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The state of water in drug decomposition in the moist solid state: Description and modelling

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Summary

The state of moisture as it is involved in decomposition of drugs in a moist solid state is classified and described. Equations useful for describing such decomposition are discussed in the light of reported experimental data.

Introduction

The effect of moisture on the stability of pharmaceuticals in the solid state is usually visualized as the water being sorbed onto the drug particles as a type of bulk layer, which in turn is saturated with drug (Carstensen, 1977). The decomposition is accounted for almost solely by breakdown of the drug in this layer. This is referred to as the Leeson-Mattocks model (Leeson and Mattocks, 1958; Li Wan Po and Mroso, 1984) and leads to a pseudo-zero decomposition behavior, i.e.

$$M = M_0 - k_0 t \tag{1}$$

where M is the mass of intact drug, t denotes time and k_0 is the pseudo-zero-order rate constant given by:

$$k_0 = k_1 S V \tag{2}$$

S represents the solubility of the drug in the aqueous phase, V is the amount of water and k_1 denotes the rate constant for decomposition of the drug in the aqueous layer. The latter process is often of pseudo-first order, since many decomposition reactions are hydrolyses.

In anhydrous solids, the profile is usually a sigmoid decomposition curve, dictated by kinetics according to the description either of Prout and Tompkins (1944) in the absence of liquid decomposition products or of Bawn (1955) in the presence of one or more decomposition products. The Prout-Tompkins pattern is described by:

$$\ln\left[x/(1-\{x/2x_i\})\right] = k'(t - t_i) \tag{3}$$

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where x denotes the fraction of drug decomposed and x_i is the fraction decomposed at the time (t_i) of the inflection point of the curve. k' is a propagation rate constant and, usually, has a high activation energy.

In Bawn-type kinetics, the first part of the curve can be modelled by:

$$\ln[1 - (A/k'')x] = -k''t \qquad (4)$$

where k'' is the rate constant in the solid phase. At time t^*, at which the last amount of solid disappears, the system becomes a solution system, and the latter part of the curve is pseudo-first order. The two parts of the curve, together, form an S-shaped curve.

Kinetics in the dry versus moist state

Pothisiri (1974) and Carstensen and Pothisiri (1975) have pointed out that if a study is carried out of the decomposition of a moistened drug, as a function of the moisture content, then it is possible to extrapolate the pseudo-zero-order rate constants down to 0% water (anhydrous). The extrapolated value and the extrapolated mechanism differ from those observed in experiments where moisture is excluded (pseudo-zero-order vs sigmoid behavior).

It has become of interest, therefore, to examine the nature of the water in the transition stage between the anhydrous and very moist states, since the models alluded to in the Introduction are the extreme cases of very 'dry' and very 'wet'. The model is depicted in Fig. 1.

Classes of Surface Moisture

The following nomenclature is used for the various situations that may occur:

Limited water Here, water is consumed during the course of decomposition, but the amount of water is insufficient for the complete decomposition of all of the drug present.

Adequate water This corresponds to the situation where the moisture available for the decomposition suffices to react completely with the drug substance.

Excess water This refers to an amount of water equal to, or in excess of, the amount necessary to dissolve the drug (Fig. 1e). This situation may not be present at zero time, but may develop as the mass of intact drug decreases during decomposition. An example of this is described in the work by Morris (1990) and Morris and Carstensen (1991) where the system studied was indomethacin/water at 130°C. After a short storage period, a eutectic (indomethacin/decomposition products/water) is formed, and decomposition from this point on simply follows first-order solution kinetics (Fig. 2). The length of

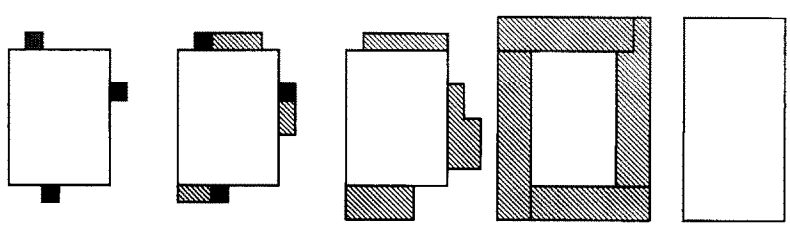

Fig. 1. (a) Anhydrous solid with active sites (cross-hatched); (b) solid with less than monolayer coverage of moisture; (c) solid with more than monolayer coverage, where the active sites have disappeared; (d) bulk sorbed moisture and (e) moisture in an amount sufficient to dissolve completely the solid.

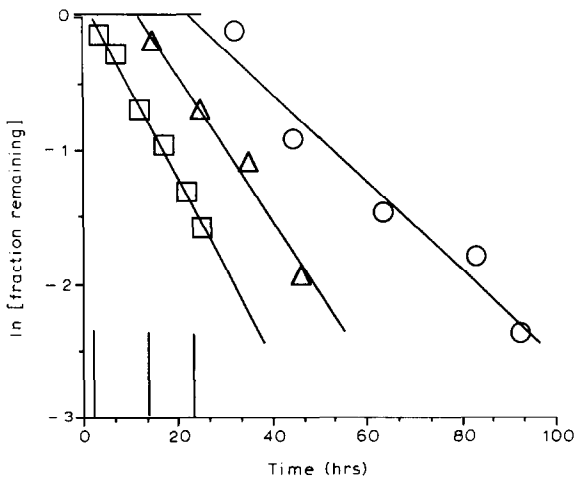

Fig. 2. Decomposition of indomethacin in the presence of moisture at 130°C. Graphs constructed from the data of Morris (1990). For the sake of clarity, only three curves are shown, corresponding to the three relative humidity (RH) values of (○) 60%, (△) 80% and (□) just below 100%.

time (t') required for liquefaction is linearly related to the relative humidity (a) as follows:

$$t' = \beta - q'a \tag{5}$$

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

Other examples of the above have been described in the work by Yoshioka and Uchiyama (1986a,b), Carstensen et al. (1987) and Yoshioka and Carstensen (1990a,b), all relating to propantheline bromide. Carstensen et al. (1987) have introduced the concept of critical relative humidity (CRH) as the point where the relative humidity is just at that of the saturated solution and have shown a shift in mechanism above and below this point. Above the CRH, the decomposition is a combination of (i) dissolution up to the point of complete dissolution, and then (ii) further condensation until the concentration of the now dissolved drug corresponds to the relative humidity of the test station.

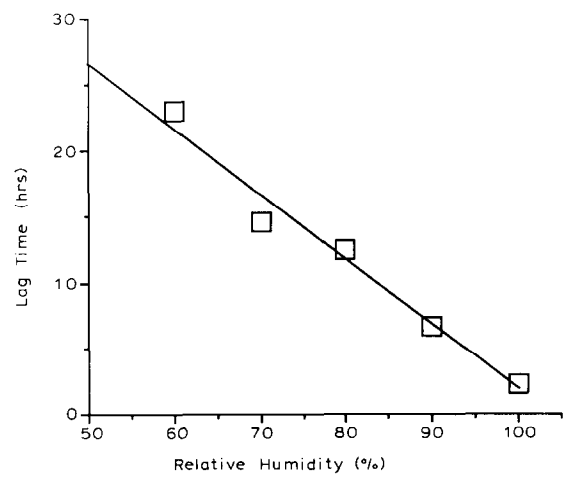

Fig. 3. Lag times (□) from Fig. 2 plotted vs relative humidity.

The Leeson-Mattocks model

This model assumes a *bulk sorbed moisture* layer and corresponds to situation (d) in Fig. 1. It might be argued on thermodynamic grounds that a bulk sorbed moisture layer should not apply until the moisture content is sufficiently high, so that the relative humidity above the solid is equal to or in excess of that of a saturated solution of the drug. This would lead to the conclusion that the Leeson-Mattocks equation would only hold above the CRH, but in fact it does hold, both above and below the CRH. Decomposition of phenobarbital in the presence of phosphate buffer of pH 6.7 at 80°C is an illustration of a case where, during the initial stages of decomposition, the model holds (Gerhardt and Carstensen, 1989). Another example is that reported by Morris and Carstensen (1990b).

The decomposition is governed by Eqn 2, so that knowledge of k_1, V and S should show correspondence between the solid and solution decomposition patterns. This is often the case (e.g., Pothisiri, 1974) but also fails frequently (e.g., Janahsouz et al., 1990).

Carstensen and Attarchi (1988) have pointed out that one way of explaining the discrepancy between decomposition of aspirin in the moist solid state and in saturated solution was to assume a value for the solubility in the solid layer of 3-times that of the bulk solubility. It is possible that the condensed layers of moisture beyond the first adsorbed layer are themselves sufficiently energetic to allow for such an increase.

The point that solubilities may be higher in the sorbed layer, and that a bulk layer should not,

thermodynamically, exist in the region described by Fig. 1d, might tempt one to think of it as being an amorphous state. Such a state would exhibit greater solubility than a crystalline state, and, hence, a lower vapor pressure than the crystalline modification upon which it would be resting, so that, from the viewpoint of solubility as well as of vapor pressure, the dilemma of the critical moisture content would be solved.

A further expansion of this is the thought that the water dissolves in the solid (Ahlneck and Zografi, 1990). This would undoubtedly be true for truly amorphous compounds, but for crystalline compounds it would necessitate loss of crystallinity, an assumption which has not been shown to hold. If, indeed, the moisture formed a 'hot spot' of amorphous material on the surface of the crystal, then at a given relative humidity the amount of moisture ad/absorbed would correspond to the amorphate/water composition in equilibrium at the given moisture activity. Carstensen and VanScoik (1990) have shown that, for small molecules such as sucrose, the moisture activities over such 'supersaturated' solutions are simply an extension of those of saturated and unsaturated solutions. Whether one desires to think of this as water dissolved in the solid or solid dissolved in the water is less important than the linear relationship between the amount sorbed and the water activity assuming ideality. It should be noted that for high molecular weight polymers, *S*-shaped isotherms apply (e.g., microcrystalline cellulose as reported by Marshall et al. (1972) and Holenbeck et al. (1978)).

Therefore, if an amorphate hypothesis held in the systems studied and reported here, then the pseudo-zero-order rate constants should be approximately linearly related to the relative humidity of the study. Fig. 4 shows data reported by Morris and Carstensen (1990a,b) in which crystalline indomethacin was allowed to decompose at different relative humidities. The data obviously fit a pseudo-zero-order profile, but when the rate constants are plotted vs relative humidity, a straight line does not ensue (Fig. 4). One cannot prove the validity of a model by curve fitting (Mroso et al., 1982; Li Wan Po et al., 1983), but an unsuitable model can be eliminated

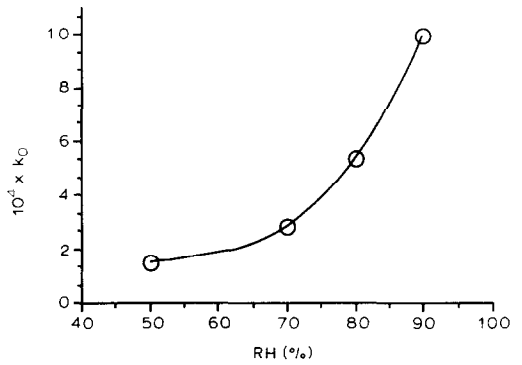

Fig. 4. Data from Fig. 2. Pseudo-zero-order rate constants plotted as a function of relative humidity.

on the basis of a lack of fit. It should be cautioned that there could be non-ideality in the system, but the deviation from linearity shown in Fig. 4 is quite drastic.

However, studies in the moisture range, studied by Morris and Carstensen (1990a,b), show that the kinetics are related to BET (or other non-linear) isotherms. The amount of moisture adsorbed during a process modelled by a BET isotherm (with high c value) would follow the equation:

$$V = v_m/[1 - a] \qquad (6)$$

where v_m is the volume of a monolayer, and a represents the water activity (i.e., the relative humidity divided by 100). Hence, the k_0 value should be linear when plotted vs $\{1/[1 - a]\}$ for the case of the bulk-water model. Data plotted in this fashion are shown in Fig. 5.

It would appear, therefore, at least for the systems tested, that *the amorphate model is unnecessary*. Furthermore, during the study conducted by Morris (1990), amorphous indomethacin was investigated in the presence of moisture, but the conversion to the crystalline form was so rapid that kinetic data could not be gathered. In practical systems therefore, the sorbed layer indeed acts as a bulk solution and the decomposition products affect (i) the solubility of the drug, (ii) the kinetic parameters for the decomposition of the drug and (iii) since the decomposition products themselves are solutes,

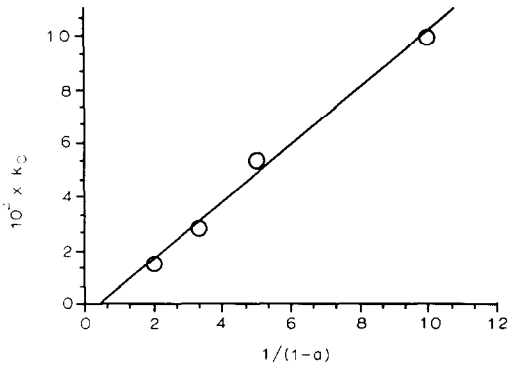

Fig. 5. Rate constants derived from plots of the type shown in Fig. 2, plotted as a function of the BET isotherm parameter, $1/\{1-(1/a)\}$. Equation for curve fit: $y = -0.46550 + 1.0585x$, $r^2 = 0.991$.

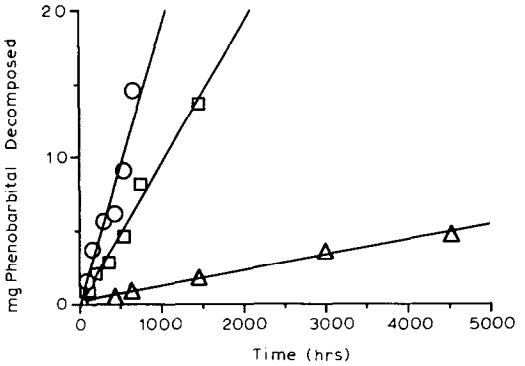

Fig. 6. Decomposition of phenobarbital in the solid state at 80°C, in the presence of phosphate buffer of pH 6.7. For purposes of clarity, only three of seven moisture levels are shown. (△) 27 μl H_2O (equation for curve fit: $y = 0.13083 + 1.0762e-3x$, $r^2 = 0.993$); (□) 45 μl H_2O (equation: $y = -0.14400 + 9.6594e-3x$, $r^2 = 0.989$); (○) 58 μl H_2O (equation: $y = -0.20315 + 1.9206e-2x$, $r^2 = 0.934$).

they decrease the water vapor pressure above the sorbed layer so that the vapor pressure criterion is not violated. Gerhardt and Carstensen (1989) and Gerhardt (1990) have shown that salting-in and kinetic salt effects can account for the decomposition profiles that phenobarbital exhibits in the presence of moisture and buffers. Carstensen and Pothisiri (1975) and Wright and Carstensen (1986) also accounted for kinetic phenomena by postulating salting-in and salting-out effects.

For soluble drug substances, the amount of water needed to reach the CRH is quite small (i.e., the relative humidity over the saturated solution is low). Conversely, for poorly soluble drugs the CRH is quite high.

Kinetically unavailable (bound) water

The observed pseudo-zero-order rate constants frequently obey Eqn 2, i.e., they are directly proportional to the amount of water in the dosage form. Fig. 6 shows data reported by Gerhardt (1990) and Gerhardt and Carstensen (1989). The plots of the pseudo-zero-order rate constant vs moisture content (Fig. 7) in this case have a positive x-intercept, i.e.

$$k_0 = k_1 S[V - w^*] \qquad (7)$$

where w^* is referred to as kinetically unavailable or *bound moisture*. This phenomenon appears to occur in many cases. The bound water, for instance, may be water of crystallization. In the case of dl-calcium leucovorin, reported by Nikfar et al. (1990a,b), intermittent plateaus occur in such graphs, corresponding to a constant relative humidity over a range of moisture contents, i.e., to a salt pair. $[V - w^*]$, whether or not accountable for stoichiometrically, is referred to as the kinetically available, or simply the *available moisture*.

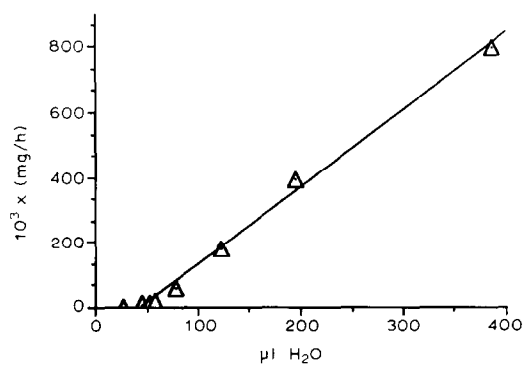

Fig. 7. Pseudo-zero-order rate constants from plots of the type in Fig. 6 as a function of added moisture. Graph constructed from the data reported by Gerhardt (1990). Equation for curve fit: $y = -107.05 + 23759x$, $r^2 = 0.993$.

Microenvironmental pH

Solid dosage forms are often formulated with solid acids (e.g., citric acid) or bases (e.g., sodium carbonates) to adjust 'the microenvironmental pH'. In the region exemplified by Fig. 1c–e, it is possible to 'buffer' a solid dosage form and the 'solid pH-profile' parallels but does not coincide with the traditional solution pH-profile as shown by Nikfar (1990), Nikfar et al. (1991) and Gerhardt (1990). This again is an indication that the layer should be thought of as having solvent properties.

The question as to how to define the microenvironmental pH has not been fully resolved as yet and is presently under investigation. The difference in the position of the solution kinetic pH profile and the values extracted from solid-state data may be due to the fact that the pH value used for plotting of the moist solid is assumed to be that of a saturated buffer solution. However, the sorbed solution may have a pH value which is shifted away from that observed in solution. It is observed in Fig. 8 (Nikfar, 1990; Nikfar et al., 1991) that a shift of 1.4 pH units for the solid-state rate constants (the shifted values being represented by squares in the figure) would make the solution and solid-state kinetic data coincide. In the work by Gerhardt (1990), a shift of 6 pH units would be required to achieve coincidence, so there are undoubtedly other factors involved as well. For example, Li Wan Po et al. (1983) have shown that, in the presence of excess water, the bulk pH fully accounted for the observed decomposition profile of salsalate.

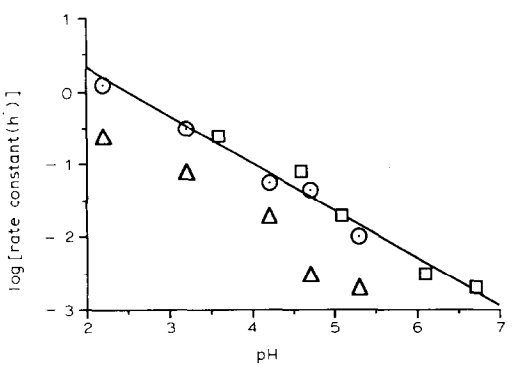

Fig. 8. Kinetics of decomposition of dl-calcium leucovorin: (△) in the moist solid state; (○) in solutions saturated in drug and buffer and in the solid state; (□) in the solid phase, assuming that the pH in the sorbed layer is 1.4 units higher than in a saturated solution of buffer and drug. The moist samples are taken from the range of moisture contents where the buffers form a double-salt pair. Equation for curve fit: $y = 1.6299 - 0.65417x$, $r^2 = 0.975$.

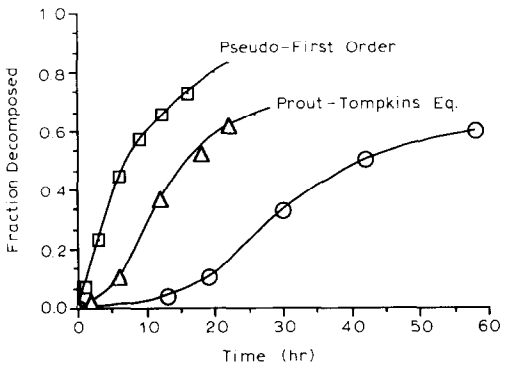

Fig. 9. Decomposition of dl-calcium leucovorin in the presence of moisture and buffers. (△) 5% moisture in the presence of a pH 2.2 buffer in the solid state; (○) 10% at pH 2.2; (□) 15% at pH 4.2. It should be noted that the buffer forms hydrates, and the percentages do not represent available moisture.

Very low moisture contents

This is the case depicted in Fig. 1b and c. The term *immobile water* has been suggested for the situation in Fig. 1c by Nikfar (1990) and Nikfar et al. (1991) who have shown that here the decomposition profile becomes *pseudo-first order* (Fig. 9). At this level of moisture, it is assumed that the active sites have disappeared through dissolution. If the solution is assumed to be immobile, i.e., only water adjacent to intact drug participates in the decomposition, then the model leads to first-order kinetics.

Alternatively, at this moisture level, it is possible to view the surface structure as amorphous, since amorphous substances containing water decompose in first-order fashion (Pikal et al., 1978; Morris, 1990). In this case, the reported data do not suffice to distinguish between linearity or the BET sigmoid profile when rate constants are plotted vs relative humidity.

As the moisture content is lowered even further (Fig. 9) the decomposition profile becomes sigmoid and is explicable by a *surface-interaction* model. The sigmoid curves in Fig. 9 are modelled well by Eqn 3. This behavior may possibly be accounted for by the assumption that the moisture preferentially adsorbs at the active sites (Fig. 1b). The amount of moisture is not sufficient to dissolve the active site, and the reaction is one of surface interaction between moisture and drug molecules at activated sites. The development of such a model has been described by Attarchi (1984) and Carstensen and Attarchi (1988).

Salting in and out

Assessing the actual values for k and S in Eqn 2 is not straightforward, since both k and S can vary as a function of the amount of decomposition product (Pothisiri, 1974; Carstensen and Pothisiri, 1975; Wright and Carstensen, 1986), ionic strength (Gerhardt, 1990) or simply sorbed layer composition (Pothisiri, 1974; Attarchi, 1984; Carstensen and Attarchi, 1988).

Conclusions

The amount of moisture sorbed onto a solid determines to a considerable extent not only the rate, but also the (reaction order) of the decomposition process. A rational subdivision of the states of the moisture is suggested in this article.

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