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Interactions of Moisture with Solids

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1. PREDOMINANT REACTION ORDERS

The ICH 1993 Stability Guidelines "do not accept the term 'room temperature'," yet it is so common that it will be used in this text in its intuitive sense. At room temperature, for a product to be marketable, decompositions are less than 15% (in fact a good deal less than 10%). Most products exhibit good content uniformity, and usually decompositions will appear zero order, i.e., be pseudo-zero-order. The mathematical approximation

$$\ln[1 - x] \approx -x \tag{7.1}$$

explains this. A reaction that is truly first order, but where x is small (less than 0.1 or at most 0.15), will, by way of Eq. (7.1), appear zero order. If M is drug present at time t and M_0 the initial amount, then it follows that

$$x = \frac{M_0 - M}{M_0} \tag{7.2}$$

hence

$$\frac{M}{M_0} = 1 - x \tag{7.3}$$

This means that the equation takes the form

$$\ln\left[\frac{M}{M_0}\right] = \ln[1 - x] \approx -x = -\frac{M_0 - M}{M_0} = -k_1 t \tag{7.4}$$

where k_1 is the first-order rate constant. One may write this

$$M = M_0 - \{M_0 k\}t = M_0 - k_0 t \tag{7.5}$$

i.e., the data will appear pseudo-zero-order with a rate constant of

$$k_0 = M_0 k_1 \tag{7.6}$$

There are other causes for pseudo-zero-order behavior, chemical and physical reasons. The effect moisture has on solid state stability is, in its simplest form, visualized by moisture being sorbed on the particles. In this sense the water would behave like a solution, a bulk layer, and it is assumed that this is saturated in drug. This is known as the Leeson–Mattocks model (Leeson and Mattocks, 1958; Li Wan Po and Mroso, 1984; Carstensen and Li Wan Po, 1993). The decomposition follows the equation

$$M = M_0 - k_0 t \tag{7.7}$$

where k_0 is the pseudo-zero-order rate constant given by

$$k_0 = k_1 SV \tag{7.8}$$

In this equation S denotes the drug solubility in the bulk aqueous phase and V denotes the volume of the layer. Most often one deals with hydrolysis and pseudo-first-order is assumed.

An assumption is that the moisture is in such excess that the term V does not change while the stability is being studied. Investigators (e.g. Kornblum and Sciarrone, 1964) have assumed that k_1 equals that from solution-kinetic studies. Quite often this is not so, because the model dictates that it is the kinetics in concentrated solutions that matters.

As seen in Chapter 9, anhydrous solids usually exhibit sigmoid profiles, i.e., Prout–Tompkins kinetics (Prout and Tompkins, 1944) or Bawn kinetics (Bawn, 1955). This is mostly not the case with decompositions when moisture is present in "large" amounts.

2. KINETICS IN THE DRY VERSUS MOIST STATE

Pothisiri (1975) and Carstensen and Pothisiri (1975) studied the decomposition of substituted *p*-aminosalicylic acids as a function of moisture content and attempted to extrapolate the pseudo-zero-order rate constants down to 0% (anhydrous). The extrapolated value (as well as the mechanism) differs from that observed in experiments where moisture is excluded (pseudo-zero-order versus sigmoid behavior).

It is therefore of interest to define the nature of the water in the transition between very low moisture contents (the anhydrous state) and the other extreme (the very moist state). The models just mentioned are extreme cases of very "dry" and very "wet." Various stages of "wetness" are depicted in Fig. 1.

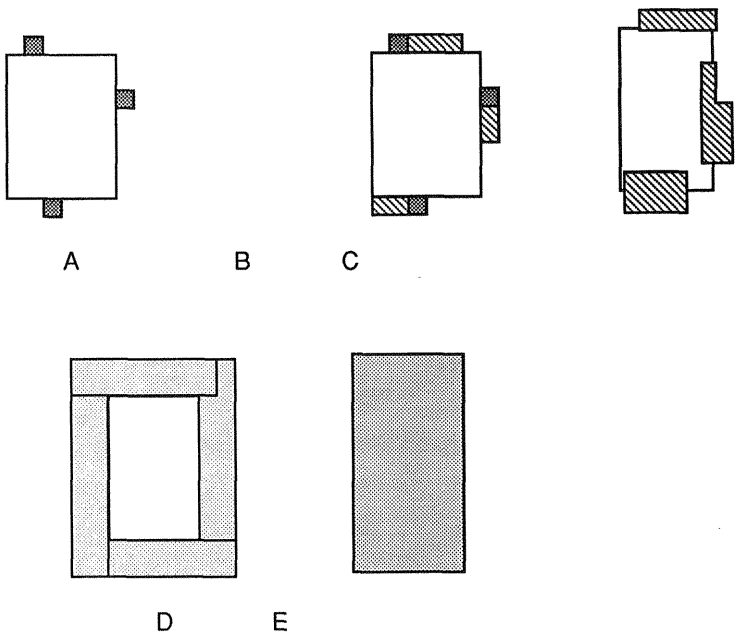

Fig. 1 (A) Anhydrous solid with active sites (cross-hatched); (B) solid with less than monolayer coverage of moisture; (C) solid with more than monolayer coverage, where the active sites have disappeared; (D) bulk sorbed moisture; and (E) moisture in an amount sufficient to dissolve the solid completely.

3. TYPES OF SURFACE MOISTURE

There are, broadly speaking, three types of situations: *Limited water*, where all the water is used up in the decomposition of the drug, but the amount is not enough to decompose all of the drug.

Adequate water, when there is enough moisture to decompose all of the drug substance.

Excess water, when the amount of water present is more than needed to dissolve the drug completely.

3.1. Excess Water

This is shown as E in Fig. 1, where the amount of water suffices to bring all of the drug into solution. This may not be applicable initially, but it occurs as the amount of parent drug decreases in time.

Examples of this are the work by Morris (1990), where the indomethacin/water system was studied in a closed system at 130°C. After a short period of time a eutectic consisting of indomethacin, decomposition products, and water is formed, and from this point in time the decomposition is first order as expected for solution kinetics (Fig. 2). The amount of time (t') required for the eutectic to form (for the mass to form a homogeneous liquid) is linear in water activity ($a = \mathrm{RH}/100$), i.e.,

$$t' = \beta - q'a \tag{7.9}$$

where β and q' are constants (Fig. 3).

Yoshioka and Uchiyama (1986a,b), Carstensen et al. (1987), and Yoshioka and Carstensen (1990a,b) have reported similarly in relationship to propantheline bromide. Yoshioka and Uchiyama (1986a) introduced *critical relative humidity* (CRH) as the point where the water activity just equals that of a solution saturated

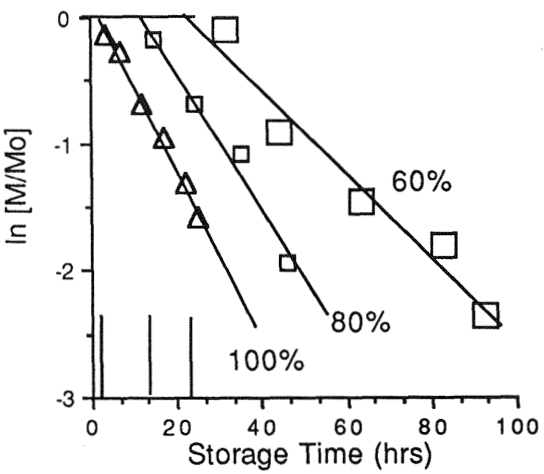

Fig. 2 Decomposition of indomethacin in the presence of moisture at 130°C. (Graphs constructed from data published by Morris, 1990.)

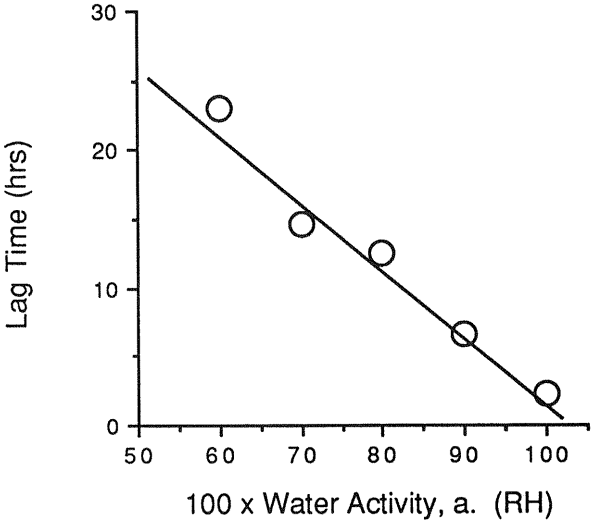

Fig. 3 Lag times from Fig. 2 plotted versus relative humidity. (Graph constructed from data published by Morris, 1990.)

in the drug (Carstensen, 1977) and they also showed that the mechanism changed at this point. At values higher than the CRH the degradation consists of (a) dissolution up to where dissolution is complete, after which (b) moisture condensation will continue until a concentration of the totally dissolved drug equals that of the RH of the atmosphere.

Koizumi et al. (1997) showed that the dependence of water concentration on the rate constant of decomposition of Lornoxicam tablets is log-log related to the log of the moisture content.

Carstensen et al. (1965) had shown this to be correct for vitamin A beadlets as well.

$$\frac{d[\mathrm{A}]}{dt} = -k[\mathrm{A}][\mathrm{H_2O}]^n \tag{7.10}$$

4. THE LEESON–MATTOCKS MODEL

This is the most frequently applicable model and it assumes that sorbed moisture forms a layer about the particles. It corresponds to situation D in Fig. 1. One might argue that such a layer (a so-called bulk sorbed moisture layer) could not be created until the moisture content is high enough, so that the RH of the atmosphere surrounding solid equals or is in excess of the RH of a saturated solution of the drug. One might then conclude that the Leeson–Mattocks model only holds at RH values in excess of the critical relative humidity (CRH). However *rather than that being true it holds below the CRH*. For a certain range of RH values less than the CRH, the Leeson–Mattocks model applies, and degradations are pseudo zero order. Phenobarbital when it decomposes at 80°C in the presence of phosphate buffer at pH 6.7 is an example of a case where, in the initial stages of decomposition, this

holds (Gerhardt 1990). Another case is that reported by Morris (1990) and Morris and Carstensen (1990a,b).

Equation (7.9) applies to the decomposition, hence one must know k_1, V, and S, which should allow for elucidation of the mechanism. This often holds true (Pothisiri, 1975; Pothisiri and Carstensen, 1975), but it has also been known to fail (e.g. Janahsouz et al., 1990).

Carstensen and Attarchi (1988) elucidated the discrepancy between the rate with which aspirin decomposes as a solid with water present and its behavior in saturated solution. If they presumed that the solubility in the moisture layer were three times that of the bulk solubility, then their calculated data corresponded to the experimental data. Whether it is possible that the condensed layers of water are so energetic that they would allow for such an increase is doubtful.

The speculation that the solubility might be increased in the sorbed moisture layer (Fig. 1D) might lead one to consider it akin to an amorphous state. An amorphous state would exhibit increased higher solubility over that of crystalline states, and would also possess a higher vapor pressure than would a crystalline form, the form that it would rest upon, posing the question of why and where the critical moisture content would exist.

A further extension of this, though, is that water dissolves into the solid. As mentioned, this happens for a wholly amorphous compound, but for a crystalline compound the crystallinity would have to be lost, an assumption that has no basis in fact. If the moisture molecules really created a "hot spot" of amorphous solid on the crystal surface, then at a certain given RH value the mass of moisture ad/absorbed should be equivalent to the composition of the amorphate/water in equilibrium at the RH in question.

Carstensen and VanScoik (1990) have demonstrated for small molecules (sucrose) that the water activity over this type of supersaturation of water in solid is simply an extrapolation of the RH values of saturated and unsaturated solutions at the other end of the diagram. One might consider this as water that is dissolved in the solid or as solid that is dissolved in the water, but in either view the important aspect is that (ideality assumed) the mass of water sorbed is linearly dependent on the RH. (For polymers of high molecular weight the isotherms are S-shaped, an example being microcrystalline cellulose reported by Hollenbeck et al., 1978, and by Marshall et al., 1972).

If an amorphate "hot spot" hypothesis were correct then the pseudo rate constants should be linearly related to the water activity (the relative humidity) used in the study. Figure 4 shows the profiles with which crystalline indomethacin decomposes at different water activities (RH values). Pseudo zero order obviously prevails, but the plot of rate constants versus water activities (RH values) is not a straight line (Fig. 5). As mentioned in the last chapter, one cannot "prove" a model by statistically comparing curve fittings, but one can eliminate models (Li Wan Po, 1984; Mroso et al., 1982) when a fit is lacking. An assumption made in Fig. 8.18 is, it is conceded, that ideality prevails, but for the "hot spot" model to hold, nonideality in the case would have to be drastic.

A different interpretation of the indomethacin data was forwarded by Morris (1990) and Morris and Carstensen (1990a,b), by demonstrating that the rate constants are related to a BET (or possibly to some other nonlinear) water adsorption

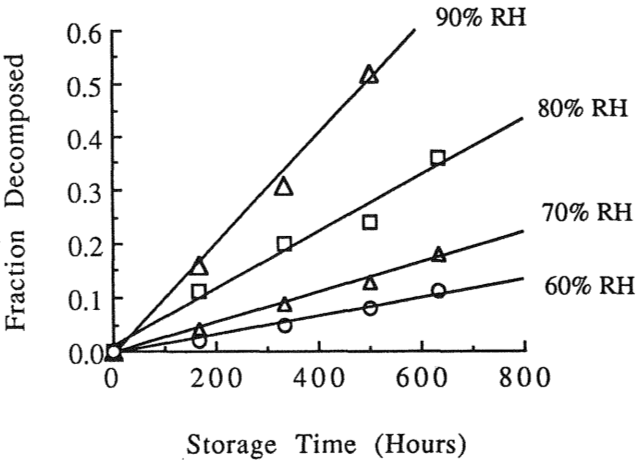

Fig. 4 Indomethacin decomposition at 115°C. This decomposition follows zero-order kinetics at the onset. (Graph constructed from data published by Morris, 1990, and Morris and Carstensen, 1990a,b.)

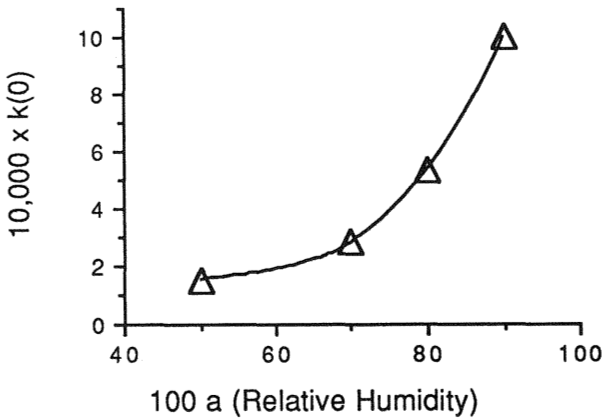

Fig. 5 Data from Fig. 4 of Chapter 10. Rate constants as a function of RH. (Graph constructed from data published by Morris, 1990, and Morris and Carstensen, 1990a,b.)

isotherm. The volume of water, V, adsorbed when a BET isotherm with high c value applies would be of the type

$$V = \frac{v_m}{[1-a]} \tag{7.11}$$

v_m is here a monolayer volume, and the symbol a is used to denote the water activity (RH/100). The k_0 value should, therefore, be linearly related to $[1-a]$. That this is the case is shown in Fig. 6.

It would therefore seem (at least in the case of indomethacin) that the amorphate "hot spot" model does not apply. In addition to this, Morris (1990) tested

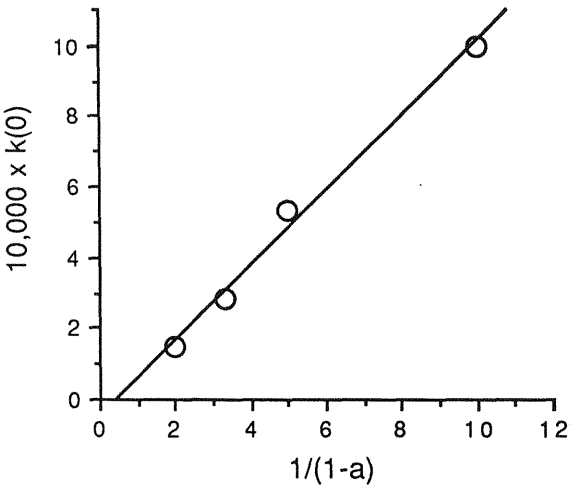

Fig. 6 Rate constants from graphs of the type shown in Fig. 2, plotted versus a BET-isotherm parameter $1/\{1-(1/a)\}$.

amorphous indomethacin with moisture present, but at high temperatures conversion to crystallinity was rapid to such an extent that kinetic data could not be obtained in reasonable time periods.

The "hot spot" theory is not new. In fact, work by Gluzman (1954, 1956, 1958) and Gluzman and Arlozorov (1957) postulated that "part of a surface of a solid was actually in a liquid like state"—in other words, in appearance being a solid, but with random molecular arrangement, and usually referred to as an amorphate.

Guillory and Higuchi (1962) hypothesized that if such a theory were correct, then the logarithm of the rate constant at a given temperature, T_d, of a series of analogous compounds in solid form should be inversely proportional to the inverse of the melting point, i.e.,

$$\ln[k] = -Q\left\{\frac{1}{T_d} - \frac{1}{T_m}\right\} \tag{7.12}$$

This has been found to be true in certain cases, e.g., for vitamin A esters at 55°C (Guillory and Higuchi, 1962) and substituted *p*-aminobenzoic acids (Carstensen and Musa, 1972), but in other cases, e.g., *p*-aminosalicylic acids, it does not hold well (Pothisiri and Carstensen, 1975).

More plausible than the "hot spot" amorphate theory is the hypothesis that the sorbed moisture layer acts as a solution layer and that degradation compounds (a) increase or decrease the drug solubility, (b) increase or decrease the kinetic parameter values of the drug, and (c) (noting that the degradants are solutes) cause a decrease in the water vapor pressure with which the moisture layer is in contact, so that in this manner the vapor pressure relationship is not violated. Gerhardt (1990) and Gerhardt and Carstensen (1989) have demonstrated that kinetic salt effects and salting-in of the drug into the moisture layer can explain the decomposition profiles exhibited by phenobarbital when moisture and buffers

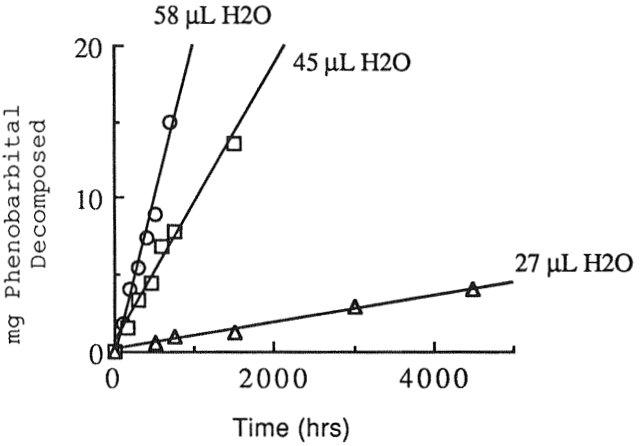

Fig. 7 Phenobarbital decomposition in the solid state at 80°C, with phosphate buffer present corresponding to a "pH" of 6.7.

are present. Carstensen and Pothisiri (1975) and Wright and Carstensen (1986) have done likewise.

In the case of very soluble drugs, e.g., ranitidine (Franchini and Carstensen, 1995; Carstensen and Franchini, 1995) the amount of moisture necessary to reach the CRH is small (i.e., the water activity (RH/100) over a saturated solution is of low magnitude). On the other hand, it is high for poorly soluble drugs.

5. KINETICALLY UNAVAILABLE (BOUND) WATER

Solid state rate constants often follow Eq. (7.2), in that they appear directly in proportion to the mass or volume of water the dosage form contains. Figure 7 presents data from the work of Gerhardt (1990) and Gerhardt and Carstensen (1989). The rate constants are pseudo zero order and are plotted versus moisture levels (Fig. 8). It is noted that the intercepts are nonzero, i.e.,

$$k_0 = k_1 S[V - w^*] \tag{7.13}$$

w^* is often called kinetically unavailable moisture or *bound water*. This is the case in many solid state reactions. The bound moisture, at times, is water of crystallization. For D,L-calcium leucovorin (Nikfar et al., 1990a,b), there are intermittent plateaus that correspond to a constant water activity (RH/100) for a series of water contents, i.e., akin to a salt pair. $[V - w^*]$ is denoted kinetically available, or more simply, *available moisture*.

Aso et al. (1997) have determined the decomposition rates of cephalotin in mixtures with pharmaceutical excipients and the effect of moisture. They found a linear relation between mobile water percentage and decomposition rate constants.

6. MICROENVIRONMENTAL pH

If a formulator is aware that a compound is more stable in an acid than in a neutral or basic environment one may often formulate it with solid acids (e.g., citric acid);

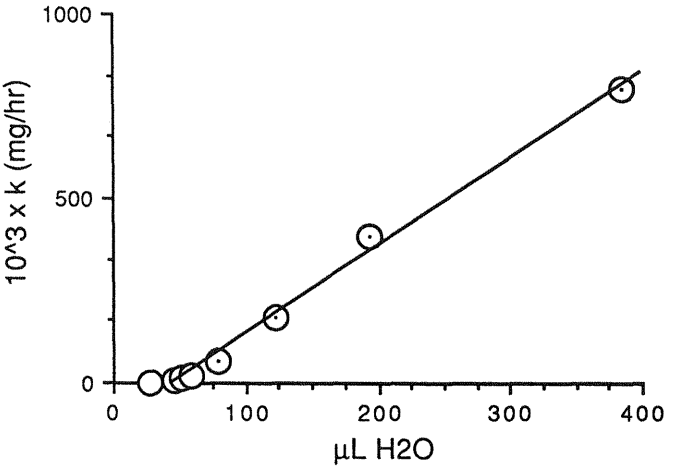

Fig. 8 Rate constants (pseudo zero order) from plots such as shown in Fig. 7 of Chapter 10, graphed versus added moisture. (Figure constructed from data published by Gerhardt, 1990, and Gerhardt and Carstensen, 1989.)

conversely, if it is acid-sensitive, one may employ bases (e.g., sodium carbonates) in an attempt to make an adjustment of "the microenvironmental pH." In the area shown as Fig. 1C, D, and E, if one may "buffer" a solid dosage form, Nikfar 1990, Nikfar et al. 1990a,b, Gerhardt 1990, Gerhardt and Carstensen 1989 have demonstrated the existence of a "solid pH-profile" that parallels (but is not identical with) the traditional pH profiles of the drug in solution. This is another piece of evidence of the sorbed moisture layer having solvent properties.

But how to define the microenvironmental pH? This a question that is not fully resolved yet. The shift in position of the kinetic pH profile in solution from the values obtained from solid state decomposition may be attributed to the fact that one assumes that the pH value of a saturated buffer solution is the same pH used for graphing of data from the moist solid. But the sorbed solution could be of a pH value displaced from that observed in solution.

There is also the possibility of a kinetic salt effect. It is seen from Fig. 9 (Nikfar, 1990; Nikfar et al. 1990a,b) that a displacement of 1.4 pH units applies to the rate constants in the solid state. The displaced values are symbolized by squares in Fig. 9, and if such a shift is made, then the data in solution would coincide with those in the solid state. In the work published by Gerhardt (1990) it would be necessary to force a 6 pH unit shift to obtain coincidence, so that are still unexplained factors at work.

7. VERY LOW MOISTURE CONTENTS

Such a case is shown in Figs. 1B and 1C. Nikfar (1990) and Nikfar et al. (1990a,b) suggested the term *immobile water* for cases such as the ones depicted in Fig. 1c. They have demonstrated that the decomposition in such a case translates into a pseudo-first-order profile (Fig. 10). At these levels of moisture the active sites in a Prout–Tompkins sense disappear by dissolution somewhat like what happens

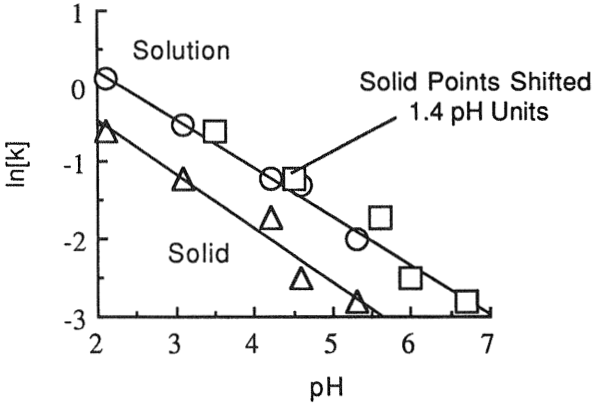

Fig. 9 pH-rate profile of first-order rate constants extracted from kinetics of decomposition of D,L-calcium leucovorin. The squares are points from solid-state decomposition shifted by 1.4 pH units.

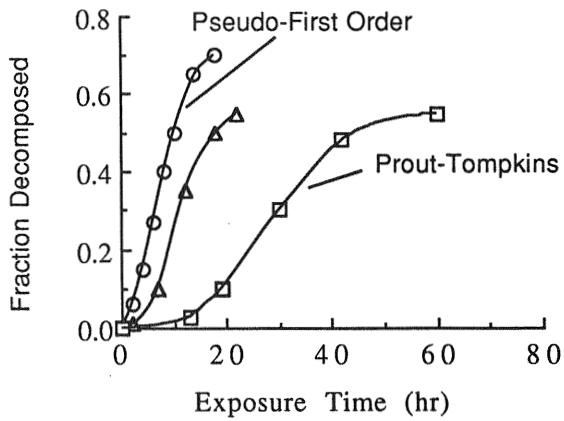

Fig. 10 D,L-calcium leucovorin with moisture and buffers added. ○: 5% water with a pH 2.2 buffer in the solid state (the buffer forms hydrates, and the water contents are percentages added and are not necessarily available moisture); △: intermediate moisture content; □: low moisture content.

in an etch-test of a metal. If one assumes that the aqueous solution is immobile, i.e., that only water molecules adjacent to intact drug molecules take part in the reaction, then first-order kinetics should prevail. One might also, at this level of moisture, consider the surface structure as amorphous, since amorphous substances in the presence of water degrade by first order (Pikal et al. 1977; Morris, 1990). Literature data are insufficient to distinguish if linearity or BET sigmoidness applies for rate constants when they are plotted as a function of relative humidity.

At even lower moisture contents (Fig. 10) the reaction profile takes on a sigmoid nature and can be explained by a surface-interaction model. The sigmoid profiles shown in Fig. 10 adhere well to Eq. (7.3). This can be explained by assuming the moisture to adsorb preferentially at the active sites (Fig. 1B and Fig. 11).

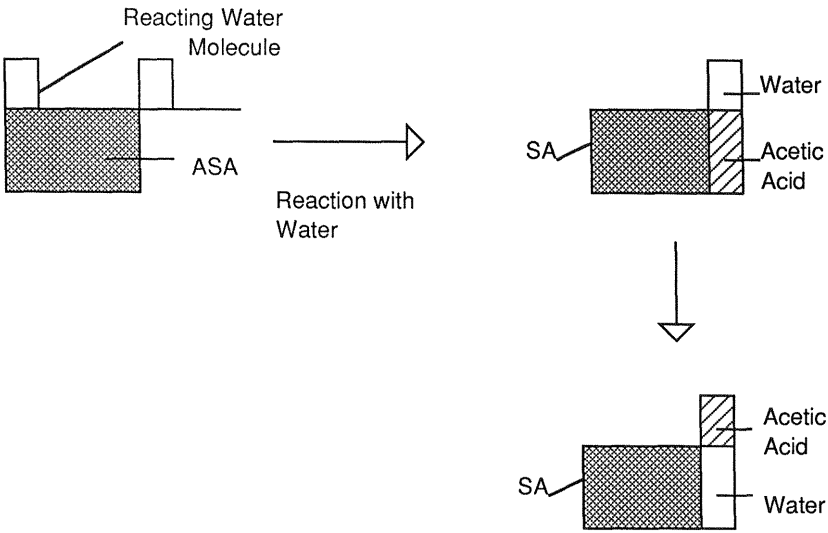

Fig. 11 Surface active site interaction using aspirin as an example. (Graph constructed from model proposed by Attarchi, 1984, and Attarchi and Carstensen, 1988.)

The amount of water does not suffice to "dissolve" the active sites, so the reaction is an interaction between moisture and drug at the activated site. The development of such a model has been published by Attarchi (1984) and Carstensen and Attarchi (1988). The applicable equation is Eq. (7.9):

$$\ln\left[\frac{x}{1-x}\right] = k(t - t_{1/2}) \tag{7.14}$$

The applicable model is presented in Fig. 11. Data plotted in this fashion is shown in Fig. 11, and the rate constants admirably follow an Arrhenius equation as shown in Fig. 12.

Obtaining the actual values of k and S in Eq. (7.2) is not as easy as might seem. As pointed out (and investigated) by Attarchi (1984) and by Carstensen and Attarchi (1988), both k and S are a function of amount of decomposition product. This was first pointed out by Pothisiri (1974), by Pothisiri and Carstensen (1975), and by Wright and Carstensen (1986). It is also a function of ionic strength, as pointed out by Gerhardt (1990) and by Gerhardt and Carstensen (1989), or simply a function of the composition of the sorbed moisture layer (Attarchi, 1984; Carstensen and Attarchi, 1988; Pothisiri, 1974).

8. DOSAGE LEVEL AND TOXICITY CONSIDERATIONS

In a great majority of cases the decomposition is zero order i.e., following Eq. (7.5). This means that the amount of decomposition product is linear in time.

If a product, for instance, is made in three dosage strengths, say 5 and 25 and 50 mg strengths, then after 3 years' storage at 25°C an amount of e.g. 0.075 mg has been decomposed, i.e., (assuming for simplicity equal molecular weights) 0.075 mg of decomposition product has formed (see Fig. 13). Since Eq. (7.5) is a

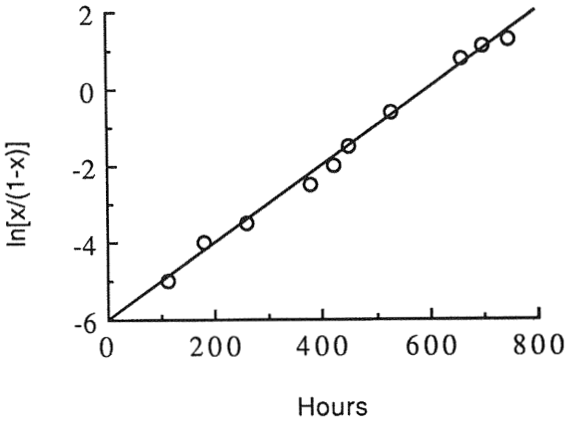

Fig. 12 Plot of aspirin decomposition data in the presence limited amounts (2.5%) of moisture. (Graph constructed from data by Carstensen and Attarchi, 1988.)

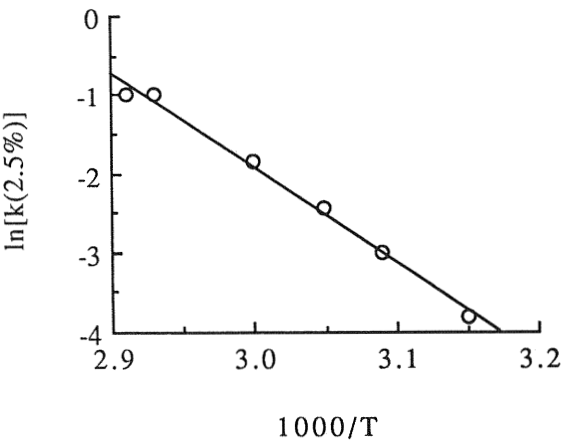

Fig. 13 Arrhenius plot of aspirin decomposition data in the presence of limited amounts of moisture. (Graph constructed from data by Carstensen and Attarchi, 1988.)

zero order reaction, this amount pertains to all the strengths, so that on a percentage basis, the 5 mg strength would have lost $100 \times 0.075/5 = 1.5\%$ of its original value, and hence (presuming an adequate precision and uniformity) would probably not meet the chemical requirement for a 3 year expiration period. The 25 mg and 50 mg strengths would have experienced 0.3% and 0.15% losses, respectively, and would be assumed to be satisfactory from a toxicity point of view.

However, often the decomposition product(s) is (are) unknown and as such are expressed as a percentage of the "main peak" if the method is HPLC (and this is usually the case). If, for instance, for toxicity reasons one assumes that the impurity peak may not exceed 1% of the area under the main peak, then in the above case, the 25 mg and 50 mg strengths would meet toxicity requirements, whereas the 5 mg would not. Nevertheless, the total amount of decomposition product is the

same in all cases. One would assume that it would be the absolute (total) amount of decomposition product that would be of importance, so that expressing the toxicity limitation as a percentage is not appropriate.

In cases where the Leeson–Mattocks model holds (but not in other cases of zero-order reactions), the above dilemma may be prevented by making the smaller dosage forms proportionally smaller, since the term V in Eq. (7.13) then becomes smaller as well.

Regulations are never immutable, and it may well be that at some future date such regulations will be modified to meet the stated need.

9. NONSTOICHIOMETRIC 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.

10. PARENTERAL SOLID PRODUCTS

When an injectable product is insufficiently stable in solution to allow marketing of a ready-made solution, there are still ways to develop a marketed product.

In the far past, there were so-called powder-filled products. Here a solid drug substance was made under exceedingly "clean" conditions so that it emerged from its synthesis as "completely" free of foreign material. In such a case it could be filled into a vial, sterilized by suitable means (heat, ethylene oxide (not used of injectables anymore), or γ-ray sterilization). Excipients used (sodium chloride, for instance) would have to be equally clean, and the practice is not, to the author's knowledge, used much any more.

Aside from the sepsis issue, there was also the problem with rate of dissolution, and from both these aspects, lyophilization offers a better (but probably more expensive) alternative.

10.1. Lyophilized Products

The process is one where a solution of the drug (+ excipients) is made and aseptically filtered. The solution is then aseptically filled into vials, which are loaded into a sterile lyophilization oven. This has cooling coils in its shelves and can be evaluated to very high vacuum.

The vials containing the solution are transferred to the oven, and coolant at very low temperature ($< 30°C$) is flowed through the tray coils. The solution freezes, and then a vacuum is applied of such magnitude (P_v torr) that it is lower than the vapor pressure of ice at the given temperature (P_i torr). This causes the ice to sublime, and then there remains a cake that either is crystalline and has an exceedingly high surface or is amorphous and also possesses a high surface area.

When this, at time of use, is reconstituted with water or diluent, the dissolution is, in both cases, rapid and the "original" solution is regained.

There are two stability issues in this case: (a) how stable is the lyophilized cake and (b) how stable is the solution after reconstruction?

10.2. Stability of Crystalline and Amorphous Lyophilates

It has been seen in Chapters 2 and 3 that a drug product in solution will possess an optimum pH. It is noted that this is accomplished by studying stability of the substance at different pH values, and that these latter are arrived at by the use of different buffers. If, for instance, the drug substance is a weak acid, then approximately speaking one may write

$$k_{obs} = k_0 + k_+[H^+] + k_-[OH^-] + k_{A^-}[A^-] + k_{HA}[HA] + k_{buffer}[HB] \tag{7.15}$$

where HB refers to buffer concentration and k_{HB} is the part of the rate constant attributable to the buffer. It is simplified, because k_{HB} is a combination of two terms, k_B and k_{HB}, but for this purpose it suffices to employ one (or at most two) terms. As discussed in Chapters 2 and 3, drugs mostly are protolytic and partly exist in ionized (A^-) and unionized (HA) form giving rise to the terms involving $k_{A^-}[A^-] + k_{HA}[HA]$, and k_0 is the part of the rate constant, which is neither acid nor base dependent. At lower pH, the term $k_-[OH^-]$ the term falls out, and $[A^-]$ and [HA] are dependent on the pH of the buffer used and of the $pK_{(a)}$ of the acid at the concentrations given. It is recalled that the $pK_{(a)}$ is also a function of ionic strength, the pK_a value being the value of $pK_{(a)}$ from which the ionic effect has been eliminated.

If such a substance in solution is allowed to cool down, then first water will freeze out as ice. The solution, hence, becomes more and more concentrated in both buffer and drug substance, and the pH changes as well. At the eutectic point (or the collapse temperature) all freezes out.

The stability of the substance as the concentrations change of course changes as well, because the buffer concentration changes, because the pH changes, and because the pK of the species in solution changes as well. Hence the optimum manufacturing pH is not the same as that of the corresponding solution. The experimental procedure to use is to make solutions of the desired concentrations of buffer and other excipients at several, say four, different pH values straddling the optimum solution pH, and then produce the lyophilized cake. The stability of this cake is then determined, and the optimum lyophilization pH determined in this manner.

10.3. The Labelling Dilemma of Parenteral Products

The FDA usually takes the strong positional stand that a different "salt form" constitutes a different drug substance and hence a new NDA is required. The drug on the label is the form of the drug in the dosage form. If for instance a product is made with a tetracycline base, then the label must state that this is the source of the antibiotic (as opposed to for instance the use of the addition salt, e.g., the hydrochloride).

But what about a lyophilized product? If one used tetracycline hydrochloride (RHCl) and buffered it at its pK value (at the given ionic strength), then, first

of all, the product would be present one half as positive ion (RH^+), one half as uncharged species (R). If the buffer is denoted HB, then, in concentrating a solution of this there would be two solubility products:

$$S_{RHCl} = [RH^+][Cl^-] \tag{7.16}$$

$$S_{RHB} = [RH^+][B^-] \tag{7.17}$$

aside from the solubilities S_{HB} and S_R. As the solution, hence, starts precipitating substances other than ice at the eutectic point, the species with the lowest S value or solubility product will at first precipitate out. This. for instance, could be RHB. As this precipitates out, both $[RH^+]$ and $[B^-]$ will decrease. At a given point R will start precipitating out. This will prevent further precipitation of RHB, because $[B^-]$ is now sufficiently low to be at the limit, had $[RH^+]$ not been affected. At a given point, because the amount of liquid water decreases as the process continues (freezing out of ice), the solubility limit of either HB or RHCl will be exceeded, and either species will then precipitate out until the remainder is left to freeze out as the last amount of water is solidified at the eutectic point.

The point is that the cake will contain four species: R, RHCl, HB, and RHB. And the question then is, under the present labelling policies, how does one properly label such a mixture?

11. OXIDATION

Oxidations are moisture mediated, as are hydrolyses. Often products that are oxidation sensitive are stored in glass rather than polymer bottles because, however good, these latter still allow permeation of oxygen.

In a glass bottle, if it is considered hermetic, and it often is, the oxygen in the head space will be consumed, and the amount of "initial" decomposition of the produce will tie in with the amount of oxygen available in the head space. It is a common phenomenon that solid dosage forms show an initial loss corresponding to the ratio between the amount of head space divided by the number of tablets in the bottle.

Often the oxygen is used up, and treatment of the data should be such that regression should be carried out on the data points after the *intial* drop.

Example 10.1.

A bottle contains 100 tablets and a head space of 25 mL of air. Each tablet contains 100 mg of drug substance of molecular weight 500. If the nonoxidative decomposition of the drug is 0.1% per month, how much would be expected, on the average, to remain after 3 years? Assume that one O_2 decomposes two drug molecules (i.e., $A + 1/2O_2 \rightarrow AO$).

Answer.

25 mL of air space at 25°C is $25/22.4 = 1.11$ moles of air, containing 22% of oxygen, so that the amount of available oxygen in the headspace is 0.22 millimoles.

This means that $0.22/100 = 2.44 \cdot 10^{-3}$ millimoles of oxygen will decompose an equal molar amount of drug *per tablet*. Each tablet contains $100/500 = 200 \cdot$

Over three years $36 \cdot 0.1 = 3.6\%$ of the drug will decompose by other means, so that a total of $2.4 + 3.6 = 6\%$ will decompose.

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