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STABILITY OF SOLIDS AND DISPERSE SYSTEMS

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ABSTRACT

The stability of solids and semisolid dosage forms is characterized by either being a stability of the drug per se, in which case one of the phases of Prout-Tompkins equation holds (leading to either pseudo-first or pseudo-zero order reactions) or by being an interaction. For interactions with water in small amounts, or with trace reactants, an equilibrium is reached. When larger amounts of water are present, then Leeson-Mattocks kinetics hold, and a pseudo-zero order reaction applies.

INTRODUCTION

In the text to follow, the following symbols will be used. The symbols will not be explained at any other point in the text but below:

A = drug compound or area (cm^2)

B = other compound

C = concentration (g/cm^3)

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D = diffusion coefficient (cm^2/sec)

E = activation energy

f = fraction of water in a tablet (or %)

H = heat of solution

I_0 = amount of drug decomposed as a result of interaction with a trace amount of reactant

k_0 = zero order rate constant (subscript denoting order), g/time

k_1 = first order rate constant (subscript denoting order), time

k^* = pseudo-order rate constant, K = dissolution rate constant

S = solubility (g/cm^3)

t = time (e.g., month)

t_A, t_B, t_C = designated times on a curve

T = absolute temperature (°K)

x = fraction decomposed

η = viscosity

V = volume (cm^3)

Z = preexponential kinetic term (e.g., as collision factor)

$h\eta$ = light quantum

DISCUSSION

Decomposition of Solid Dosage Forms

In the decomposition of solids, there are several distinct types of situations:

(a) Decomposition of the solid drug per se. Knowledge of such schemes are of importance broadly and explain a certain number of stability situations.

(b) Decomposition of the solid drug in presence of (i) an "excess" amount of moisture and (ii) a trace amount of moisture or trace element or compound.

(c) Decomposition of the solid drug by interaction with other dosage form components (excipients or other drugs) present in (i) "excess" amounts of (ii) trace amounts.

(d) Loss of the solid drug through the vapor phase.

Decomposition Per Se

This typically shows a sigmoid curve such as shown in Fig. 1[1-4]. The time scale shown is arbitrary; but if, e.g., t_B is at

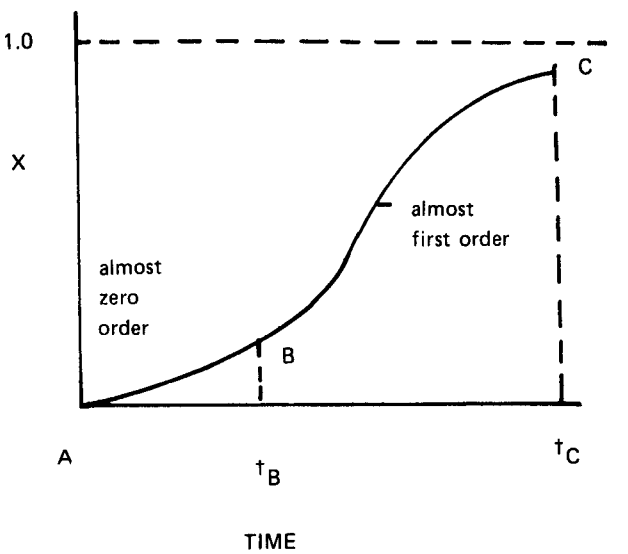

Fig. 1 Prout-Tompkins or Bawn decomposition curve showing how solid state decomposition of a drug per se could approach either zero or first order.

ten years, then the decomposition will appear to be zero order[5]

$$M = M_0 - k_0^* t \qquad \text{(Eq. 1)}$$

If on the other hand t_B is short, e.g., one month, then the curve will appear to be first order:

$$\ln(M/M_0) = -k_1^* t \qquad \text{(Eq. 2)}$$

For drugs where interactions are minimal, one may therefore expect either first or zero order reactions schemes. t_B can be long at low temperatures and short at higher temperatures, so that Arrhenius plotting can be fallacious, since the reaction will appear zero order (with a k_0^*) at higher temperature, making (direct) extrapolation unfeasible. The situation described, however, is rare. When it happens, the entire curve must be represented in closed mathematical form[6,7]. This allows calculation of the actual kinetic parameters which then <u>are</u> treatable by the Arrhenius Equation, i.e.,

$$\ln k = -(E/R)(1/T) + Z \qquad \text{(Eq. 3)}$$

The above underlines the fact that an Arrhenius or Boltzmann equation <u>always applies if the pertinent parameters are known</u>. But if they are not, then the observed rate constant (which are different from the actual kinetic parameters) may fail to obey Eq. 3.

<u>Decomposition in Presence of Water in Excess</u>

By "excess" is meant that there is more equivalent moles of water than of drug. The effect of water in solid dosage forms is probably the most common contributor to drug instability. Leeson and Mattocks[8] in work later confirmed by others[9,10] have shown that for many systems the situation in Fig. 2 applies. Water is

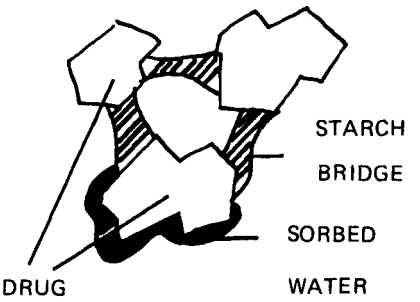

Fig. 2. Example of a starch granulated material showing bound moisture (in drug and in starch bridge) and sorbed water.

assumed present as a bulk phase, and a layer of water will surround the drug particles. Drug will dissolve and form a saturated solution, and the actual decomposition is accounted for by the decomposition in the saturated solution. For the solution, the decomposition is pseudo-first order, i.e.,

$$dC/dt = k_1 C = -k_1 S \qquad \text{(Eq. 4)}$$

The latter equality existing because the solution is assumed to be saturated at all times. If a tablet (or capsule) weighs m grams and contains a fraction f of water (assumed of density one), then the tablet contains (mf) grams or cc of water. If the concentration is multiplied by this volume, then the amount decomposed is

$$-dM/dt = -k_1 mfS$$

which integrates to

$$M = M_0 - k_1 mfS\ t = M_0 - k_0^*\ t \qquad \text{(Eq. 5)}$$

in other words, zero order with rate constant

$$k_0^* = k_1 mfS$$

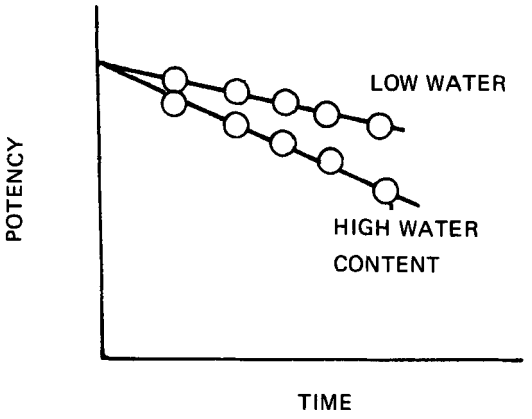

Fig. 3 Pseudo-zero order decomposition at low and high moisture content.

Hence:

(a) the decomposition is (pseudo-)zero order (Fig. 3)

(b) the slope of the Arrhenius plot is (E+H)

(c) the rate constant (i.e., the rapidity of degradation) is proportional to the amount of water present (f) and the solubility (S).

An interesting case of improvement of stability by a lowered solubility is the case of thiamine mononitrate vis-a-vis hydrochloride. A case where the amount of water present plays a part is that of vitamin A beadlets in multi-vitamin tablets (Fig. 4).

Stability programs should always include a moisture stress test to insure that this type decomposition does not occur. This can be done by "adding" titrated amounts of moisture (through vapor phase addition in a desiccator) to tablets and submitting them to stability tests in hermetic containers. If the product is moisture sensitive as described above, then the stability stress tests can be used to set meaningful moisture specifications.

Arrhenius plotting in the case described is only meaningful in hermetic containers. Containers allowing water transmission will allow excessive drying of the product at, e.g., 55°C, and the stability may appear better at the higher temperatures.

Trace Amounts of Water or Reactant

If for instance a 300 mg tablet contains 5.6 mg of drug of equivalent molecular weight of 140 and 0.18% free moisture, then the maximum decomposition by hydrolysis would be as follows: the tablet contains 5.6/140 = 0.04 milliequivalents of drug and 0.18 x 300/(100 x 18) = 0.03 milliequivalents of water, so that at most this amount of drug can be hydrolyzed. Hence, the maximum decomposition is I_0 = 75%, and the equilibrium potency level is M_0-I_0 = 25%. This reaction extent applies to other temperatures as well so that I_0 is temperature independent. This is depicted in Fig. 4A.

If another reaction takes place also, then the curves have the shape shown in Fig. 4b, and here again I_0 is temperature independent, but is batch dependent (since the amount of water or impurity may vary from batch to batch).

Initial curvature, hence, is important in stability programs since they indicate trace interactions.

Interactions

There are several types of interactions. The first is one of direct interaction and the second most important one where the reaction takes place via the vapor phase.

If the drug A reacts with an excipient B (in excess), then the reaction becomes pseudo-first order in A. Here it should be

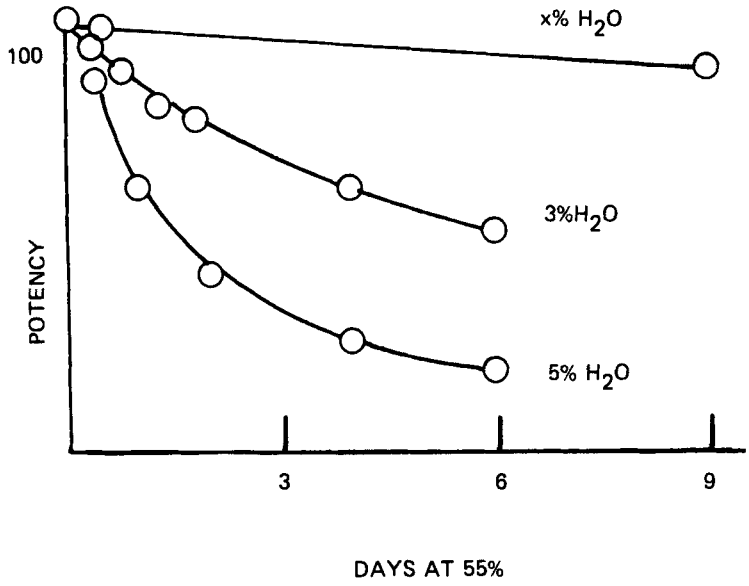

Fig. 4A Decomposition of thiamine hydrochloride in microcrystalline cellulose base tablets.

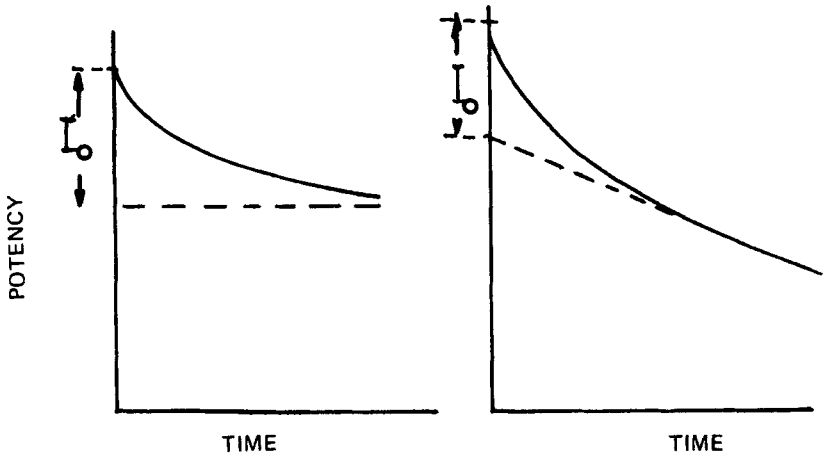

Fig. 4B Decomposition in the presence of a limited amount of moisture (or trace reactant. In the first case the only reaction taking place is the interaction. In the second case there is both an interaction and a decomposition of the drug per se.

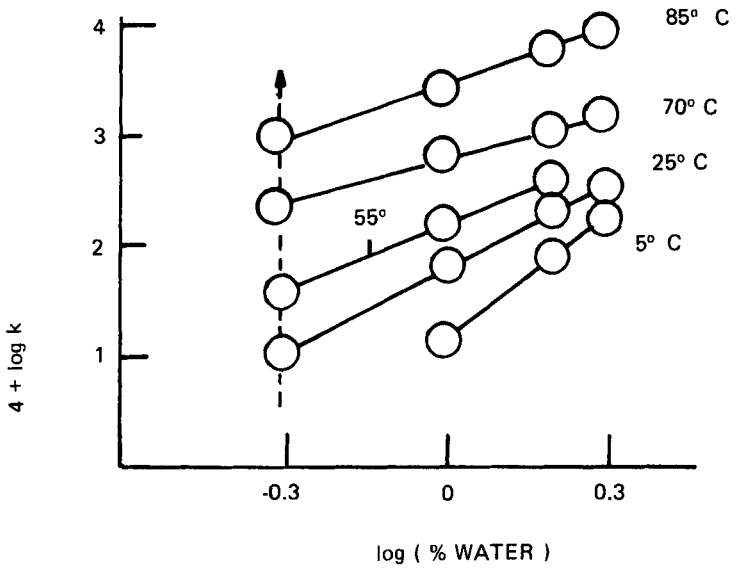

Fig. 4C. Decomposition of vitamin A beadlets in lactose-base tablets as a function of moisture added to the tablets.

noted (as is also the case with other first order reactions AT ROOM TEMPERATURE) that a satisfactory preparation rarely exhibits more than 10-15% decomposition during market life. The amount M retained is (Eq. 2):

$$\ln(M/M_0) = \ln(1-x) = -k_1 * t \qquad \text{(Eq. 7)}$$

If $x < 0.15$, then the mathematical approximation below holds:

$$\ln(1-x) \sim -x \qquad \text{(Eq. 8)}$$

Since $x = (M_0-M)/M_0$, it follows that

$$\ln(M/M_0) = \ln(1-x) \sim =x = -k_1 * t \qquad \text{(Eq. 9)}$$

or

$$M = M_0(1-k_1 t) = M_0 - k_0 * t \qquad \text{(Eq. 10)}$$

i.e., the first order reaction turns into a pseudo-zero order reaction AT ROOM TEMPERATURE, and the rate constant is

$$k_o^* = M_o k_1 \qquad \text{(Eq. 11)}$$

At higher temperatures, x may easily exceed 15%, and Arrhenius plots are therefore best treated as first order at all temperatures in this case. The extrapolated k_1 value can, at room temperature, be converted to k_o^* via Eq. 11. If the reactant (B) is not in excess, then the decomposition becomes akin to the case of trace interaction (Section I-3).

Interaction via Vapor Phase or Consecutive Reaction

This has been reported, e.g., for combinations of aspirin and phenylepherine[11] and for aspirin and codeine[12]. The data by Troop and Mitchner[11] are shown in Fig. 5. Here the reaction scheme is:

Reaction 1: $C_6H_4(OCOCH_3)COOH + H_2O = C_6H_4(OH)COOH + CH_3COOH$

Reaction 2: $CH_3COOH + R_1R_2NH = R_1R_2N\text{-}CO\text{-}CH_3 + H_2O$

It is noted that the water consumed is regenerated. The acetic acid is liquid and could react as such, or it could react through the vapor phase since it has a sizable vapor pressure.

Loss of Solid Through Evaporation

This is usually not a point of consideration except for a very few cases, one of which, however, has been quite important. Some drugs exhibit significant vapor pressures at room temperature. In such cases, an equilibrium amount will always be lost to the interior of the bottle - the larger the head space, the larger the "loss." If the vapor can migrate through the wall of the bottle (e.g., a plastic bottle), then of course the loss becomes diffusion controlled.

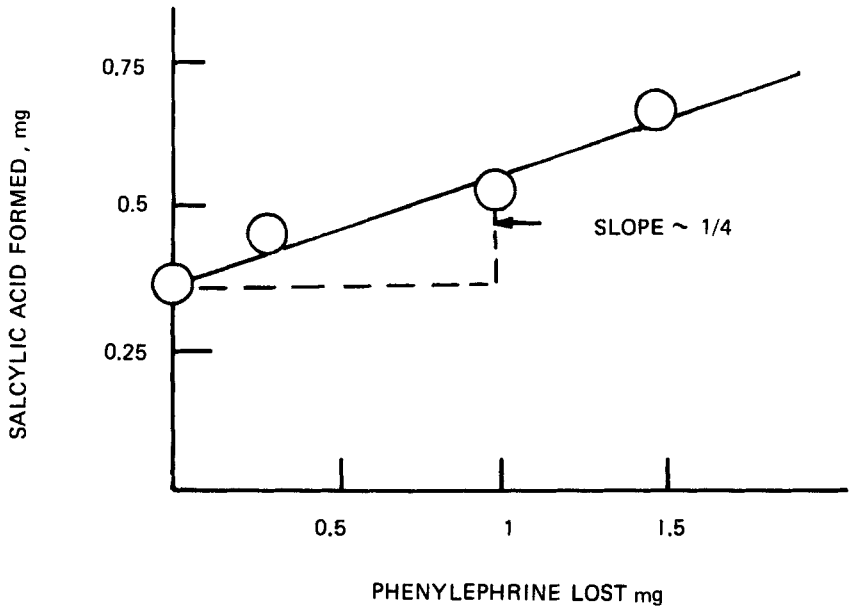

Fig. 5A. Aspirin-phenylephrine interaction. Figure is drawn from data publsihed by Troup and Mitchner (11)

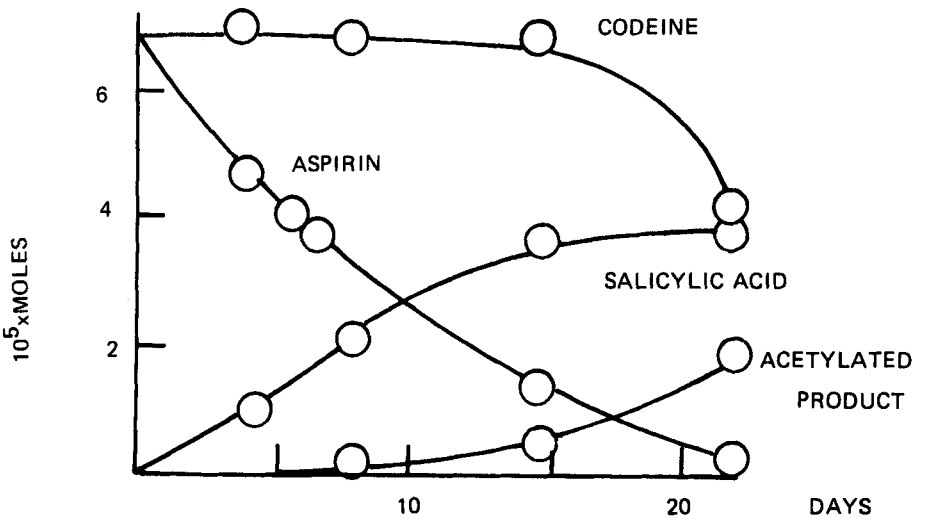

Fig. 5B. Aspirin-codeine interaction. Figure is drawn from data published by Jacobs et al. (12).

A famous example of loss through evaporation is nitroglycerin. The data by Fusari et al.[13] are shown in Fig. 6. For nitroglycerin the situation is further complicated by the fact that it is strongly sorbed to cotton so that if cotton is present then a situation occurs which can be described by:

$$Drug_{solid} \rightleftharpoons Drug_{vapor} \rightleftharpoons Drug_{adsorbed}$$

This results in somewhat complicated kinetics. Since several rate constants are involved, simple Arrhenius plotting is not applicable.

Stability of Semisolid and Dispersion Dosage Forms

In the case of semisolids, these may vary from very liquid systems (suspensions) to almost solid systems (e.g., ointments). The distinction between the two is vague, but grosso modo one may think of the very liquid systems as being pseudo-Newtonian (i.e., having low or zero yield values) and the almost solid systems having large yileld values and, e.g., also include thixotropic preparations with strain rate depending yield values. For the liquid systems, the kinetic situation is principally iodentical to that described in section I-2 (which is virtually a very concentrated suspension), i.e., (re: Fig. 7B)[15]

$$M = M_0 - k_1 VS\ t \qquad \text{(Eq. 12)}$$

where V now is the volume of the dose (e.g., the volume corresponding to one gram). This, for instance, would be the case of somewhat liquid petrolatum suspensions. If the solubility is VERY low, the decomposition pattern may be controlled by the decomposition in solid state, e.g., be identical to that described in section I-1.

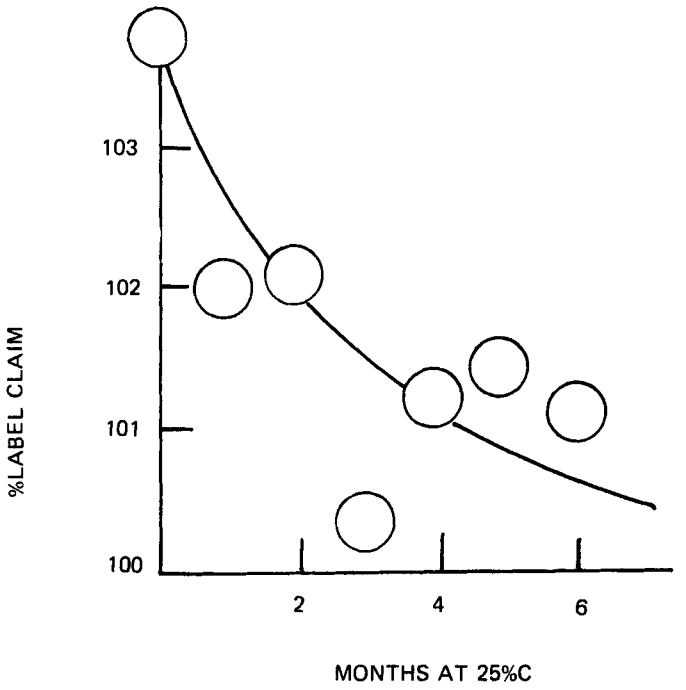

Fig. 6A. Apparent potency loss of nitroglycerin in tablets as a function of time. The figure has been constructed from data published by Fusari (13)

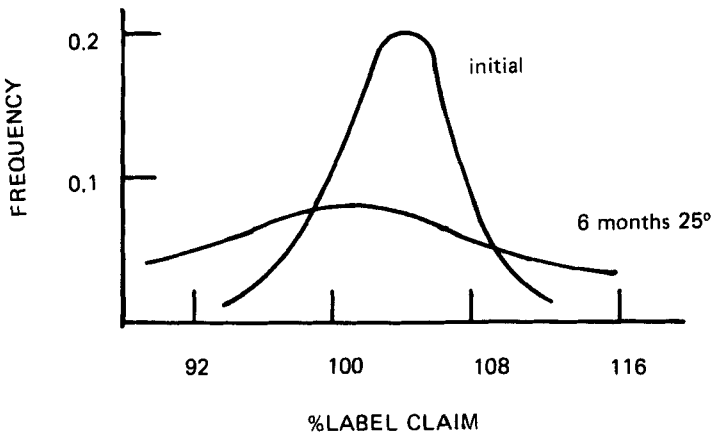

Fig. 6B. Distribution of assays as a function of time. The figure has been constructed based on data published by Fusari (13)

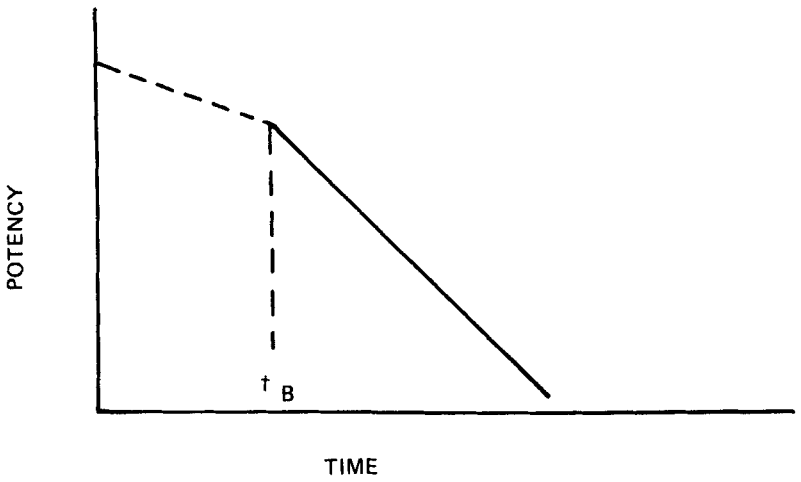

Fig. 7 Kinetics of degradation for a viscous system.

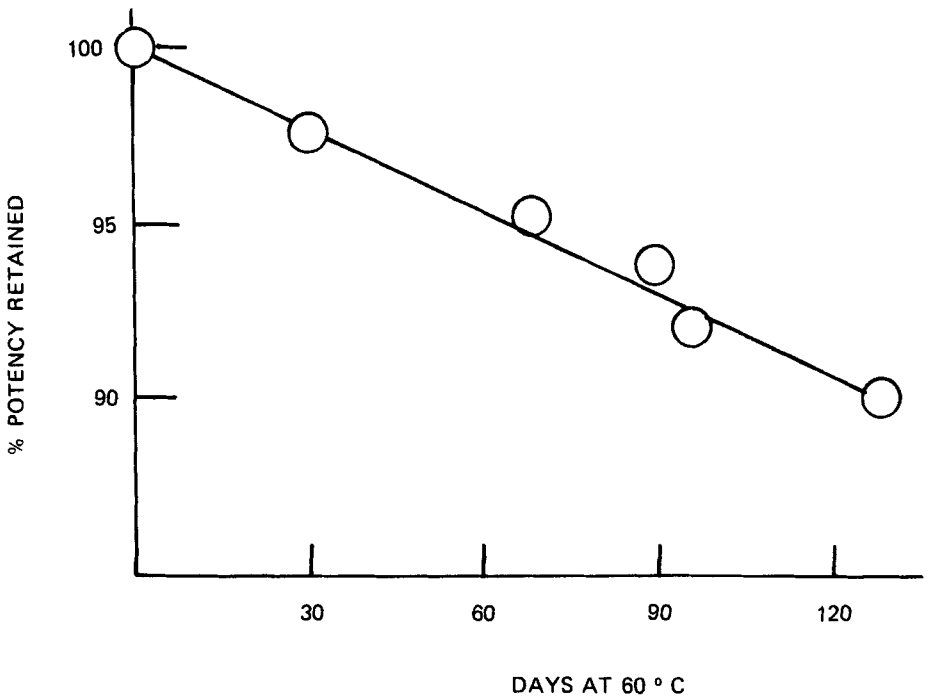

Fig. 7B. Pseudo-zero order decomposition of hydrocortisone in an ointment base. The figure is constructed from data published by Allen and Das Gupta (15)

It is noted that the considerations leading to Eq. 13 assume that every time a molecule decomposes in the liquid phase, it is replaced by one dissolving. The dissolution rate constant K is given by the Noyes-Whitney equation:

$$dC/dt = K\ A\ (S-C) \qquad \text{(Eq. 13)}$$

For very viscous systems, the kinetics of degradation may (partially) be dissolution rate controlled. The rate of disappearance at time t, from liquid solution is $-k_1C$, and the rate of appearance is given by Eq. 13 so that the overall decrease in concentration in the liquid phase is given by:

$$dC/dt = -k_1C + KA(S-C) \qquad \text{(Eq. 14)}$$

The solution to this differential equation is:

$$C = (\exp(-(k_1+AK)t))\ S\ KA/(k_1+KA) \qquad \text{(Eq. 15)}$$

At high t-values

$$C = S\ A\ K/(k_1 + KA) \qquad \text{(Eq. 16)}$$

and the rate equation for decomposition, at high t, becomes

$$M = M_0 - k_1AKSV/(k_1+AK)\ t \qquad \text{(Eq. 17)}$$

This, again, is zero order, but the slope is different than that predicted by Eq. 12. An example is shown in Fig. 7A.

It is noted that K is proportional to D. Hence

(i) since D is inversely proportional to η, the viscosity, it follows that the more viscous is the preparation, the more stable will it be. In the limiting case, however (as for the liquid systems), the stability of the solid compound per se will be rate limiting.

(ii) for hydrophilic molecules, small amounts of water will increase D, and decrease stability,

(iii) the larger the surface area, the larger K, and the less stable the preparation. However, A must often be kept large for reasons of bioavailability.

The length of time t_B in Fig. 7 is when $\exp(-k_1+KA)t_B)$ 0.1, i.e., when

$$t_B = 2.3/(k_1+KA) \qquad \text{(Eq. 18)}$$

The larger k_1, K, or A, the longer is this lag time.

Light Stability

Light stability of pharmaceutical products is best checked, using the light cabinet described by Lachmann et al.[16] This makes use of a fluorescent bulb which is the "average" of what might be encountered in a pharmacy in the U.S. Acceleration is obtained by (a) increasing the intensity of the bulb, and (b) by placing the sample close to the bulb. The cabinet is well ventilated so that the temperature of the samples will not rise (significantly). Acceleration by lowering the wavelength of the light (U.V. as, e.g., in Fadeometers) is not realistic, since it may provoke reactions which require higher energetics than encountered in pharmaceutical practice.

Lachmann et al.[17] and others[18] have shown that photolysis per se, i.e.,

$$A + h\eta \rightarrow \text{degradation} \qquad \text{(Eq. 19)}$$

is confined to the upper layer of a tablet. Kaminski et al.[19] on the other hand have shown that if the light initiates a reaction between drug (A) and an excipient (B), then the reaction

$$A + B \xrightarrow{h\eta} \text{Degradation} \qquad \text{(Eq. 20)}$$

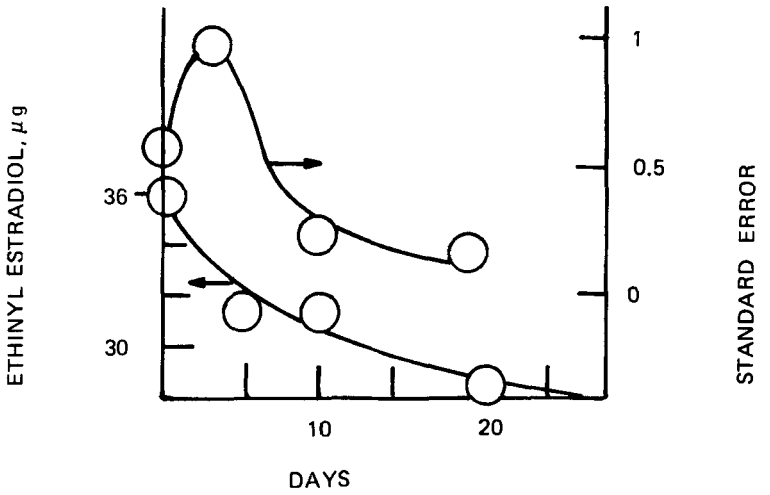

Fig. 8 Sensitivity of dyed tablets to light measured by reflectance. The figure is drawn based on data published by Lachman et al. (16)

will proceed throughout the whole tablet. It is interesting that if $C_B < C_A$, then an equilibrium results (Fig. 9) at C_A-C_B. The standard deviation of the assay increases while the reaction goes on (Fig. 9) and then levels off as it equilibrates (somewhat akin to the finding of Fusari[13], Fig. 6B in another connection, i.e., evaporation of nitroglycerin).

Oxidation

This type of reaction with respect to solids of semisolids has not been extensively reported in the pharmaceutical literature. Nevertheless, it is of great importance. For instance the most burning stability problem in the early 50's was the stability of vitamin A oils in solid preparations. These oxidized rapidly, and it was not until the inception of gelatin-coated vitamin A that the problem was solved.

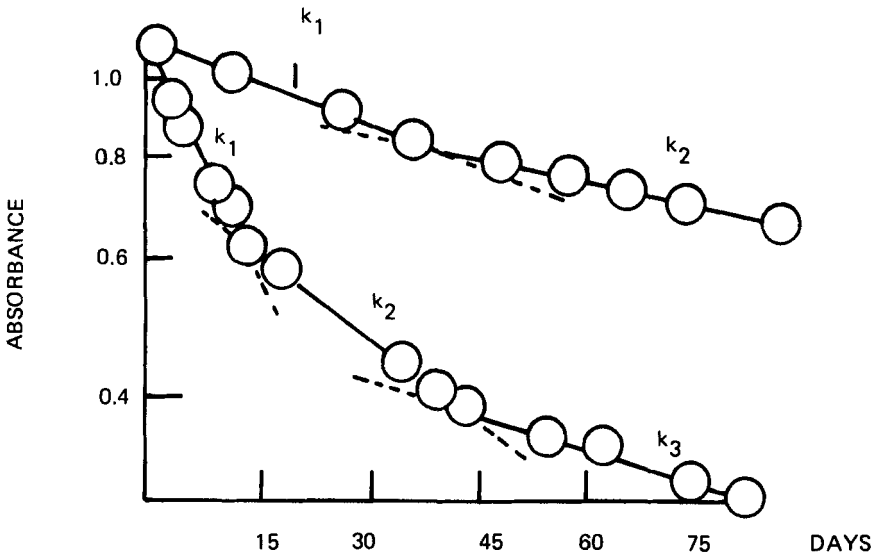

Fig. 9 Ethinyl estradiol potency and standard error as a function of time. The figure is constructed from data published by Kaminski et al. (J.Pharm.Sci., 68 368 (1979))

Several processes suggest themselves in general in the oxidation of a solid: (A) oxygen adsorption followed by reaction, (b) the same but with autocatalysis, and (c) intermediate complexes. In the latter category is the work on fumalgillin reported by Garrett[19] where the drug (A) oxidizes via an active complex hence showing second order kinetics:

$$A + O_2 \rightarrow AO_2 \overset{\uparrow \downarrow A}{} 2AO \qquad \text{(Eq. 21)}$$

Darkening of sodium ascorbate in the solid state is another (probable) substance in the category of oxidation, although the scheme is complex and also entails hydrolysis. Here yellowing occurs, and the progression of the appearance, i.e., extrapolation of appearance, can be done by use of tristimulus light exposure meter as described by Carstensen et al.[21]

For semisolids, oxygen permeation is probably rate controlling in the cases where oxidation applies. The kinetics of this have been worked out (albeit in another connection) by Hom et al.[20]

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