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EFFECT OF MOISTURE ON THE STABILITY OF SOLID DOSAGE FORMS

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It has long been known that moisture affects the stability of some drug substances. Aspirin is a classical example. Aspirin is not wet granulated. Even though the water is driven off in a wet granulation, there is still sufficient moisture stress in the process to induce excessive decomposition on subsequent storage. Dry methods (slugging, roller compaction) are therefore resorted to. In other instances, the moisture sensitivity of a drug may warrant using a hard shall capsule approach. This presumes that the drug substance is not particularly hygroscopic, since, otherwise, the capsule shell will provide an unwanted source of moisture.

1. THE STATE OF MOISTURE IN SOLID DOSAGE FORMS.

The moisture may be bound or unbound. These terms (no pun intended) are somewhat loose, but for the sake of

discussion they are defined as follows: unbound moisture is available in a decomposition that requires moisture. Bound moisture is not.

That the moisture is available may be visualized in several ways:

(a) Available moisture may be such that it is involved in a reaction:

$$A + H_2O \longrightarrow \text{Decomposition.} \qquad (1)$$

(b) Available moisture may provide a sorbed moisture layer or a rubbery phase in which the decomposition can occur in solution or in dissolved state

The decomposition, of course, may be a combination of (a) and (b). Since in case (a) the amount of availble moisture decreases with time, one distinguishes between cases of

(1) abundant moisture

This would be the case in an open jar, and also to some degree in a permeable bottle (Fig. 1)

(2) limited moisture.

Case (2) is complicated because the dosage form, with time, will experience a decrease in available moisture, assumedly , the water vapor pressure, P_{H20}, will decrease. If this does not affect the amount of bound moisture, then the situation may be described as simply one where the decomposition rate of the reaction will decrease in a describable manner as the moisture content decreases with time. If, however, the bound moisture is a function of the water vapor pressure, then the

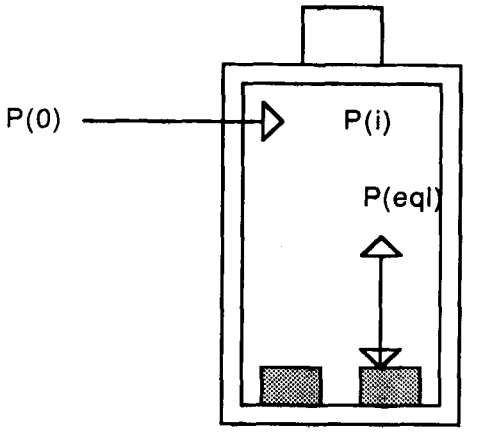

Fig. 1. Schematic of Permeable Bottle

situation becomes quite complex. These situations will be treated one by one in the following.

2. Equilibrium Moisture Content

When a solid, containing moisture, is placed in a vacuum, moisture will evaporate, until an equilibrium is established. There will, hence, be a certain moisture content in the solid, x, corresponding to a water vapor pressure, P_{H2O}, and the function

$$P_{H2O} = f(x) \qquad (2)$$

is denoted the moisture equilibrium curve (MEC). There are two main categories: (a) smooth and (b) stepwise equilibrium moisture curves.

2-1 Stepwise Moisture Equilibrium Curves.

Many drug substances and excipients, form stoichiometric hydrates. Ampicillin trihydrate is an example of the former, lactose hydrate and dicalcium phosphate dihydrate are examples of the latter. One way of presenting the hydration state of a hydrate is by way of its moisture vapor pressure diagram. The *conventional* manner of graphing this is discussed in the following.

The simplest case is where a substance, B, forms an *x*-hydrate:

$$B + xH_2O \longrightarrow B.xH_2O \qquad (2\text{-}1)$$

Given a sample of the x-hydrate, its vapor pressure is P. If the anhydrate is placed in an evacuated container (Fig. 2) and water vapor is allowed to be added by way of the stopcock, then the vapor pressure will increase, but *none* of the B will be converted until the vapor pressure P_s has been reached. The presssure will simply increase by the gas law (i.e. be a function of *n*, the number of moles of water vapor added), i.e.

$$P_{H2O} = nRT/V \qquad (2\text{-}2)$$

where

$$P_{H2O} < P_x \qquad (2\text{-}3)$$

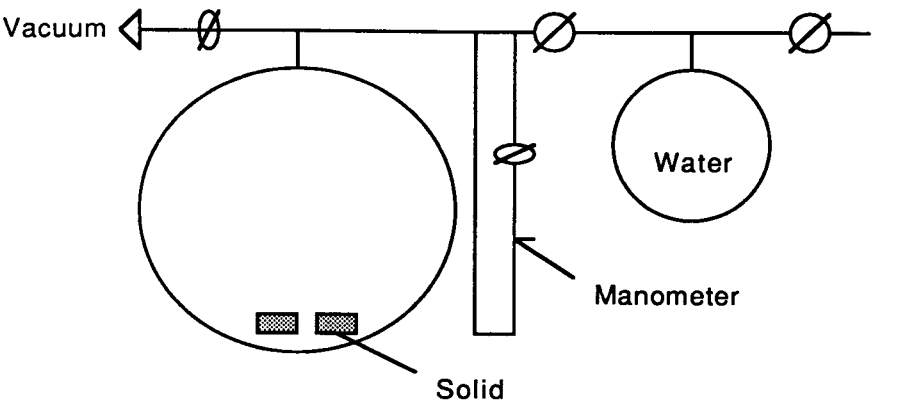

Fig. 2 Salt/hydrate in Container Attached to Moisture Source

P_x is a critical pressure, which is the vapor pressure of the 0/x salt pair of B. Once the vapor pressure in the container reaches P_x, further addition of water vapor through the stopcock will *not* change the vapor pressure but rather the water will be used to convert anhydrate to x-hydrate by way of Eq. 3. This will continue (i.e. P_{H2O} will remain constant) until Eq. 3 has come to completion. This is shown in Fig. 3. The limit of this, of course, is when the moisture content of the solid is *x* moles of water per mole of *B*.. It is noted that the vapor pressure is constant (P_x) for moisture contents between 0 and x, and this vapor pressure is denoted the water vapor pressure of the salt pair 0/x.

Once a moisture content of *x* has been reached, further addition of water through the stopcock will cause the vapor

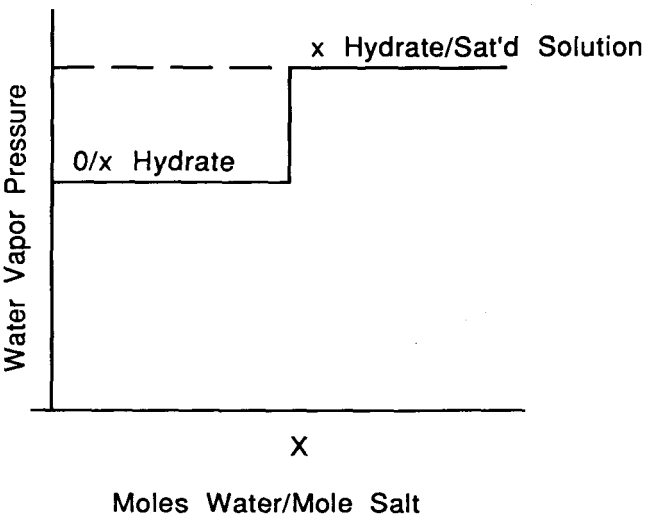

Fig. 3 Vapor Pressure Diagrams of Salt/Hydrate

pressure to rise by way of the gas law (Eq. 2-2), until a pressure, P_s has been reached. This pressure is the vapor pressure over a saturated solution of *B* in water. Further addition of water, then, will cause no change in P ($=P_s$), but rather the added water will be consumed in dissolving *B* to form saturated solution. Complete conversion to saturated solution will have occurred when when the total amount of water added is *x+y* moles of water per mole of *B* . The solubility of *B* in water, hence, is (1/(x+y)):

$B.XH_2O + yH_2O \longrightarrow$ B dissolved in (x+y) moles of H_2O (2-4)

The fact that the vapor pressure stays constant between

moisture contents of x to x+y moles of water per mole of salt, i.e. during the stage where both solid salt hydrate and saturated solution are present, is used to create constant humidity atmospheres in desiccators.

Beyond the point where all solid has dissolved, the vapor pressure by further addition of water vapor through the stopcock will increase steadily until it approaches that of water's vapor pressure (P').

The manner in which this latter step happens is visualized by assuming the solution of B in water to be an ideal solution. The water vapor pressure will, therefore,decrease linearly as more and more B is dissolved in water. This will continue until the saturation point, where the concentration of B is

$$S = 55/(x+y) \text{ molal.} \qquad (2\text{-}5)$$

The vapor pressures over the unsaturated solutions are given by

$$P_{H2O} = P'[1 - 1/(1+n')] \qquad (2\text{-}6)$$

where n' is the number of moles of water added to one mole of B. The shape of this curve is as shown in Fig. 3

As temperature increases (Carstensen, 1986), the moisture equilibrium curves will change. Assuming that

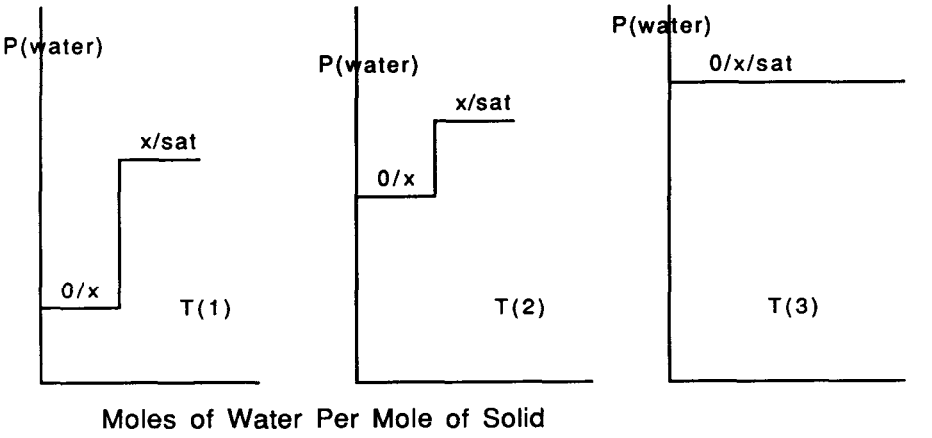

Fig. 4. Vapor Pressure Diagram of Salt/Hydrate at Different Temperatures.

solubility increases with temperature, there will be a decrease in the value of y. P_s and P' will increase. This is shown in Fig. 4. T_3 is the highest temperature, at which the hydrate exists. If this is a fairly low temperature (e.g. below 100°C) then T_3 is the conversiton temperature of the hydrate. If T_3 is higher than the decomposition temperature of the compound, then the hydrate is "stable". But this does not mean it cannot lose water.

Again making reference to Fig. 4 (a), i.e. the situation at a temperature of T_1. it follows that if B is an excipient and is placed at a water vapor pressure below P_{x1}, then it will lose water. Above P_{y1} it will take up water. Hence, *in order that*

no physical change occur in the state of the water of hydration the salt must be stored between vapor pressures of P_x and P_y. This is denoted the RH stability range.

At T_2 it must be stored between P_{x2} and P_{y2} and so on. For accelerated testing to be meaningful, it is necessary that $B.xH_2O$ remain as such, i.e. not convert to $B + xH_2O$. Otherwise, this latter would result in x moles of water converting from bound to available moisture, and then the reaction profile of the solid dosage form would change. Hence, to be meaningful, relative humidity conditions should be selected where $B.xH_2O$ stays as such at all test temperatures. This can, of course, be accomplished artificially, if there is only one salt.hydrate in the dosage form system. The ranges could be created, e.g. in desiccators, at the various temperatures, by use of the appropriate salt-solutions.

The value of P_y, of course, changes with temperature as well. the relation of S to T is given by:

$$\ln S = -(\Delta H/R)(1/T) + ß \qquad (2\text{-}7)$$

Introducing Eq. 2-5 into this yields

$$\ln(x+y) = (\Delta H/R)(1/T) + \ln(ß\ 55) \qquad (2\text{-}8)$$

It is obvious that with more than one hydrate in a solid dosage

form it would be difficult (and in many cases impossible) to find relative humidity ranges at higher temperatures which would retain the state of hydration for all the hydrates. In general in accelerated studies *that are used for extrapolatory purposes*, the dosage form is placed in a hermetic container, which is then placed at the appropriate temperature. It is then tacitly assumed that the possible changes in state of hydration will not greatly affect the stability. However, this, at times, can be quite fallacious.

One thing, however,that is important, is to maintain hermetic conditions for such accelerated studies that are used to predict stability at other temperatures. If a bottle is not hermetic, and then is heated, the dosage form will dry out, and may show faultily good stability at the higher temperature. Many stability studies at accelerated stations are not carried out for the purpose of prediction, and these are often carried out in e.g. polyethylene bottles that are not hermetic. Such tests are at best, qualitative.

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.

2-2 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

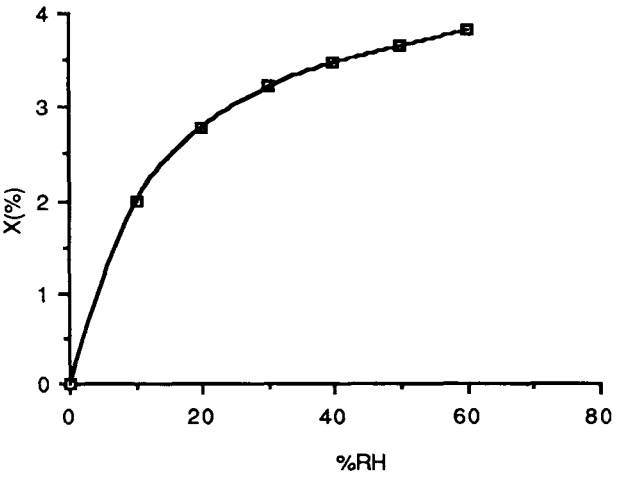

Fig. 5 Smooth Moisture Isotherm

shown in Fig. 5. These are referred to as moisture isotherms, and it is noted that the presentation mode is the inverse of Fig. 3, i.e. x is plotted on the ordinate and P on the abscissa.

As a dry sample is exposed to increasingly higher vapor pressures, P_u (*u* for "up"), moisture contents y_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 then decreased, then, e.g. at P_d (*d* for "down ") the moisture content will be y_d, i.e. higher than during the up-curve. The hysteresis loops shown in Fig. 5 are exaggerated for graphical clarity. Such curves can be shown to be variants of the BET equation or the GAB (Guggenheim, Andersobn and deBoer) equation (C.VanDen Berg, 1981,Zografi and Kontny, 1986, Grandolfi, 1986). It is noted that y_d is *not* an

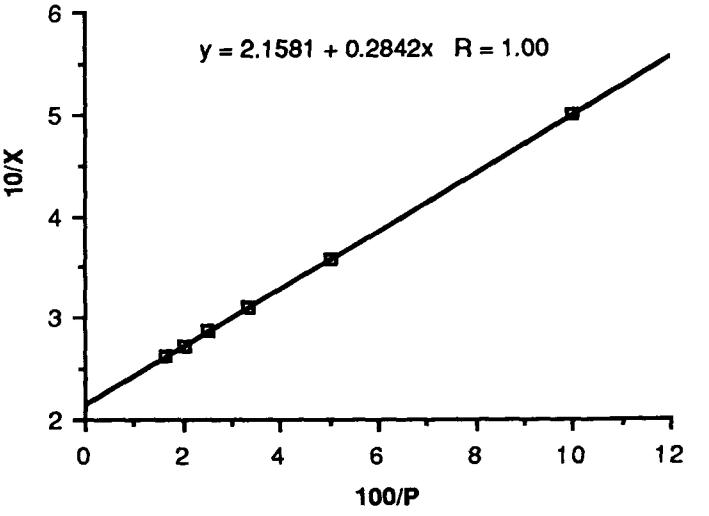

Fig. 6 Langmuir Plot

equilibrium conditions. Obviously ΔG is negative in going from the down-curve to the up-curve, because

$$\Delta G = V \int_{Pd}^{Pu} VdP = V[P_u - P_d] < 0 \qquad (2\text{-}10)$$

Several common tablet exipients give rise to Langmuir isotherms. Fig. 6 shows such data plotted as a Langmuir isotherm, i.e.

$$1/y = (A/P) + B \qquad (Eq.\ 2\text{-}11)$$

Usually, in chemical and surface literature, the moisture equilibrium curves are shown in a sense opposite to

that shown in Fig. 5., i.e.

$$y = \phi(P) \qquad (2\text{-}12)$$

It is noted that the hydrate curve (Fig. 3) is shown in this fashion. Also, the very high RH tail of the curve is usually above 85% RH and therefore not applicable to most realistic pharmaceutical conditions.

2-4 Moisture Exchange Between Dosage Form Ingredients

If two moisture-containing substances are present in a dosage form, then their (abbreviated) moisture equilibrium curves are suitably represented as shown in Fig. 7 (Carstensen, 1980). If the over-all water content is W, then I and II would have different moisture vapor pressures (P_1 and P_2). There would, hence, be a shift in moisture content upon storage. II would gain moisture by b% and I would lose moisture by b%, so that the new compositions would both have a common moisture equilibrium pressure of P_a.

It is noted that the curve for *I* is a down-curve on the hysteresis loop, but in general differences are slight.

These types of exchange have been considered in terms of BET equations (Grandolfi, 1986), but the method is cumbersome beyond being practical.

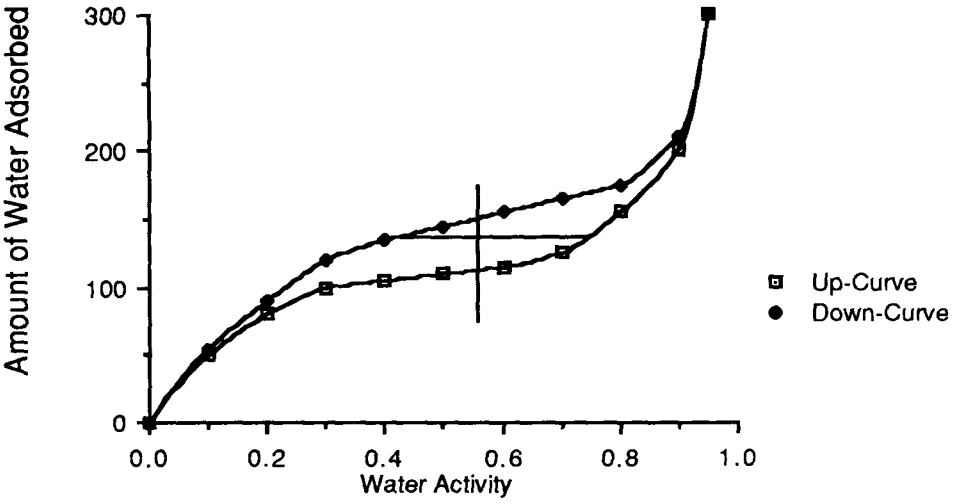

Fig. 7 Moisture Sorption and Desorption Isotherm

It is a sufficiently good approximation to consider the isotherms to be parabolae (i.e. Freundlich isotherms). The initial curves, prior to equilibrization are given by

$$y_I = A_I P_I^{1/n} \qquad (2\text{-}4\text{-}1)$$

$$y_{II} = A_{II} P_{II}^{1/m} \qquad (2\text{-}4\text{-}2)$$

The final conditions are given by

$$y'_I = A_I P_a^{1/n} \qquad (2\text{-}4\text{-}3)$$

$$y'_{II} = A_{II} P_a^{1/m} \qquad (2\text{-}4\text{-}4)$$

so that the shifts in moisture content will be

$$\text{For I: } \Delta y_I = y_I' - y_I = A_I[P_a^{1/n} - P_I^{1/n}] \qquad (2\text{-}4\text{-}5)$$

$$\text{For II } \Delta y_2 = A_{II}[P_a^{1/m} - P_I^{1/m}] \qquad (2\text{-}4\text{-}6)$$

If there are 100 m_1 and 100 m_2 grams (dry weight) of I and II then

$$100\ m_1\ A_I[P_a^{1/n} - P_I^{1/n}] + 100\ m_{II}A_{II}[P_a^{1/m} - P_{II}^{1/m}] = 0 \qquad (2\text{-}4\text{-}7)$$

Since the original isotherms are known, and the composition is known, then the only unknown is P_a, which can then be calculated (by iterative means). The new y-values can then be determined from P_a.

3 Decomposition with Non-Depleting Moisture.

It was mentioned earlier that one of the typical situations is one where there is an abundant amount of moisture present in the system being tested. This situation occurs if a large amount of moisture exists in the dosage form in a closed bottle. It also occurs if the dosage form is exposed (openly) to an infinite moisture reservoir of above critical RH.

This occurs e.g. if a tablet is exposed on a Petri dish to plain water in a desiccator (or if the Petri dish is placed in a constant humidity oven.)

An intermediate situation occurs if a dosage form is placed in a water permeable container (e.g. a polyethlyne bottle) placed in a constant humidity oven at high relative humidity.

Finally it occurs in situations of limited amounts of water in a closed bottle, when the decomposition reaction does not consume water (e.g. para-aminosalicylic acid, Carstensen and Pothisiri, 1975).

3-1 Leeson-Mattocks Kinetics

The kinetics governing the above situation are denoted Leeson and Mattocks kinetics (Leeson and Mattocks, 1958), and are, probably, the most common situation in solid dosage forms. It is assumed (Fig. 8) that the unbound moisture forms a sorbed moisture layer. This behaves like a bulk liquid phase, and the drug substance will form a saturated solution (S molar) in the water layer. It is also assumed that the decomposition can be totally accounted for by the decomposition of dissolved drug. It is assumed below that the decomposition reaction is a hydrolysis, with a forward, second order rate constant, k_2. Denoting by C the concentration of drug in the moisture layer (which is assumed to have a volume

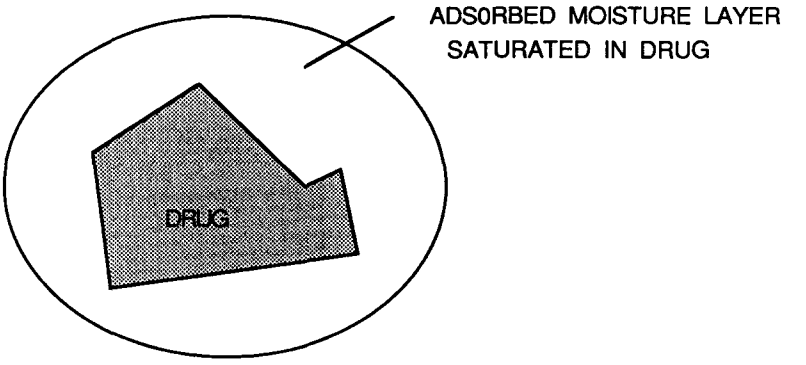

Fig. 8 Schematic of Leeson Mattocks Model

of V liters), the following equation will hold:

$$dC/dt = - k_2 C[H_2O] \qquad (2\text{-}4\text{-}1)$$

Since the moisture is in abundance, the water concentration, $[H_2O]$ will not change during the course of the reaction. Furthermore it is assumed that every decomposed molecule will rapidly be replaced by a dissolving one, it is noted that the concentration will always be S (as long as solid drug is present). With these assumptions, Eq. 2-4-1 becomes:

$$dC/dt = - k_2 S [H_2O] \qquad (2\text{-}4\text{-}2)$$

The decomposition rate in terms of moles decomposed per time unit (-dM/dt) is obtained by multiplying the

concentration by the volume of the adsorbed water phase, V, i.e.

$$-dM/dt = V\ k_2\ 55\ S \qquad (2\text{-}4\text{-}3)$$

where 55 has been substituted for the molar concentration of water (1000/18). It is noted that this is a pseudozero order reaction:

$$M = M_0 - k_0^* t \qquad (2\text{-}4\text{-}4)$$

where the zero order rate constant is given by

$$k^*_0 = 55\ k_2 V\ S \qquad (2\text{-}4\text{-}5)$$

It is a good practice, in stability programs, to subdivide the stability sample of an experimental batch of (e.g. clinical) material into several smaller batches. These can then be allowed to pick up various amounts of water, by placing them on Petri dishes in desiccators over water, and removing the various sublots at different times. The added moisture is the weight gain of the tablets. Placing each of these sublots on stability will give stability profiles for e.g. 4 different moisture levels. Curves such as shown in Fig. 9 will result. If the slopes are plotted as a function of moisture content, then a plot such as shown in Fig. 10 will result. The slope of this

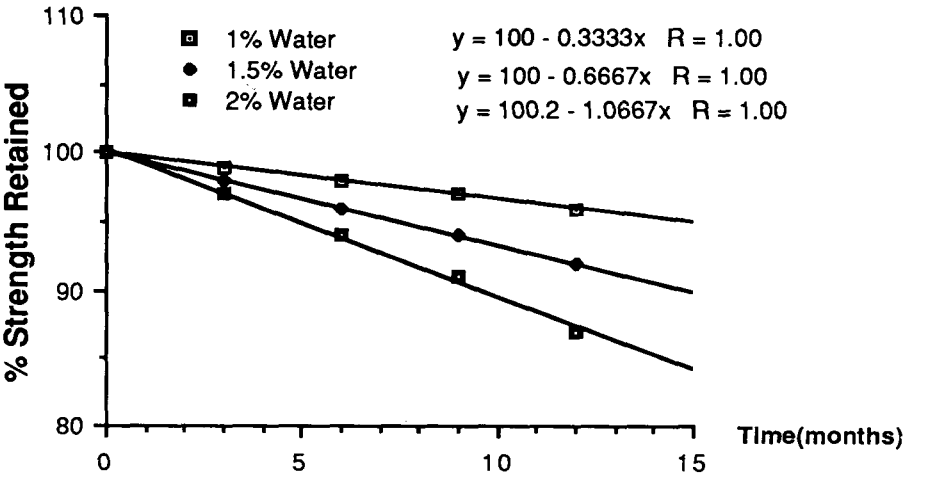

Fig. 9 Decomposition at Various Moisture Contents

line is, of course 55 k_2S, so that if S is known, it is possible to calculate k_2. Leeson and Mattocks (1958) showed that (in a somewhat more complicated situation), the rate constants obtained from aspirin in studies in the solid state, such as just described, corresponded well with those reported in literature (Edwards, 1952).

It is noted that the line in Fig. 10 does not intersect at the origin. The reason for this is that the intercept corresponds to the bound moisture.

If the rate constants are plotted via an Arrhenius equation, then:

$$\ln k_o^* = \ln S + \ln k_2 + \ln[55] = -[\Delta H + E_a]/(RT) + \beta \quad (2\text{-}4\text{-}6)$$

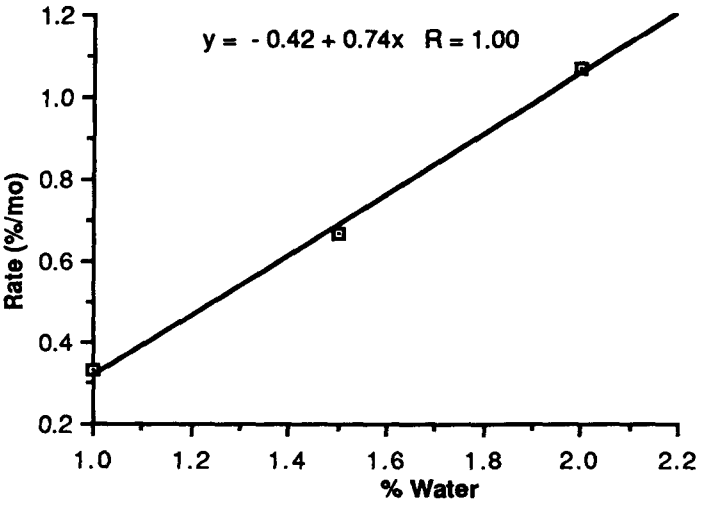

Fig. 10 Slopes From Fig. 9 Plotted Versus Water Content

where ΔH is the enthalpy of solution of the drug substance into the aqueous layer. Hence the apparent activation energy will be larger for a solid state Leeson-Mattocks reaction than for the comparable reaction in solution.

The described mechanism only holds as long as there is solid drug left. (Yoshioka et al., 1986 and Carstensen et al. 1987) have shown examples of drugs (propantheline bromide), where, even at low moisture content, complete solubilization of the drug fraction takes place in short periods of time.

Assuming, as above, that the decomposition is a hydrolysis, is no limitation to the model. If it is a first order decomposition of non-hydrolytic nature, then

$$dC/dt = - k_1 S \qquad (2\text{-}4\text{-}8)$$

So that all the subsequent equations hold, by simply omitting the term $[H_2O]$ or the factor 55, and substituting k_1 for k_2

2-5 Carstensen-Pothisiri's Model.

It occurs that the solid itself decomposes with a measurable rate, so the the decomposition is a sum of the decomposition occurring in the solid and in the dissolved state (Carstensen and Pothisiri, l975). If there are M_0 moles of drug at time zero, then at time *t* M moles will remain undecomposed. The volume of aqueous phase is V (liter), and the solubility of the compound is S, so that SV moles are dissolved, and M-SV moles are undissolved. The former decompose with a rate constant of k, the latter with one of k', so that the governing rate equatin is

$$-dM/dt = k'[M-SV] + kSV \qquad (2\text{-}5\text{-}1)$$

or

$$-dM/dt = k'M + [k-k']SV = k'\{Q + M\} \qquad (2\text{-}5\text{-}2)$$

where

$$Q = [k-k']SV/k' \qquad (2\text{-}5\text{-}3)$$

Eq. 2-5-2 integrates to

$$\ln[Q+M] = k't + \ln[Q+M_0] \qquad (2\text{-}5\text{-}4)$$

Q can be obtained by iteration, k' is obtained from the slope and k can now be obtained from Eq. 2-5-3. The value can be compared with k-values from solution studies and the two values were found to be quite close. Alternatively, the Q values can be plotted versus amount of water (V), and the slope of this line according to Eq. 2-5-3 should be [k-k']S/k' giving a least squares fit estimate of k.

3. Decomposition in the Presence of Limited Amounts of Water

The considerations, so far, have assumed that there was so much moisture present that, in the case of hydrolysis, the amount consumed by reaction was small compared to the total amount. This is not always true, and in fact, when the case is closed bottles, is quite frequently not the case. It should be pointed out that the amounts of comparison are molar amounts, so that if a 500 mg tablet contains 1% free moisture, then this corresponds to 5/18 = ca. 0.25 millimoles. Drug substances are often of molecular weights of 300, so that if the drug content were more than 0.25 300 = 75 mg per tablet, then there would be insufficient moisture present to decompose all the drug. The word "limited" in the following will apply to (a) a reaction where moisture is consumed, and where (b) the relative amounts of drug and water are such that not all the drug can be degraded by the water.

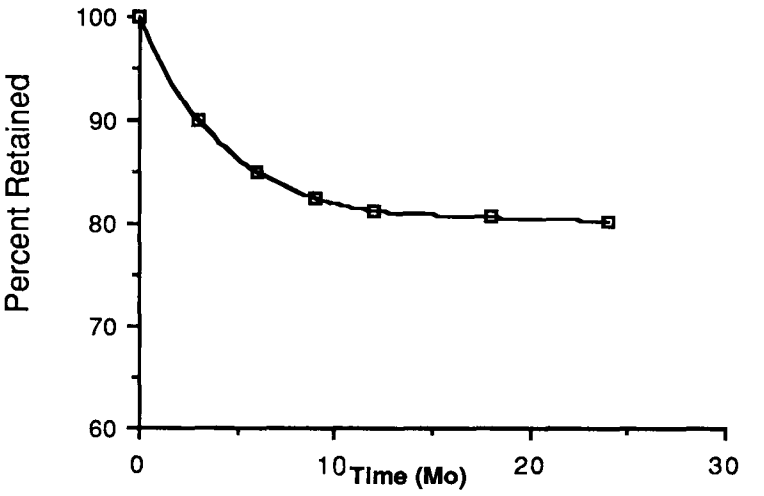

Fig. 11. Decomposition With Equilibrium

3-1 Over-All Pattern with Limited Moisture Amounts.

From an over-all point of view, this situation would lead to one of the two situations in Fig. 11 and 12. In the first case, the hydrolysis is the only reaction taking place. The content of active drug will decrease until it levels off at M_o - W, where *W* is the number of moles of water present in the dosage form at time zero. It is noted that *this level is not dependent of temperature*, although, of course, the rate with which it is approached is. If the reaction is slow, then the equilibrium may not be reached within the testing period. If the moisture content is say one tenth the number of moles of drug, then, as shown in Fig. 11A, the decomposition data will show distinct curvature. As has been stated, for simple first

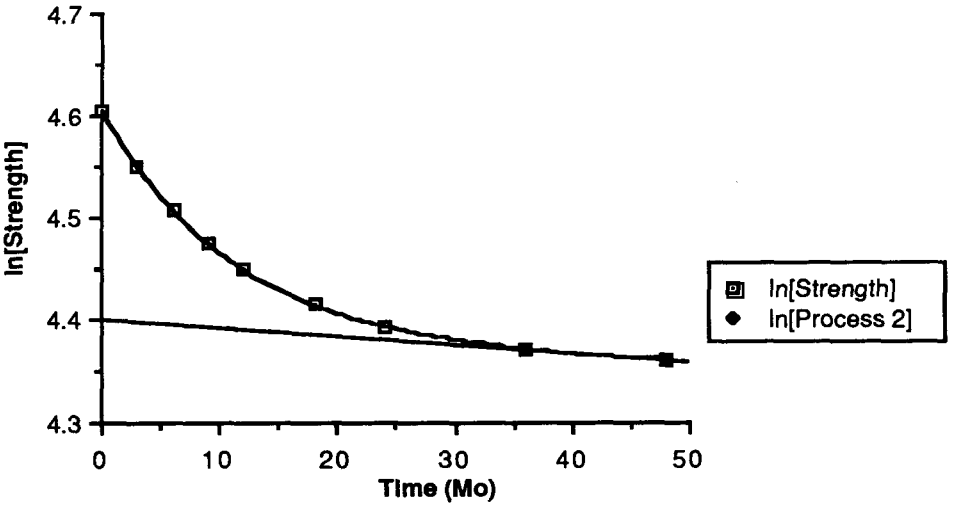

Fig. 12 Decomposition with one Equilibrium and one Non-Equilibrium Reaction.

order reactions, it is difficult to show the curvature, when only 15% or less of the drug substance has decomposed. But in the case depicted in Fig. 11, when 10% of the drug has decomposed, essentially half of the material that can decompose has decomposed, and this will give rise to distinct curvature.

The second situation is where there are two parallel reactions, one a hydrolysis, the other a non-hydrolysis. In this case there will be an additive effect. If the reactions are studied at different temperatures (Fig. 11B), then the terminal lines will intersect the y-axis at a common point, which corresponds to the number of moles of water. There are other reasons for this type of behavior as shall be elaborated on below.

A situation which can give rise to this type of behavior is when a compound decomposes by the following scheme:

$$A \rightarrow C \text{ (rate constant } k_1) \qquad (3\text{-}1)$$

and simultaneously

$$A \leftrightarrow B \text{ (rate constants } k_2 \text{ and } k_3) \qquad (3\text{-}2)$$

The rate equation for this (using D = d/dt) is

$$DA = -k_1 A - k_3 A + k_2 B \qquad (3\text{-}3)$$

$$DB = -k_2 B + k_3 A \qquad (3\text{-}4)$$

Solving these for A gives

$$D^2 A + aDA + bA = 0 \qquad (3\text{-}5)$$

where

$$a = k_1 + k_2 + k_3 \qquad (3\text{-}6)$$

and

$$b = k_1 k_2 \qquad (3\text{-}7)$$

LaPlace transforms of 3-5 now gives:

$$(s^2 + as + b)\, L(f(t)) = g + sA_0 \qquad (3\text{-}8)$$

where

$$g = A_0 + A_0' \qquad (3\text{-}9)$$

where the apostrophe denotes t-derivative. The roots of the quadratic expression in *s* in the parenthesis are denoted -i and -h, i.e.

$$i = (a/2) + [(a^2/4)-b]^{0.5} \qquad (3\text{-}10)$$

and

$$h = (a/2) - [(a^2/4)-b]^{0.5} \qquad (3\text{-}11)$$

Eq. 3-8 may now be written

$$L(f(t)) = (Z/(s+i)) + (Q/(s+h) \qquad (3\text{-}12)$$

where

$$Z = [-g+(iA_0)]/(i-h) \qquad (3\text{-}13)$$

and

$$Q = [g-(hA_0)]/(i-h) \qquad (3\text{-}14)$$

It is assumed below that the values of *g*, i and h are such that both Z and Q are positive.

The antiLaplacian of Eq. 3-12 is

$$A = f(t) = Z\exp(-it) + Q\exp(-ht) \qquad (3\text{-}15)$$

The profile shown in Fig. 12 is of this type where Z = 0.8, Q = 0.2, i = 0.002 and h = 0.5.

The situation dealing with bound moisture is not quite as clean-cut as described. It is obvious, that only athe "bound" moisture would correspond to the equilibrium level, and if a tablet or capsule contained only compounds that only existed as anhydrates, then this would be true. However, as pointed out in the aforesaid, each constituent in a tablet formula has a given moisture equilibrium curve. If the "available" moisture were reduced enough by the reaction, then some of the "bound" water might become available. There are, of course, cases where bound moisture will not be available. Magnesium chloride hexahydrate is such a case (Merck Index,7th Edition, pg. 626): at 100^{o}C it will lose two moles of water, but further heating removed hydrochloride, leaving magnesium oxide behind. The concept of bound moisture in its simplest form is easy to handle, both conceptually and mathematically, and will be followed in the writings here.

4. Other Equilibrium Situations.

There are several situations that lead to pseudo-equilibriae. One is the situation where the hydrolysis is accompanied by a drop in pH. This happens if, for instance,

an ester hydrolyzes. The solubility of a compound is usually a function of pH. Often it increases sharply around the pK, because (if an acid) the acid is usually fairly insoluble, but the salts are fairly soluble. In the case of an amine hydrochloride the situation is the reverse.

The lower part of a Henderson-Hasselbach dictated solubility curve like that would be

$$S = S_0 \exp(s\text{pH}) \qquad (4\text{-}1)$$

Reaction kinetics are usually a function of pH, and in the simplest type of profile, log k_1 would simply decrease with pH. Hence the rate constant in solution would be a function of pH by the following equation:

$$k_1 = k_0 \exp(-k\text{pH}) \qquad (4\text{-}2)$$

Let us now assume that as the reaction proceeds in the tablet or capsule powder, the pH drops as a result of the hydrolysis, i.e.

$$\text{pH} = a - q\,x \qquad (4\text{-}3)$$

where x is fraction decomposed and where a and q are constants. From Eq. 2-4-3 it is seen that

$$dx/dt = [k_1 SV/(M_o)] \quad (4\text{-}4)$$

Inserting Eqs. 3-1 to 3-3 now gives:

$$dx/dt = [k_o S_o V/M_o] \exp\{(s-k)(a-qx)\} \quad (4\text{-}5)$$

This may be rewritten:

$$\exp\{-(s-k)(a-qx)l\}dx = Qdt \quad (4\text{-}6)$$

where

$$Q = k_o S_o V/M_o \quad (4\text{-}7)$$

This integrates to

$$-\exp[-(s-k)(qx-a)] + \exp[-a(s-k)] = Lt \quad (4\text{-}8)$$

where

$$L = q(s-k)Q = q\,(s-k)\,S_o k_o V/M_o \quad (4\text{-}9)$$

Eq. 3-8 may be written:

$$\exp[(s-k)a]\ [\ 1 - \exp[(s-k)qx] = Lt \quad (4\text{-}10)$$

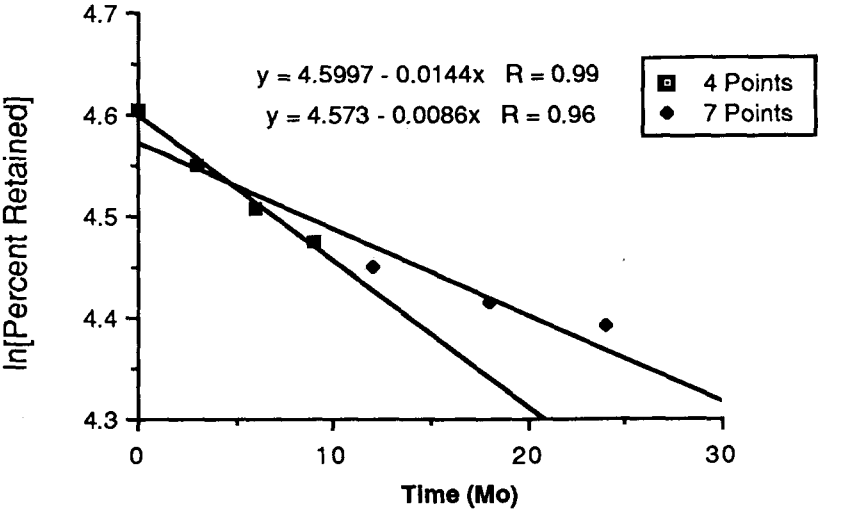

Fig. 13. Example of Pseudo-Equilibrium.

If s>k , i.e. if the drop in solubility as the pH drops is more important than the increased hydrolysis rate, then this curve will have the shape shown in Fig. 14, i.e. x will seem to taper off. If k > s, i.e. if the kinetics are more important than the solubility, then the shape will be such that x will increase at a higher and higher rate.

4-2 Accounting for Salting-In

The problem that arises with limited amounts of moisture and the bulk moisture theory have been investigated by Carstensen and Pothisiri (1975), by Wright and Carstensen (1985) and by Carstensen and Attarchi (1986, 1988a, 1988b).

The latter authors investigated the aspirin-moisture system. Typical decomposition curves are shown in Fig. 14.

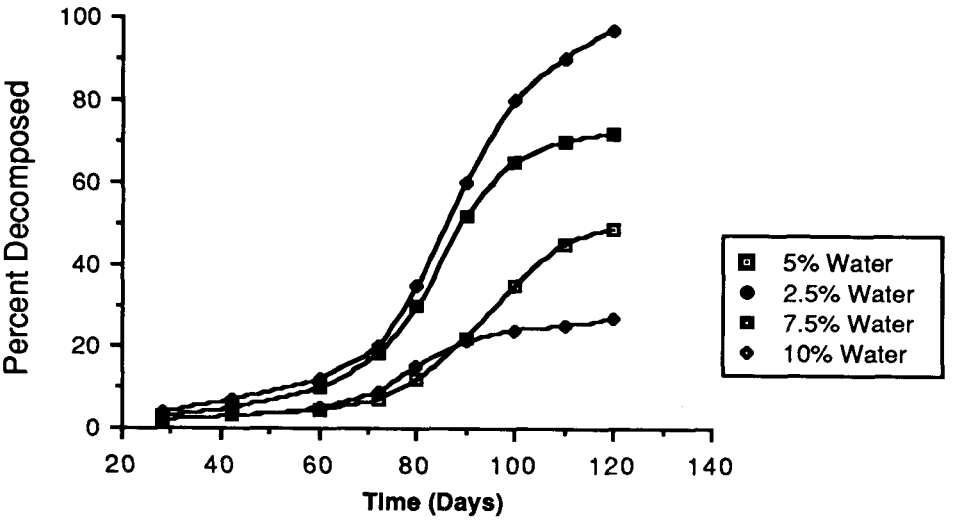

Fig. 14. Aspirin Decomposition In the Presence of Water

It is noted that the decomposition levels off at the point where all the moisture has been consumed. (The molecular weight of aspirin (ASA) is 180, that of water 18, so 7.5% moisture would correspond to 75% of the aspirin decomposed at infinite time).

It is noted that the the reaction is

$$C_6H_4(O\text{-}COCH_3)COOH + H_2O \longrightarrow HOC_6H_4COOH + CH_3COOH \quad (4\text{-}2\text{-}1)$$

Hence the sorbed liquid layer will be less and less rich in water, and richer and richer in acetic acid (and at the final point will be all acetic acid). Both the solubility of aspirin and salicylic acid will be a function of the concentration of

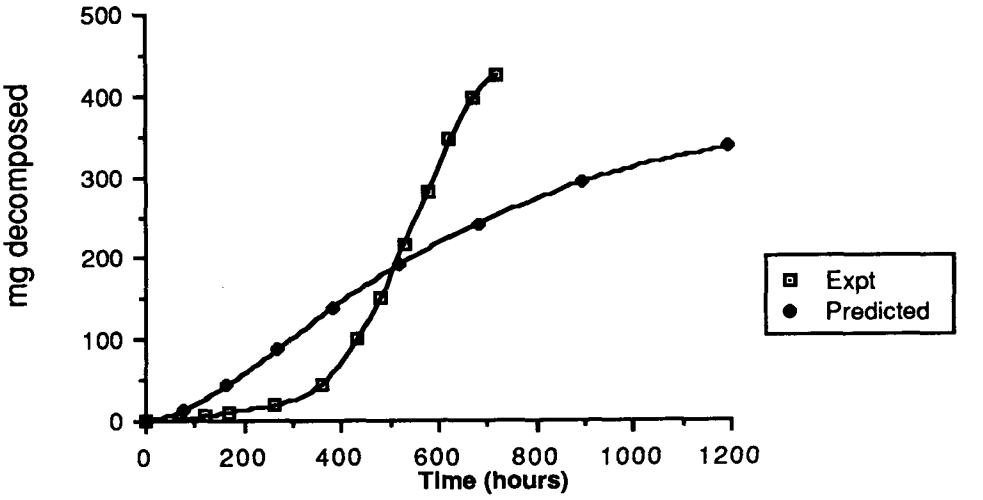

Fig. 15 Data From Carstensen and Attarchi. Aspirin With 5% Moisture at 60°C

acetic acid in the sorbed layer. The authors determined the two solubilities as well as the second order rate constant as a function of acetic acid concentration. This allowed them to calculate the value of the volume of the layer as a function of time (salicylic acid concentration), and the solubility and the rate constant, so that

$$-dM/dt = -VdC/dt = - V k_2 C_{H2O} S_{ASA} \qquad (4\text{-}2\text{-}2)$$

could be determined functionally as a function of time. The function is complicated, and graphical integration is necessary, but the point is that a theoretical curve could be

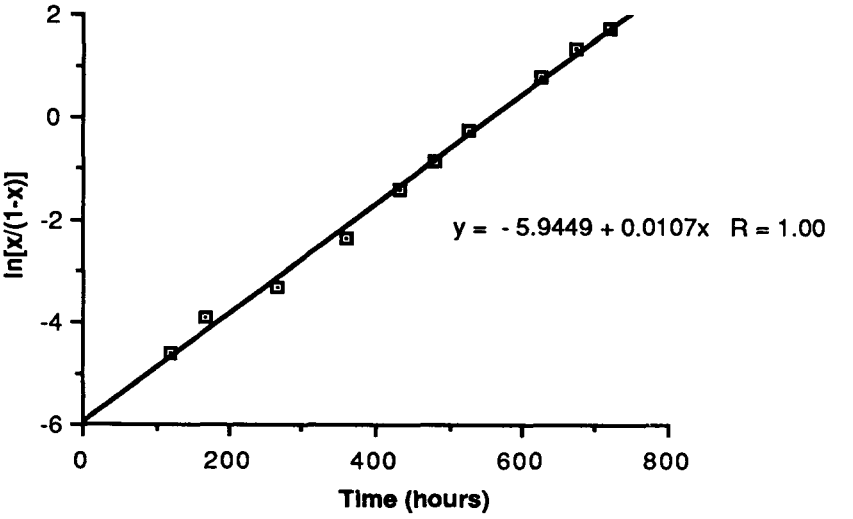

Fig. 16 Schematic of Surface Reaction Model.

constructed and compared with the actual curve. This comparison is shown in Fig. 15.

It is possible to make the two curves overlap if one assumes a long lag time, and a three fold solubility, or a three fold rate constant, but these assumptions are rather unrealistic. More reasonable is the assumption that the bulk moisture theory does not hold when there is limited amount of moisture present. Fig. 16 shows a more probable model.

It is assumed that the moisture is positioned on the surface of the aspirin crystals. The sequence of events will the be:

(a) a surface molecule of aspirin will react with a neighboring water.

(b) The water and the formed acetic acid will exchange

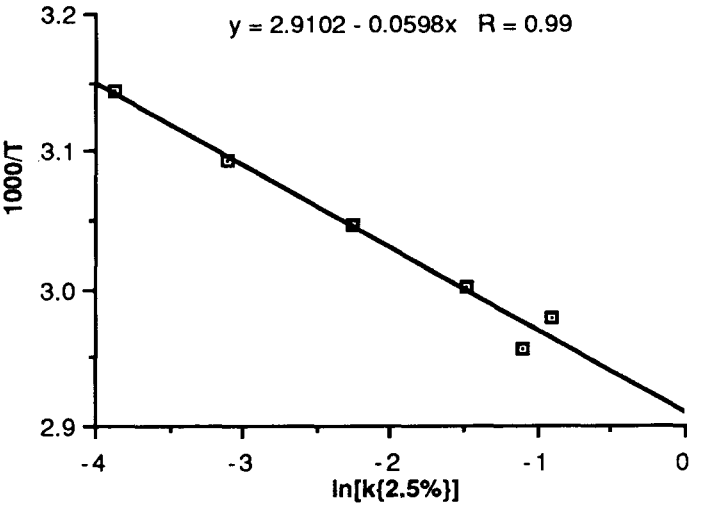

Fig. 17. Data Treated According to Surface Interaction Mode.

(c) This water will react with a neighboring aspirin molecule.

The sequence is based on the assumption that (a) there are active sites on the surface (ridges, defects, etc), and that the aspirin at these sites is more prone to react that the remainder. (b) once a salicylic acid molecule is formed it constitutes a different geometry (volume, for instance), and hence its neighbors become activated. The reaction will therefore proceed in chains, much like a Prout-Tompkins reaction, and hence the resulting equation should be

$$\ln[x/(1-x)] = -k(t-t_{1/2}) \qquad (4\text{-}2\text{-}3)$$

The excellent adherance to this equation is seen in Fig. 17.

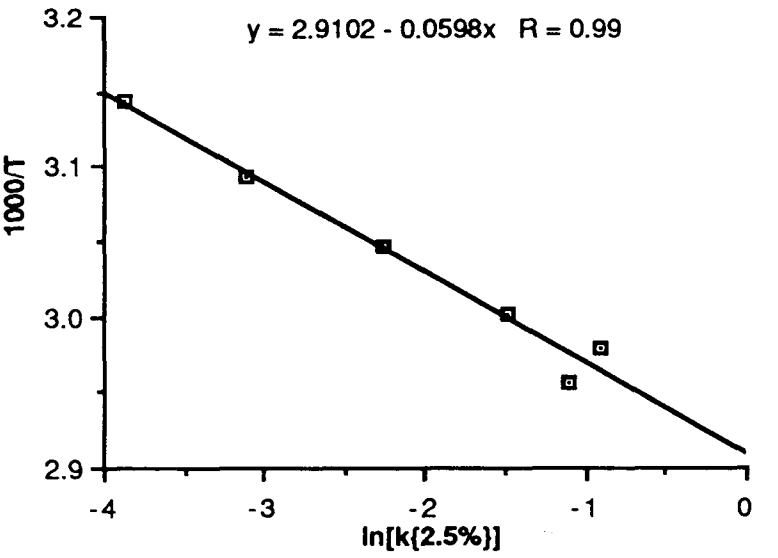

Fig. 18. Arrhenius Plot of Rate Constants From Surface Model.

The rate constants adhere well to an Arrhenius relationship (Fig. 18)

5. Non-Stoichiometric Interactions with Water

It is sometimes a pharmaceutical practice to "coat" labile pharmaceuticals. One such example is vitamin A beadlets which are an emulsion of vitamin A ester in a gelatin solution which has then been converted into drops and dried. The beadlets are therefore a matrix of gelatin with droplets of oil in the interior. The protection offered is one against oxidation

6. Specific Excipients

Some of the more common tablet and capsule excipients that are moisture contributors are discussed briefly below:

Corn Starch has been discussed by York (1980) and shown to be of a BET type, and by Zografi (1962) with the same conclusion. Later work (Zografi and Kontny, 1986) shows that a GAB Isotherm is better in describing it. When treated by a Freundlich equation (Carstensen, 1980), the A and n-values are as shown in Table I.

Corn starch is used as a binder and as a disintegrant. In the former case it is first hydrolyzed, and the *starch bridges* are what hold the particles together in larger granules. These bridges form an integral part of the bond that is finally formed in the tablet, i.e. what gives rise to the *hardness* of the tablet.

First of all, the degree of hydrolysis the starch has been subjected to may vary greatly from batch to batch. Little is known about the moisture isotherms of hydrolyzed starch, so that the facets of the tablet stability profile tied into this isotherm may vary from batch to batch, and may not be subject to direct quantitative assessment. The change of hardness with time of storage may in some cases be attributed to moisture shifts from the starch bridges to other ingredients by the process described in the aforementioned It is obvious that the change in hardness will take place in the time it takes for the moisture to equilibrate in the tablet. This, assumedly, is not a long period of time (months at the most), and this corresponds well with the fact, that hardness changes occur rather rapidly. They hence do not have to be gauged by high temperature stress, and in fact, results from high temperature usually defy analysis.

Gelatin, likewise, has been reported by York. His values have been recalculated to fit a Freundlich equation, and the parameter values listed in Table I. This is particularly important in the case of *hard shell capsules.*. Some substances are sufficiently hygroscopic (i.e. curve II is low in Fig. 5, or the value of *A* is small) so that they will pull out moisture from the gelatin shell. An example is experimental batches of capsules of Dalmane disulfate. This substance is so hygroscopic, that the water removed from the shell, will dissolve the strongly acidic disulfate, the free sulfuric acid will replace the stearic acid in the magnesium stearate used in the preparation, and the powder mass becomes a solid plug, which does not dissolve very well. Other examples are choline salts.

Microcrystalline Cellulose (Avicel) has been reported by Marshall and Sixsmith (l974/75). Zografi and Kontny (1986) has shown that the internal surface area (water adsorption) is many times that of the external (nitrogen adsorption). Microcrystalline cellulose/water/drug interactions have been reported by Carstensen et al. in the case of thiamine hydrochloride (l969) and by Carstensen and Kothari in the case of furoic acid (l983).

Lactose Hydrate is USP and contains one mole of water per mole of lactose, i.e. about 5%. It is fairly soluble, and is frequently used as the main excipient in the formulation of poorly soluble drug (the so-called soluble/insoluble rule). The

stability RH range at 25-30°C for lactose has not been reported in literature, but is presumably 10-60%.

To determine the upper range of this, the following experiment has been carried out: Moisture uptake rates have been determined at several different relative humidities, and the moisture uptake rates then plotted versus relative humidity. This should result in a straight line (Carstenen, l977), that intersects the x-axis at the upper limit of the RH stability range.

Calcium Phosphates. These are used to a fair extent in pharmaceutical products. The rationale for using them is often in vitamin-mineral supplements, but often they are used simply as excipients. They are inexpensive, non-toxic, reproducible, and a list of products using some variant of calcium phosphate strictly as excipient would include: Mediatric™ (Ayerst), Deconamine™ Tablets (Berlex), Actifed™ (Burroughs Wellcome), Ludiomil™ (Ciba), Dista™ (Lilly), Nalfon™ (Lilly), just to mention a few.

There are several calcium phosphates of interest to the pharmaceutical scientist:

Dicalcium Phosphate Dihydrate (DCPD). There are two grades of this, viz. (a) granular and (b) granular (direct compression grade). The latter is marketed as Ditab™ (Stauffer) and Encompress™ (Mendel). The former is frequently used in wet granulated products. There is an old rule, that it is advantageous to compound a soluble drug with an insoluble

excipient and vice versa. When dicalcium phosphate dihydrate is heated, it will dehydrate:

$$CaHPO_4.2H_2O \longrightarrow CaHPO_4 + 2H_2O \qquad (6\text{-}1)$$

It is interesting to note that once dehydrated it will not rehydrate, i.e. Eq. 7-1 does not appear to be an equilibrium. It is, however, possible that the activation energy for the reverse reaction is inordinately high. The other possibility is that the dihydrate is a metastable form. Proper treatment of it will certainly maintain it such for prolonged periods (easily through the five year period considered maximum for pharmaceuticals). The compound appears to have a RH stability range at 25°C between 10 and 85% RH. At higher temperatures, however, it will be prone to dehydration. The rate of this is accelerated by the presence of water (i.e. is akin to decarboxylation of sodium bicarbonate)., i.e., denoting the dihydrate C, and the anhydrate B, it follows that

$$-dM/dt = k\ S\ V \qquad (6\text{-}2)$$

where M is amount of dihydrate remaining, where S is the solubility in water of the dihydrate and where V is the volume of whatever available moisture is in the system. S is, of course, rather small, but acts like a mediator of the reaction. This is also akin to the behavior of sodium bicarbonate.

The mass of water produced in the reaction at time t is

$$W = 2[M_0-M]/D \qquad (6\text{-}3)$$

where D is the density of the dihydrate. This, inserted in Eq. 4-2 yields:

$$-dM/dt = -(kS2/D)[M_0-M] \qquad (6\text{-}4)$$

which integrates to

$$\ln[M_0-M] = -[kS2/D]\ t \qquad (6\text{-}5)$$

The reaction scheme in Eq. 6-1 is oversimplified. Depending on drying conditions higher phosphates may form, for instance

$$4CaHPO_4.2H_2O \longrightarrow (Ca_4H(PO_4)_3 + H_3PO_4 \qquad (6\text{-}6)$$

might occur intermittently under certain substances. It could be followed by partial recombinations, and species such as hydroxyapatite and calcium monophosphate may occur. Such species, under drying conditions, would be present with large surface areas, and would be quite reactive, and could be responsible for some occasional incompatibilities. It is, therefore, important to control the drying conditions of

granulations to minimize the above. In particular, excessive drying should be avoided. The correct drying, of course, can be ascertained by mass balance, and drying conditions should always be established by model batches (containing only granulating liquid and dicalcium phosphate dihydrate).

Dicalcium Phosphate Anhydrate. This material adheres to USP as well, and is commercially available, but is not used nearly to the same extent as is the dihydrate. It is not self-compressible, and hence is not used in direct compression, and it is usually not used in wet granulations (although it could perfectly well be, since it will not rehydrate), since in general the practitioner would feel it more logical to use a hydrate when water is added in process anyway.

Hydroxyapatite, marketed as Tritab™ (Stauffer). The composition of this is $Ca_4(OH)(PO_3)_4$. It forms no hydrate, and is not hygroscopic. It has a much larger surface area (70 m^2/g) than the other phosphate (all in the range of 5 m^2/g). Drugs with *high* alkaline sensitivity (e.g. aspirin) are usually not compatible with the ex`cipient. Compounds with moderate or no alkaline sensitivity can be compounded with hydroxyapatite. Hydroxyapatite is often referred to as tricalcium phosphate. This latter form ($Ca_3(PO_4)_2$) does exist, but is not much used.

Sucrose has many hydroxyl groups, and a free aldehyde group. This latter makes it incompatible with primary and with many

secondary amines. It is very soluble. When it is wet granulated (or used as a granulating agent) the dissolved portion of the sugar precipitates out on drying either as a very fine crystalline mass, or as amorphous sugar. Amorphous sugar converts to crystalline (VanScoik and Carstensen, 1988) at RH above 16%. The disintegration time and hardness will both increase when this conversion takes place. Invert sugar slows down (or under certain circumstances prevents) the conversion. As mentioned before, hardness and disintegration data obtained from accelerated stations cannot be logically extrapolated to room temperature, but the changes in both disintegration and hardness of sugar containing tablets usually manifest themselves rather rapidly at room temperature, so the accelerated data is actually not necessary for predictive purposes (but may serve other purposes).

Mannitol is anhydrous and non-hygroscopic and fairly inert. It is expensive compared to *Sorbitol*. This forms no hydrate, but is very soluble, hence quite hygroscopic.

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