DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(15), 2267-2281 (1990)

EFFECT OF MOISTURE ON SOLID DOSAGE FORMS. CAN THE ARRHENIUS EQUATION BE USED AS A PREDICTOR?

J.T.Carstensen*, A. Gerhardt, T.Morris, and F.Nikfar,
School of Pharmacy, University of Wisconsin, Madison WI 53706.

ABSTRACT

It is shown that for pure (organic) solids, the Arrhenius equation is valid, except it may be difficult to elucidate the rate controlling parameter andor the predominant mechanism. The two most predominant mechanisms are Prout-Tompkins and Bawn kinetics.

One aspects of kinetic investigations is to extrapolate so-called accelerated data (e.g. elevated temperature data), to other temperatures (e.g. room temperature). In such cases the Arrhenius equation is usually resorted to, but it is necessary, always, to establish the correct mechanism, extract from it the pertinent, rate-controlling parameters, and extrapolate *these* to room temperature. At times it is possible to obtain phenomenological parameters which can be extrapolated.

In cases where solids are stored in the presence of moisture there are several subdivisions (a) cases where the moisture is in excess (plain Leeson-Mattocks model of non-ionizing substance) (b) cases where some of the moisture present is "bound", i.e. not free to react, (c) the case of less than molar ratios of moisture to drug, (d) the case of adsorbed moisture, (e) the case of drug hydrates/anhydrate pairs.

Presented at the Royal Society of Chemistry Meeting in Belfast, Faraday Society, Tuesday April 10, 1990.

*To whom inquiries should be directed.

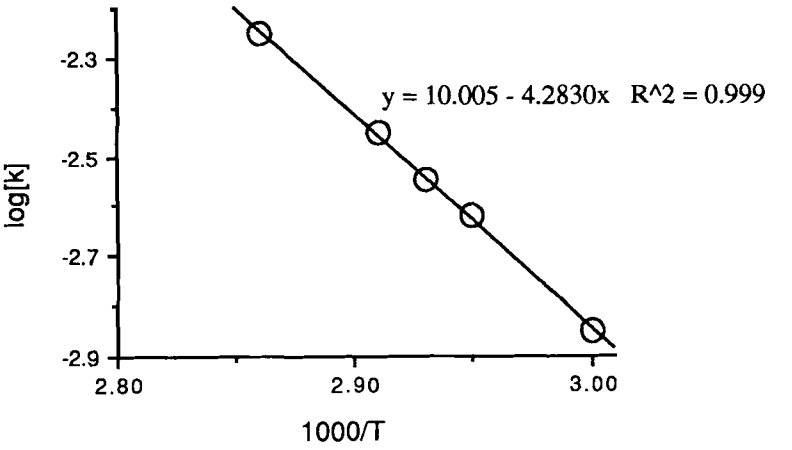

Fig. 1. Arrhenius plot for p-aminosalicylic acid. (Carstensen and Pothisiri, 1975)

PURE SOLIDS

If a pure solid is stored at a given temperature, T°K, then its decomposition can be broadly characterized by two mechanisms: (a) one where the decomposition products are not liquid and (b) one where at least one of the decomposition products is liquid. In case (a) the so-called Prout-Tompkins (Prout and Topmpkins, 1944) kinetics apply, and in case (b) so-called Bawn kinetics apply (Bawn, 1955). Prout-Tomkins kinetics are characterized by S-shaped curves adhering to the following equation,:

$$\ln[x/(1-x)] = -k\{t-t_i\} \qquad \text{(Eq. 1)}$$

where x denotes fraction decomposed. The equation as written assumes that the inflection point in the S is at x=0.5 (which is most often the case). This occurs at time t_i. The equation can easily be expanded to include inflections at other time points. Fig. 1 shows that k adheres well to Arrhenius treatment (Carstensen and Pothisiri, 1975).

Studies of this type are done *in-vacuo*, i.e. a state of purity of environment solely designed to study the mechanism. More realistic storage, as shall be dealt with below, involves exposure to oxygen and moisture.

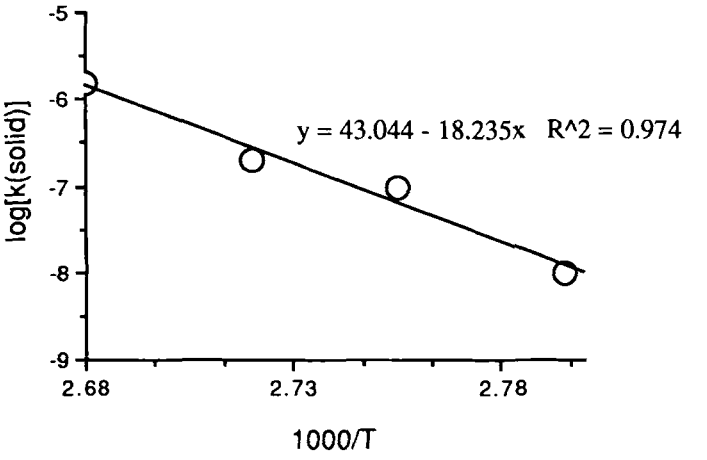

Fig. 2. Arrhenius plot of k_s for alkoxyfuroic acid (n=14) (Carstensen and Kothari, 1981)

In Bawn kinetics, the decomposition of the parent compound occurs both in the solid state and in solution (in the decomposition liquid), and the first part of these curves adheres to an equation of the type:

$$\ln[1+Ax] = k_s t \qquad \text{(Eq. 2)}$$

where A is an adjustable parameter:

$$A = k_1 S - k_s S - k_s \qquad \text{(Eq. 3)}$$

where k_1 is the rate constant of the parent compound in solution in the decomposition product, S is its solubility in the decomposition product, and k_s is an (assumed) first order decomposition rate constant in the solid itself.

Again, in systems of this type, Arrhenius kinetics are well adhered to as seen in Fig. 2.

The distinction between the two situations is sometimes vague, e.g. at higher temperatures p-aminosalicylic acid becomes a Bawn-reaction. This is best illustrated by a eutectic diagram (Fig. 3). There is a change in the mechanism at the eutectic temperature.

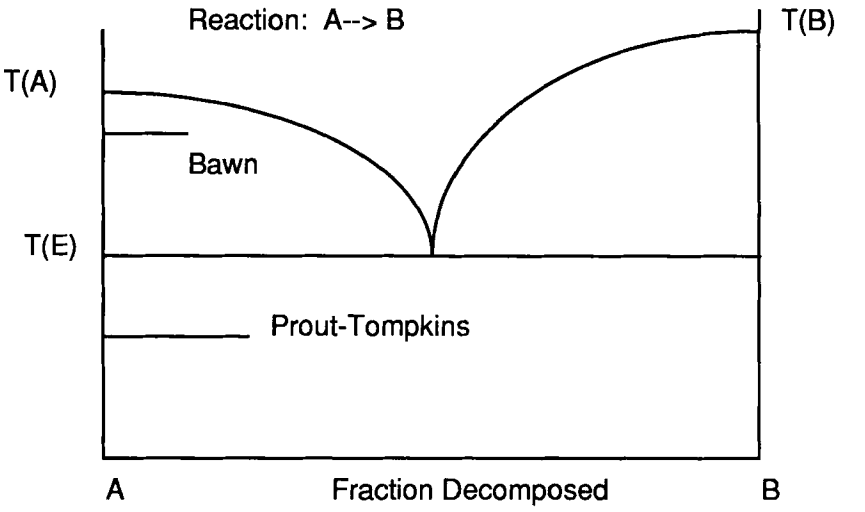

Fig. 3. Distinction between areas of Prout-Tompkins and Bawn kinetics

Both Prout-Tomkins and Bawn kinetics apply only to reactions that are sufficiently rapid to be followed below the melting point. Frequently the activation energies are high, so that there is only a very narrow temperature range, T_b-T_h ,in which the reaction can be studied: below T_b the reaction is too slow to be followed in a reasonable experimental interval, and above T_h it is too fast to monitor. Such intervals are frequently what is referred to as a decomposition range in tables of e.g. melting points.

AMORPHOUS COMPOUNDS.

Whereas Prout-Tompkins is based on reactions initiated in the surface, amorphous compounds represent a different picture. Carstensen and Musa (l972) and Pothisiri and Carstensen (l975) showed that for a series of p-substituted benzoic acids the reaction rate increased with increasing Hammett σ–value (i.e. the reaction parameter, ρ, was positive), whereas for p-substituted salicylic acids the reaction rate decreased with increasing Hammett σ–value (i.e. the reaction parameter, ρ, was negative). Although this is trend indicating only, the difference between the two groups lies in the fact that the former crystallizes with molecular

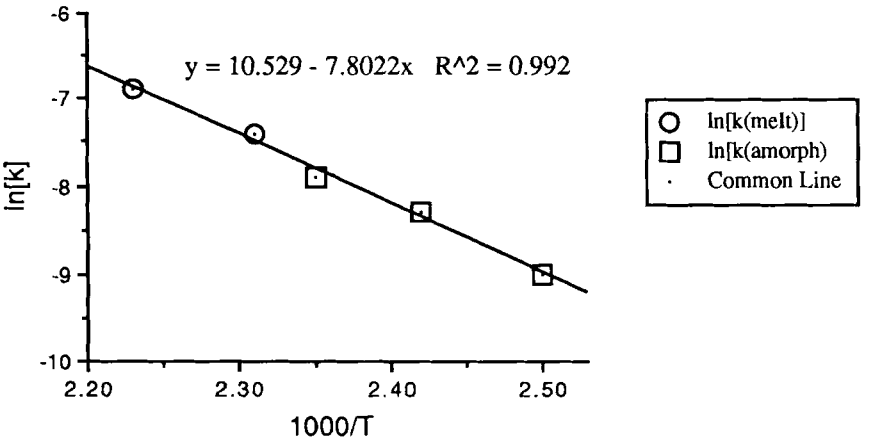

Fig. 4. Arrhenius plot of amorphous and melted indomethacin.

entities at each lattice site, whereas the latter crystallizes as twins. In the former case there is, therefore, the possibility of intermolecular interaction (e.g. between the parasubstituent and the carboxylic acid group), whereas in the latter the interaction is presumably between two molecules in a dimer. For amorphous indomethacin, plots of fraction decomposed, x, versus time, t, are quite linear (pseudo-zero order), so that the reaction can be assumed not to be a surface reaction.

If a substance is in an amorphous state above the glass transition temperature, then there should be fairly random orientation of the molecules, and intermolecular interaction should be more favored than in a crystalline state where the molecules are favorably aligned. (If they are unfavorably aligned in the crystal, then the amorphous compound could, conceivably be more stable than the crystalline). Morris has shown that for indomethacin, the decomposition rate constants for amorphous material lies on the same Arrhenius line as the melt (Fig. 4).
and that, hence, this is one more property (other than e.g. heat capacity), where the glass has a liquid-like structure, rather than a solid-like structure.

SYSTEMS WITH MOISTURE PRESENT

Real life systems are characterized by the presence of moisture and oxygen (air). The effect of moisture is characterized by three regions

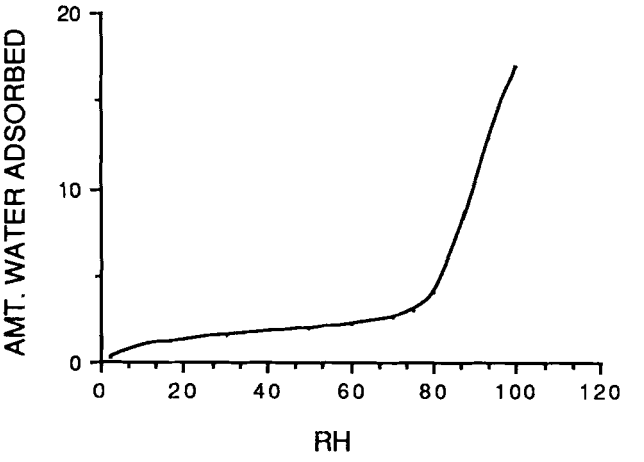

Fig. 5. Typical BET-isotherm.

of moisture content: (a) sorbed moisture (i.e. small amounts of moisture), (b) semi-bulk amounts of moisture (denoted modest amounts in the following). In this case, for instance, if a drug is subject to hydrolysis there would be insufficient moisture to decompose all the solid , and (c) bulk-moisture amounts, where there is a larger number of moles of moisture than drug present.

SORBED MOISTURE MODELS.

If a small amount of moisture is present with the decomposing organic substance in a closed system, then part of the moisture will be in the atmosphere above the solid, part of it be adsorbed onto the solid. This type of adsorption is usually governed by a BET-isotherm (Fig. 5).

The (abbreviated) equation for the BET-isotherm is:

$$RH/[V\{100-RH\}] = (1/V_m)(RH/100) \qquad \text{(Eq. 4)}$$

V is volume (STP) adsorbed, V_m is the volume (STP of a monolayer. If sufficiently small amounts of water is present in the system so that the layers about the solid are of the molecular layer order of magnitude, i.e. there is fractional to triple or quadruple coverage, then Eq. 4 should govern the amount of moisture present on the surface, and should therefore govern the kinetics. Fig. 6 shows data by Morris (l990) for indomethacin.

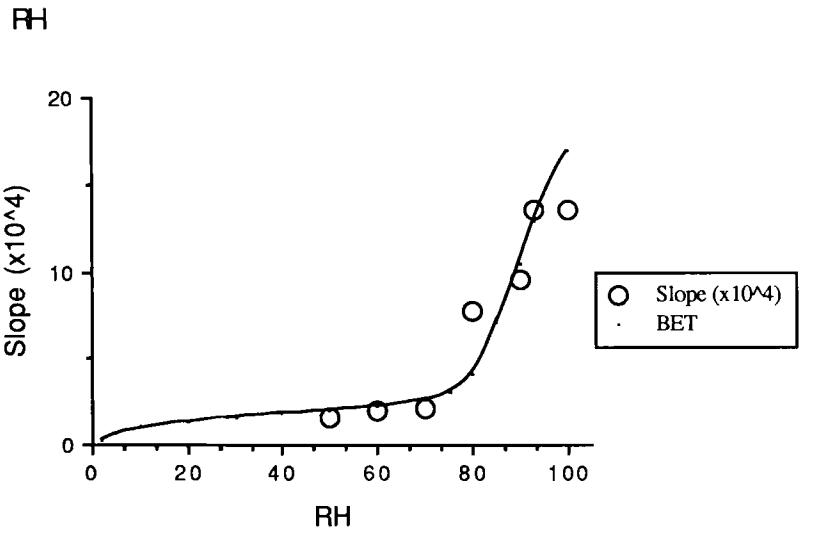

Fig. 6. Indomethacin decomposition at different RH values.

If a solution/suspension rate constant (as shall be discussed shortly) is inserted in Eq. 4, then this equation becomes:

$$k = \alpha/[100\text{-}RH] \qquad \text{(Eq. 5)}$$

Data treated in this manner are shown in Fig. 7.

To treat data of this type by Arrhenius equations, one given coverage would have to apply at all temperatures. Hence for such studies to be completely rational, adsorption isotherms should be known at all the test temperatures. The compound should be stored over a suitable salt/saturated salt solution giving the reuqired RH for the coverage being studied.

THE LEESON-MATTOCKS MODEL

The oldest model dealing with the subject of moisture effects on kinetics in the solid state is that of Leeson and Mattocks (l958). These authors suggested that moisture may be considered a bulk layer about the drug particles. The decomposition is then one of the decomposition of the

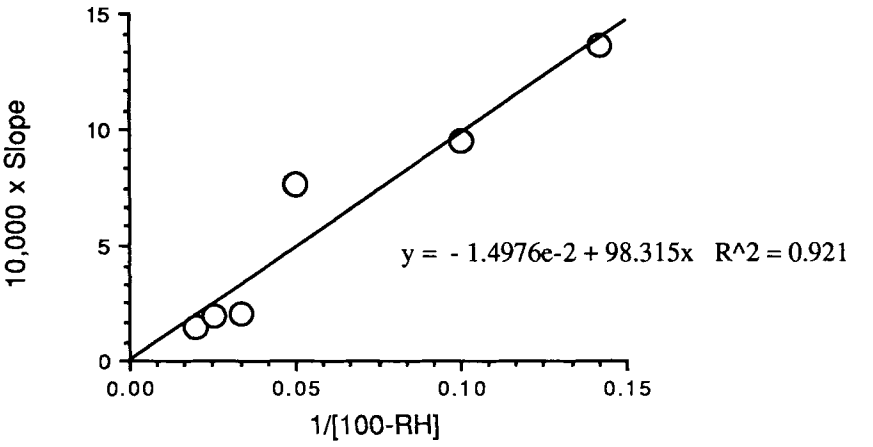

Fig. 7. Data from Fig. 6 treated by Eq. 5

drug in (saturated) solution in this layer, a sort of very concentrated suspension, and leads to the conventional suspension equation:

$$M = M_0\text{-}kt \qquad \text{(Eq. 6)}$$

where

$$k = k_1 SV \qquad \text{(Eq. 7)}$$

k_1 is the pseudo-first order rate constant of a solution, S is solubility, and V is the amount of water. Many systems exhibit the pseudo-zero order relationship predicted by Eq. 6, (e.g. phenobarbital, Gerhardt and Carstensen, 1989) as shown in Fig. 8.

Such graphs, particularly at lower moisture contents, are quite linear, and often the rate constants of preparations made with different moisture contents (V) show decomposition rate constants that are directly proportional to the amount of moisture present.

In some cases some of the moisture is bound, and the rate constants are linear in added moisture with a positive x-intercept, which represents the bound moisture. This can be the case with both salt hydrate excipients and polymer excipients (e.g. microcrystalline cellulose). It is obvious that it is important whether the moisture is bound as water of hydration or not.

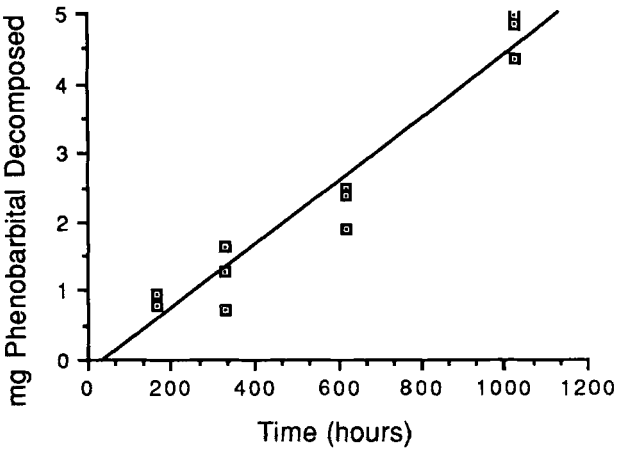

Fig. 8. Decomposition of phenobarbital in the presence of sodium diphosphate

For accelerated studies, the compoiunds should be kept in hermetically sealed containers. Since an excess of moisture is present in this situation, the saturation of the headspace at the higher temperatures is not significantly mass consuming. (A calculation via the ideal gas law to assure this should always be done. It is, for instance, a function of the size of the container). Hence V in Eq. 7 is fairly invariant.

Arrhenius plotting is often possible in these situations, but it is noted that the slope is not simply the activation energy, E, but the sum of this and the head of solution, ΔH:

$$\ln[k] = -[(\Delta H+E)/R](1/T) + q \qquad \text{(Eq. 8)}$$

In the case of very soluble hydrates, small amounts of water will completely dissolve the buffer system. In such cases (or in cases where one buffer species is dissolved and the other not), the correlation between pseudo-zero order rate constant and water content can be shown to be of a log-log nature, as shown in Fig. 9.

HYDRATES

A different situation may exist for hydrate-forming organic compounds, as pointed out by Mooney (l988) and by Carstensen (l987). Fig.

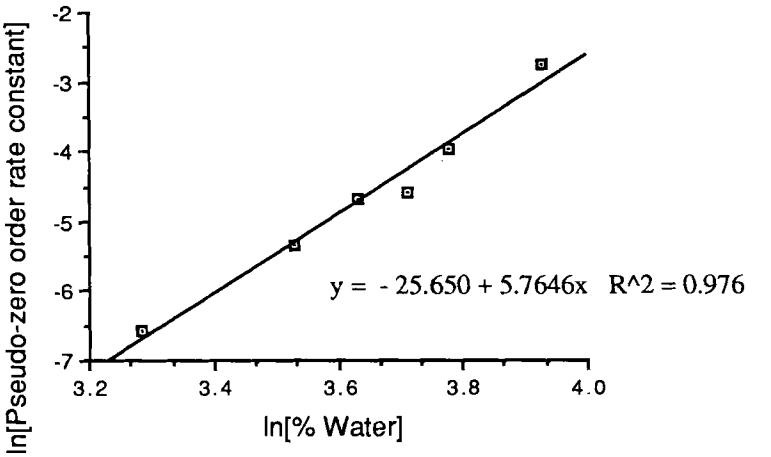

Fig. 9. Pseudo-zero order rate constants for the solid state decomposition of phenobarbital in the presence of disodium phosphate and different amounts of moisture.

10 shows an example of a drug hydrate which is assumed to exist as an anhydrate and as an x-hydrate.

The stability humidity range for the x-hydrate would be represented by the vertical line. The length of this vertical line decreases as temperature increases, and at a given temperature, T*, becomes zero. Here there is then a triple point with zero degrees of freedom. If the critical temperature, T*, is exceeded, then the x-hydrate cannot exist at all. At lower temperatures it may exist within the relative humidity range limited by the vertical line. Above T*, hence, the "bound" moisture is released, and is available for reaction. Hence accelerated studies for drug substances which form hydrates must be carried out such that the relative humidity is within the stability range of the hydrate.

A notable example of an excipient of this type is dicalcium phosphate dihydrate for which the critical temperature, T*, is 40-42°C. Above this temperature, hence, all the water of crystallization will be given up, and be available for decomposition, and studies carried out for moisture sensitive compounds above 45°C will therefore be unfavorably biased, showing degress of decomposition (high V in Eq. 7) which would never apply at 25°C.

Cephalosporins usually exist as stable hydrates and unstable anhydrates. The latter are often amorphous. A "stabilizer" in such

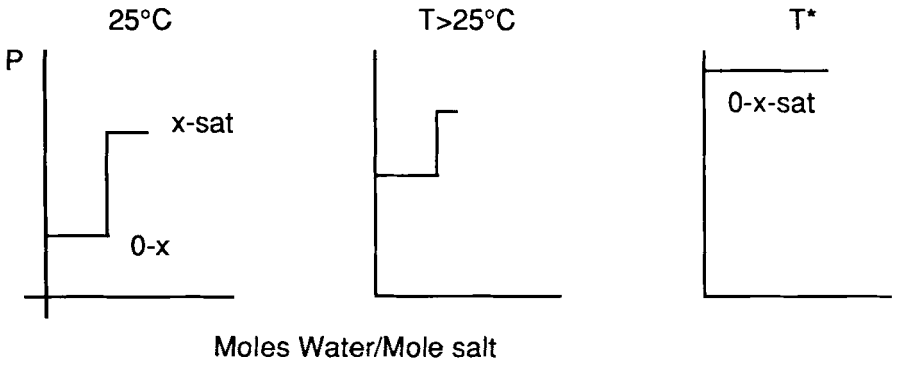

Fig. 10. Salt hydrate water vapor pressure curve at different temperatures

systems is a salt or double salt multiyhydrate, which furnishes the correct relative humidity for the drug at all the test temperatures.

MODEST AMOUNTS OF MOISTURE.

In most model systems, moisture is added in quite large quantity. If it is added in less than molar equivalents of the drug, then the Leeson-Mattocks equation often fails. First of all (e.g. aspirin), if the moisture is used up in a hydrolysis, then the quantity, V, in Eq. 7 is no longer constant. Furthermore, S may be altered if the bulk layer is altered. In the case of aspirin, the layer becomes richer and richer in acetic acid and less and less moisture is present, so that Eq. 2, now becomes:

$$k = k_1(t)S(t)V(t) \qquad \text{(Eq. 9)}$$

where "(t)" denotes function of time. This point which has been elaborated on by Yoshioka (l990). Suffice it here to say that curves calculated from Eq. 3 do not coincide with experimental data, and that a surface reaction model, treatable by a Prout-Tompkins-like equation is more likely. This gives rise to curves such as shown in Fig. 11.

The curves can be linearized by plotting ln[x/(1-x)] versus time in the same manner as Prout-Tompkins reactions.

Once this is known, it is possible to treat the data by an Arrhenius equation, as shown in Fig. 12. One might now ask, whether

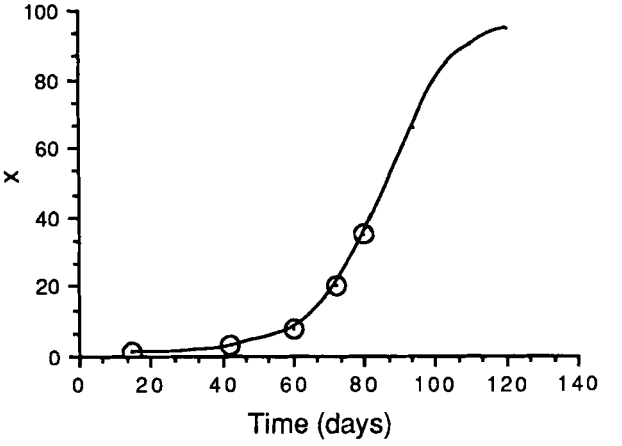

Fig.11. Decomposition of Aspirin with 10% added moisture. Data from Carstensen and Attarchi (l988)

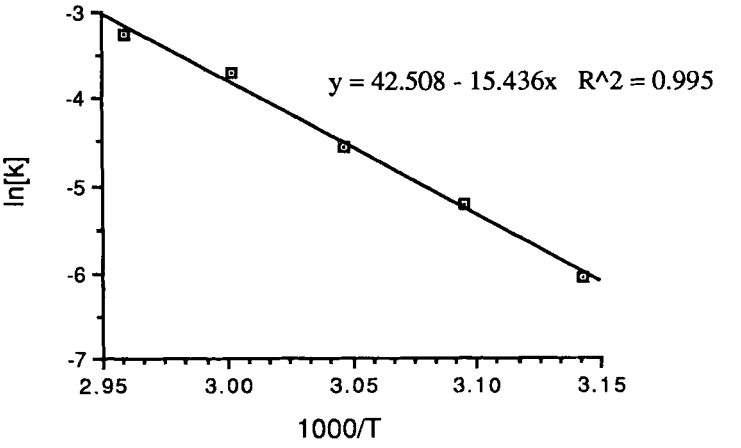

Fig.12. Arrhenius plot of aspirin data treated by surface model (Eq. 4). Data from Carstensen and Attarchi (Table I)

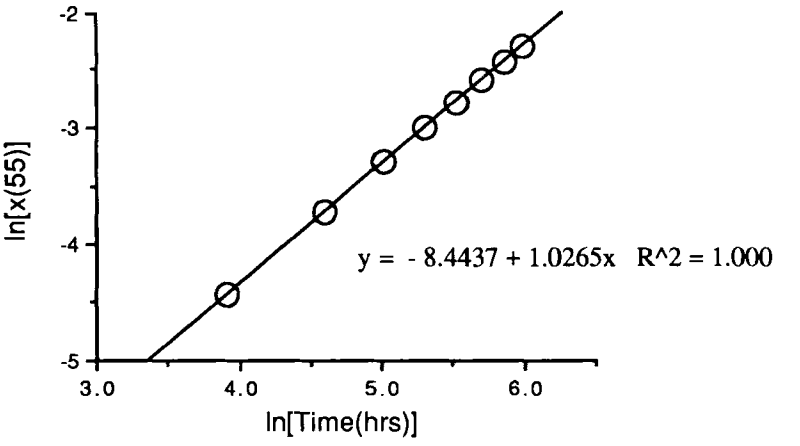

Fig. 13. Initial data points of the type in Fig. 5 treated in a log-log fashion. Data generated from the equation:
x = [exp{-0.00236(t-500)}/(1+exp{-0.00236(t-500)})] - 0.24

phenomonological treatment of the data by an empirical equation and extrapolation to room temperature, would result in a reasonable extrapolated answer.

THE YOSHIOKA EQUATION

The data in Fig. 2 are represented by:

$$\ln[x/1-x] = -kt \quad \text{or} \quad x = \exp(-kt)/[1+\exp(-kt)] \qquad \text{(Eq. 10)}$$

This can be approximated by many functions, e.g. power functions as suggested for empirical fitting, e.g. in the F.D.A. Guidelines (1987). One such power function (Yoshioka and Uchyiama, 1988a, 1988b, Yoshioka, 1990) would be:

$$y = a(x)^n \qquad \text{(Eq. 11)}$$

where a is a type rate constant, and n is a reaction parameter. If data of the type reported by Carstensen and Attarchi (1988) in Fig. 4 had simply been known at shorter time points (as represented by the open circles) and not by later time points, then they could be treated by Eq. 11 and data of the type in Fig. 13 would result.

SUMMARY

1. It is shown that for pure crystalline solids that do not form liquid decomposition products, the general decomposition scheme is by Prout-Tompkins kinetics, and that rate constants from this can be extrapolated to other temperatures.

2. If a liquid decomposition product is formed, then Bawn kinetics prevail, and again Arrhenius treatment is possible.

3. Amorphous materials presumably decompose in the same fashion as the melt of the compound

4. The case of moisture present results in three distinct cases: (a) sorbed moisture, where Arrhenius plotting would require storage at each temperature at a given relative humidity, (b) modest amounts of moisture where Prout-Tompkins like kinetics or Yoshioka kinetics apply, and where extrapolations are possible, once the correct parameters are extracted from the data, and (c) bulk sorbed moisture layers, where Leeson-Mattocks kinetics apply, and where, in most cases, Arrhenius extrapolations are quite good.

5. Oxidations and interactions have not been covered in this paper.

REFERENCES

Bawn, C. (1955) "Chemistry of the Solid State,", ed. Garner, p. 254, Academic Press, N.Y.
Carstensen, J.T. and Musa, M.N. (1972), J.Pharm.Sci., 61, 273, 1112
Carstensen, J.T. and Pothisiri, P., (1975), J.Pharm.Sci., 64, 37
Carstensen, J.T. and Kothari, R., (1981), J.Pharm.Sci., 70, 1095
Carstensen, J.T., (1986). Pharmaceutical Technology, Sept. 1986, pg. 98
Carstensen, J.T. and Attarchi, F., (1988), J.Pharm.Sci. 77, 318
Food and Drug Administration, Silver Springs, Md, U.S (1987).: Guidlines for the submission of stability data for new drug applications.
Gerhardt, A. and Carstensen, J.T. , (1989). The effect of buffers on solid state stability. Pharmaceutical Research 6, S-142
Leeson, L. and Mattocks, A., (1958) J.Am.Pharm.Assoc.,Sci.Ed., 47, 392
Mooney, G., (1988), Proc. 7th Wisc. Update Conference, Extension Services in Pharmacy, Univ. Wisc. Madison, WI 53607, pg. 263
Morris, Tommy, Ph.D. Thesis, University of Wisconsin, Madison, 1990

Morris, Tommy, and Carstensen, J.T. (1990) The Effect of Moisture on the Stability of Indomethacin, Pharmaceutical Research, submitted.
Nikfar, F. Ph.D. Thesis, University of Wisconsin, Madison, 1990
Nikfar, F. and Carstensen, J.T., (1990). The effect of buffers on solid state stability. Pharmaceutical Research, submitted.
Pothisiri, P., and Carstensen, J.T., (1975), J.Pharm.Sci., 64, 1931
Prout, E. and Tompkins, F. (1944), Trans. Faraday Soc., 40, 448
Yoshioka, S. and Uchiyama, M., (1986), J.Pharm.Sci., 75, 92, 459
Yoshioka, S., (1990), Annual Chemical Congress, Belfast, Ireland.