrm{m}} &= \frac{20PV}{RT} = 1 \times \frac{20}{82 \times 298} = 12.9 \cdot 10^{-4} \text{ moles} \\ &= 6 \times 10^{23} \times 12.9 \times 10^{-4} = 77 \times 10^{19} \text{ molecules} \end{aligned} \tag{8.35}$$

Water molecules in a monolayer will position themselves so that their cross-sectional area is $10\,\text{Å}^2 = 10 \times 10^{-16}\ \text{cm}^2$, so that in this case the entire surface area would be the number of molecules times the area of each molecule, i.e.,

$$77 \times 10^{19} \times (10 \times 10^{-16}) = 77 \times 10^{4}\,\text{cm}^2 = 77\,\text{m}^2$$

Most substances are not "hygroscopic" below 20% RH.

If a bag of silica is placed in a bottle with a dosage form, then, if there is a critical moisture content beyond which the dosage form becomes unstable, it is possible to calculate, from the isotherm of the dosage form, at which relative humidity this occurs. From the silica isotherm one can then calculate how much moisture is taken up by the silica bag at this point, and dividing this figure by the moisture penetration of the package, it is possible to calculate the length of time the product is good.

Moisture isotherms are of great significance in pharmaceutics. Cases in point are the moisture isotherms of PVP and of the complex of misoprostol and hydroxypropyl methylcellulose.

14. HYDROUS AMORPHATES

As mentioned, solids that are not crystalline are called amorphous. An important category of these are lyophilized cakes (for intravenous reconstitution). These are formed by freezing aqueous solutions. Upon such freezing (when part of the solid comes out as an atmosphere), ice will first freeze out, and then the remaining solution (which usually crystallizes as a eutectic) will supercool and will become "solid." But in this case the "solid" is simply a very viscous solution. Fig. 24 is an example of this and is constructed from data published by Her and Nail (1994).

The "solid" is (when dried) referred to as a lyophilized cake. The glass transition temperature can usually be arrived at from thermal analysis, as shown in Fig. 25. The collapse temperature is a temperature dictated by mechanical pro-

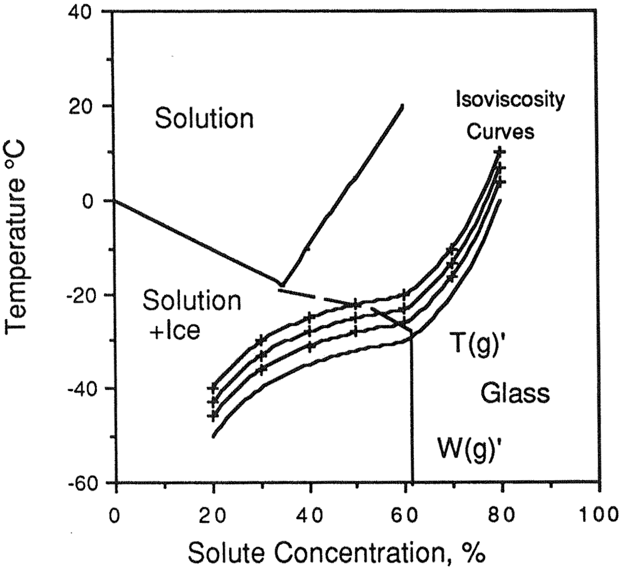

Fig. 24 Graph constructed from data published by Her and Nail (1994).

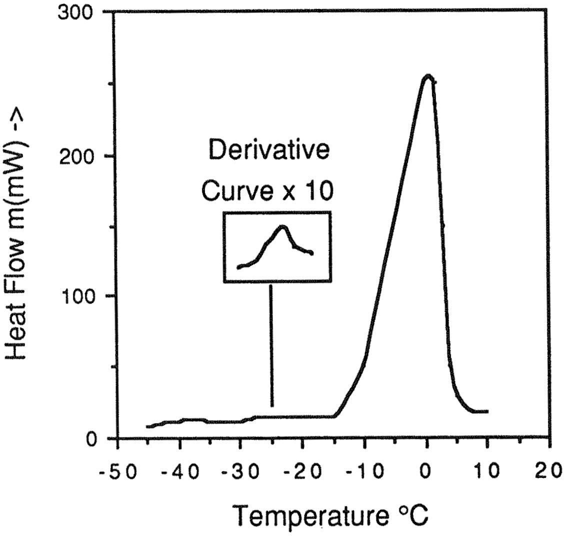

Fig. 25 Thermogram of aqueous solution of 10% PVP. The relative magnitudes of the endotherms for glass transition vis-à-vis melting is shown. (Graph constructed from data published by Her and Nail, 1994.)

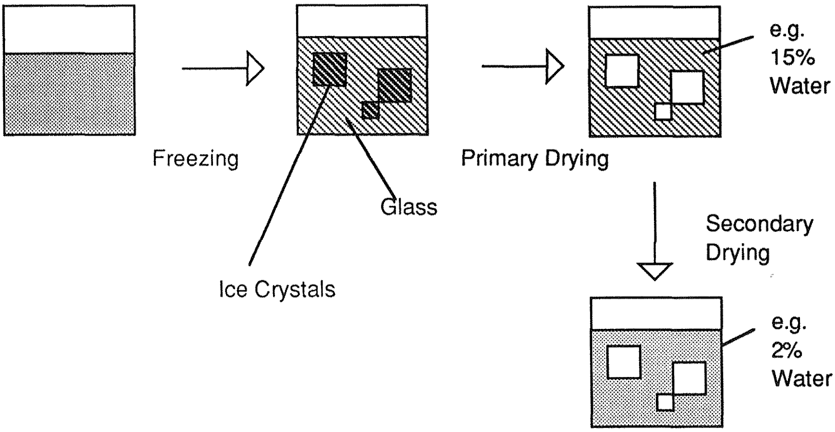

Fig. 26 Schematic of freeze-drying events.

perties. Just above the glass transition temperature, sucrose solutions, for instance, have viscosities of about 10^6 Pa/s, but below T_g this figure is 10^{12} Pa/s. The general sequence of events in freeze drying is shown in Fig. 26.

The primary drying (Fig. 26) consists of the evaporation of the crystalline ice, so that the cake is left with "holes" in it, and a glass of a water content in the range of 12–15% results. As mentioned, if the temperature is below the glass transition temperature, then this glass has a high viscosity and will dry slowly, since the diffusion coefficient, D, for evaporation of water, will be high.

If, after the primary drying, the initial freezing temperature were 240°K as shown in Fig. 26, and the solids content were 50%, then the composition would be at point C, Fig. 27, between the T_c and T_g curves. But if sublimation were continuously carried out at this temperature, then, at point B, the glass transition would be passed, and the viscosity would become very high, and sublimation would be very slow. The temperature is therefore continuously increased, so that the lyophilization temperature can stay within the bounds of the two curves.

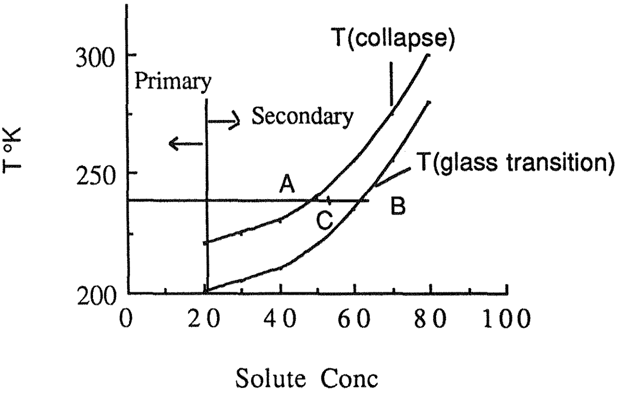

Fig. 27 Limiting phases in a lyophilization event.

Some proteins have stabilities that depend on the cooling rate, but this is primarily due to electrolytes (e.g., sodium chloride) and stabilizers (e.g., glycine) in the composition. These will crystallize out and give the cake structural strength so that T_s increases, but their presence, as well as the initial freezing rate, will modify the positions of the two curves, so that a slow cooling rate may provide a different (and sometimes worse) cake than when a fast cooling rate is employed.

These aspects have been discussed in detail by Franks (1990), Levine and Slade (1988), Mackenzie (1977) and Suzuki and Franks (1993).

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