Journal of Pharmaceutical Sciences

JANUARY 1974
VOLUME 63 NUMBER 1

REVIEW ARTICLE

Stability of Solids and Solid Dosage Forms

J. T. CARSTENSEN

Keyphrases □ Solids and solid dosage forms—stability, review, decomposition schemes, equations and rate constants, effect of moisture □ Stability of solids and solid dosage forms—review, decomposition schemes, equations and rate constants, effect of moisture □ Decomposition of solid dosage forms—review, degradation schemes, equations and rate constants, effect of moisture □ Moisture effect—decomposition of solid dosage forms, review

The topic of stability of pharmaceutical solids has not been covered extensively in the pharmaceutical literature. Only four review articles [Garrett (1, 2), Lachman (3), and Carstensen (4)] appeared in the last two decades [except for the partial coverage in the yearly literature review articles in the *Journal of Pharmaceutical Sciences* (5–12)]. The stability of pure compounds has been covered to an extent in chemical journals, and a brief outline of stability of one- and two-component systems will be given first.

STABILITY OF SINGLE CRYSTALLINE SOLIDS

The decomposition of pure solids adhering to Scheme I gives curves that are (*a*) initially steep and then approach 100% decomposition or an asymptote, or (*b*) characterized by an induction period, giving a sigmoid appearance.

There are many theories accounting for this, *e.g.*, Young's (13), but the shape denoted in *a* can usually be accounted for by geometrical contractive consideration (topochemical reactions), whereas the shape denoted in *b* may be accounted for by either nucleation theories or liquid layer theories.

CONTRACTING GEOMETRIES

The relation of decomposition to geometrical aspects was first proposed by Langmuir (14), who postulated that reactions occurred at boundaries and surfaces. Jacobs and Tompkins (15) reviewed the treatment of geometric contractions; the three most predominant cases will be outlined here.

In the contracting cylinder (Fig. 1), it is assumed that the radius of intact chemical substance decreases linearly with time, *i.e.*:

$$r = r_0 - k_1 t \qquad \text{(Eq. 1)}$$

where r_0 is the initial radius. At time t, there will be a decomposition product, B, outside of r and an unchanged chemical substance, A, inside of r. The fraction decomposed at time t is then given by:

$$x = \frac{hn\rho\pi[r_0^2 - r^2]}{hn\rho\pi r_0^2} \qquad \text{(Eq. 2)}$$

where n is the number of particles and h is their height; n and h cancel out, so that the amount retained is obtained from Eqs. 1 and 2:

$$1 - x = 1 + (k_1/r_0)^2 t^2 - (2k_1/r_0)t \qquad \text{(Eq. 3)}$$

or:

$$\sqrt{(1 - x)} = 1 - (k_1/r_0)t \qquad \text{(Eq. 4)}$$

If Fig. 2 is considered to represent a sphere, then in a similar fashion:

$$x = \frac{(4/3)\pi r_0^3 - (4/3)\pi(r_0 - k_3 t)^3}{(4/3)\pi r_0^3} = 1 - \frac{1 - k_3 t^3}{r_0} \qquad \text{(Eq. 5)}$$

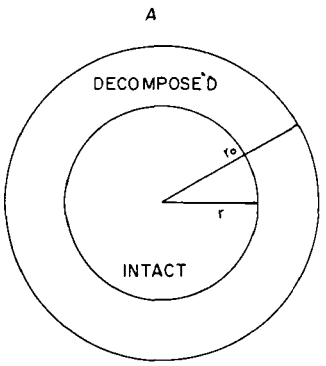

Figure 1—*Model of cylinder or sphere during decomposition.*

or:

$$(1 - x)^{1/3} = 1 - (k_3/r_0)t \qquad \text{(Eq. 6)}$$

A similar form is achieved if the starting point is a cube, and this is frequently referred to as the contracting cube equation.

Roginski and Schul'tz (16) showed that Eq. 6 held for potassium permanganate. Another geometric equation, Eq. 7, was derived by Jander (17). The equations may be summarized as:

$$(1 - x)^{1/2} = 1 - \gamma t \qquad \text{(Eq. 3}a\text{)}$$

$$(1 - x)^{1/3} = 1 - \gamma t \qquad \text{(Eq. 6}a\text{)}$$

$$(1 - x)^{1/3} = 1 - (\gamma t)^{1/2} \qquad \text{(Eq. 7)}$$

where γ has unit of time^{-1} (hr^{-1}).

A set of curves of the types described in Eqs. 3*a*, 6*a*, and 7 is shown in Fig. 2*a* and Table I. They are compared with a curve of the type:

$$1 - x = e^{-kt} \qquad \text{(Eq. 8)}$$

which is a straightforward first-order case. All curves in Fig. 2*a* are made to fit the point [3,0.28]. For small values of γt, Eqs. 3*a* and 6*a* become:

$$1 - x \sim 1 - \frac{2k_1 t}{r_0} \qquad \text{(Eq. 3}b\text{)}$$

$$1 - x \sim 1 - \frac{3k_3 t}{r_0} \qquad \text{(Eq. 6}b\text{)}$$

compared to the expansion of Eq. 8 which, for small kt values, becomes:

$$1 - x = 1 \doteq kt \qquad \text{(Eq. 8}a\text{)}$$

so that $k \sim 3k_3/r_0$ or $k \sim 2k_1/r_0$. The former comparison is shown in Table I and Fig. 2*b*. *The similarity may account for many decompositions in solid dosage forms approaching first-order kinetics.*

There are a few pharmaceutical examples of the utility of Eq. 7 such as the work of Horikoshi and Himuro (18). They studied the dehydration reactions of a series of glucuronic acid derivatives (Table II). Their data for dehydration of glucuronamide hydrate are shown in Figs. 3–5. It is seen that proper selection of treatment (*i.e., via* Eqs. 3*a*, 6*a*, or 7) leads to

$$A_{\text{solid}} \longrightarrow B_{\text{solid}} + C_{\text{gas}}$$

Scheme I

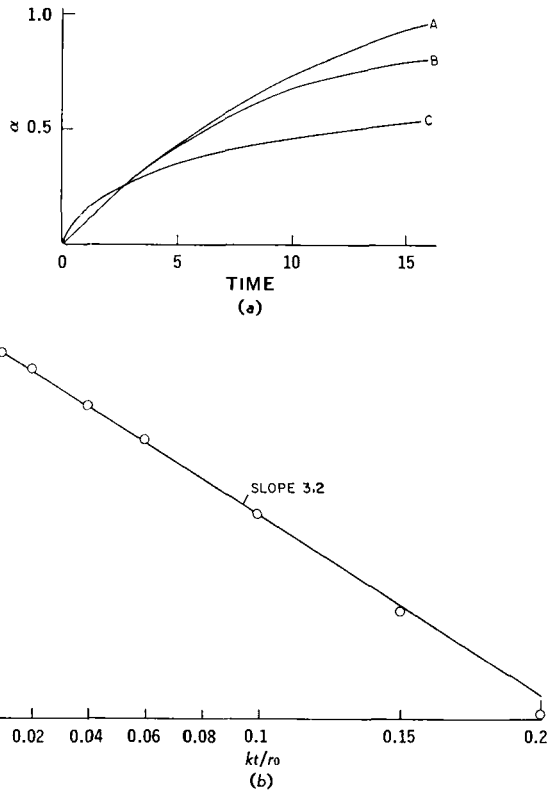

Figure 2—(a) *Decomposition curves from Table I.* A *is contracting cube or rectangle,* B *is product layer diffusion controlled, and* C *is first-order decomposition. Decomposition product is plotted* versus *time.* (b) *Data following Eq. 6 plotted* via *Eq. 8 (Table I).*

rate constants that can be treated by an Arrhenius equation.

SIGMOID DECOMPOSITION CURVES

The reaction in Scheme I can give rise to sigmoid curves when the mole fraction decomposed (x) is plotted *versus* time. There is an initial induction period (A) as shown in Fig. 6, characterized by a lag time at levels of x at $0 < x < 0.1$. This is followed by an acceleratory period (B) at levels of x at $0.1 < x < 0.5$. This is, finally, followed by the decay period (D), which is less reproducible than the two former periods. The inflection point is usually at $x = P/P_\infty = 0.5$.

The most general model explaining this type of de-

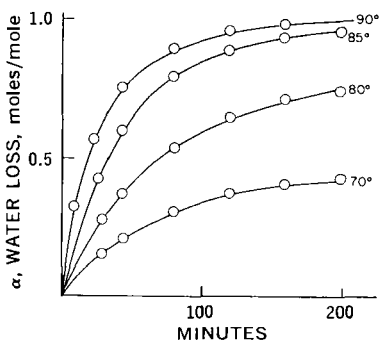

Figure 3—*Decomposition of glucuronamide hydrate. Adapted, with permission, from Ref. 18.*

Table I—Decompositions According to Eqs. 3*a*, 6*a*, 7, and 8

Time, t	γ = 0.05 hr^{-1}, Eq. 3*a*	γ = 0.035 hr^{-1}, Eq. 6*a*	γ = 0.00359 hr^{-1}, Eq. 7	γ = 0.11 hr^{-1}, Eq. 8	k_3t/r_0, Eq. 6	$1 - x$, Eq. 6	$\ln(1 - x)$
1	0.1	0.1	0.17	0.10	0.01	0.970	−0.030
2	0.19	0.20	0.23	0.20	0.02	0.941	−0.061
3	0.28	0.28	0.30	0.28	0.04	0.885	−0.122
5	0.44	0.44	0.35	0.42	0.06	0.830	−0.186
10	0.75	0.73	0.47	0.67	0.10	0.729	−0.316
15	0.94	0.89	0.55	0.81	0.15	0.614	−0.488
20			0.61		0.20	0.512	−0.669
25			0.66				

Table II—Activation Energies of Dehydration of Glucuronic Acid Derivatives (18)

Reaction	Activation Energy	Symbols
$GN \cdot H_2O \rightarrow GN + H_2O$	38.6 kcal/mole	GN = glucuronamide hydrate
$GK \cdot 2H_2O \rightarrow GK \cdot H_2O + H_2O$	4.3 kcal/mole	GK = potassium glucuronate
$GK \cdot H_2O \rightarrow GK + H_2O$	18.5 kcal/mole	
$GI \cdot 2H_2O \rightarrow GI + 2H_2O$	12.2 kcal/mole	GI = glucuronate isoniazone

composition curve for reactions of the type in Scheme I has been the Prout–Tompkins (19) model. The assumption is made that the decomposition is governed by formation and growth of active nuclei. The existence of nuclei and their growth have been substantiated by several investigators (19–23); they occur on the surface as well as inside (24) the crystals during decomposition. Prout and Tompkins (19) assumed that the reaction probability is proportional to the number of nuclei; they also assumed that the nuclei propagated with a certain probability α and terminated with a probability β. If the initial number of potential nucleus formation sites is N_0 and N is the number at time t, then:

$$dN/dt = k[N_0 - N] \qquad \text{(Eq. 9)}$$

At time t, there remain $N_0 - N$ sites to be used up. If for the moment one disregards termination, then this can be integrated with the result:

$$N = N_0[1 - \exp(-kt)] \sim N_0kt \qquad \text{(Eq. 10)}$$

where the approximation is valid for small kt values. Differentiating Eq. 10 gives:

$$dN/dt = kN_0 \qquad \text{(Eq. 11)}$$

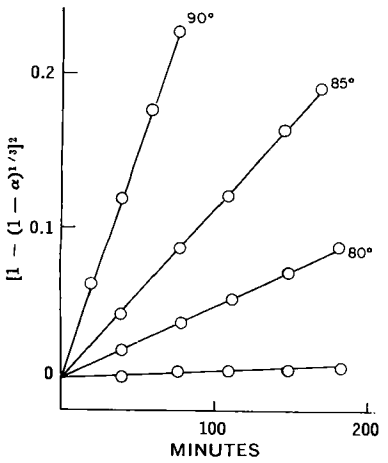

Figure 4—*Data in Fig. 3 plotted according to Eq. 7. Adapted, with permission, from Ref. 18.*

Since, however, each nucleus has a probability α of branching, this is more properly written:

$$dN/dt = kN_0 + \alpha N \qquad \text{(Eq. 12)}$$

Eventually, branches will merge (with a probability of β), so Eq. 12 should include this as well. If, in addition, the initial potential nucleation sites are used up rapidly, Eq. 12 becomes:

$$dN/dt = [\alpha - \beta]N \qquad \text{(Eq. 13)}$$

in which α and β are functions of t (and x); hence Eq. 13 cannot be directly integrated. Since $\alpha = \beta$ at $x = 0.5$ and since $\alpha = 1$ and $\beta = 0$ at $t = 0$ ($x = 0$), the functionality $\beta = 2x\alpha$ is a reasonable trial function in the model. Hence:

$$dN/dt = \alpha[1 - 2x]N \qquad \text{(Eq. 14)}$$

The decomposition rate is now assumed proportional to the number of nuclei, so that:

$$dx/dt = k_1N \qquad \text{(Eq. 15)}$$

Inserting this into Eq. 14 gives:

$$\frac{dN}{dt} = \frac{dN}{dx}\frac{dx}{dt} = \frac{\alpha[1 - 2x]}{k_1}\frac{dx}{dt} \qquad \text{(Eq. 16)}$$

so:

$$N = (\alpha/k_1)[x - x^2] \qquad \text{(Eq. 17)}$$

assuming that $N_0 \ll N$ and that $N = 0$ implies that x is approximately equal to zero. Inserting Eq. 17 into Eq. 15 then gives:

$$\ln[x/(1 - x)] = \gamma t + C \qquad \text{(Eq. 18)}$$

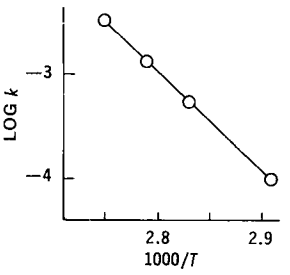

Figure 5—*Arrhenius plotting of the data in Fig. 4. For legend, see Table II. Adapted, with permission, from Ref. 18.*

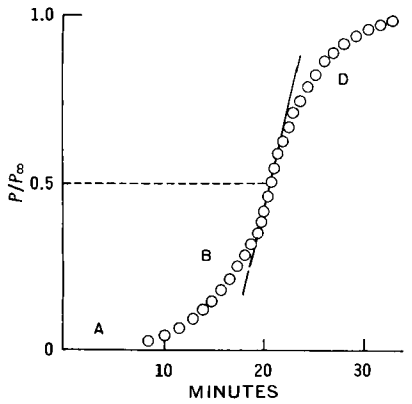

Figure 6—*Decomposition of silver permanganate. Adapted, with permission, from Ref. 26.*

where C is the lag time term and the logarithmic relation should be apparent beyond that point. Data on silver permanganate (26) are shown graphically in Figs. 7 and 8. The linearity according to Eq. 18 is apparent, and the rate constant adheres to an Arrhenius relation.

There are pharmaceutical examples of this type of degradation. In the work by Kornblum and Sciarrone (27), aminosalicylic acid was shown to decompose by a pattern similar to that described in Eq. 18. The decomposition of aspirin anhydride reported by Garrett *et al.* (28) is another example where Prout–Tompkins (19) kinetics may apply at the higher temperatures studied (60–70°).

To establish curves of the type discussed, it is necessary to assay at frequent intervals in the early stages; the problem of thermal equilibration is difficult to gauge when solids are stored at temperatures above 25° (29).

SYSTEMS WITH LIQUID DECOMPOSITION PRODUCT LAYERS

If the general reaction is as shown in Scheme II rather than Scheme I, the decomposition pattern changes. Carstensen and Musa (30) reported on the decomposition of a series of substituted benzoic acids, all decomposing into a liquid and a gas. For example, aminobenzoic acid decomposes into aniline and carbon dioxide. The aminobenzoic acid dissolves in the formed aniline to an extent of S moles/mole of aniline, so that at a particular time t, when x moles are decomposed, there are Sx moles of aminobenzoic acid in solution and $[1 - x - Sx]$ moles in the solid state. By denoting k_s and k_a as the first-order rate constants of the decomposition in the solid and liquid states, respectively, the following equation governs the decomposition:

$$dx/dt = k_s[1 - x - Sx] + k_aSx = k_s + \Gamma x \quad \text{(Eq. 19)}$$

where:

$$\Gamma = -[k_s + k_sS - k_aS] \quad \text{(Eq. 20)}$$

Integrated, this gives:

$$\ln[1 + (\Gamma x/k_s)] = \Gamma t \quad \text{(Eq. 21)}$$

so that Γ/k_s can be found as an adjustable parameter. Since Γ is known from the slope, k_s can be found through division. S can be determined from the point on the curve in Fig. 9 where liquefaction takes place (this can be done fairly accurately by visual means). Beyond this point, the decomposition is simply a first-order decomposition in solution, and k_a can be found from this as well as from Eq. 20 (with knowledge of S and k_s). The data obeyed Eq. 21 and there was agreement between values of k_a found *via* Eq. 20 and *via* the part of the decomposition curve beyond the liquefaction point. The curves for this type of decomposition are, therefore, sigmoid as well, in that the part up to the liquefaction point is upward convex by the equation:

$$x = \frac{k_s}{\Gamma}\{e^{\Gamma t} - 1\} \quad \text{(Eq. 22)}$$

and the part beyond the liquefaction point [where $x = x' = 1/(1 + S)$ at $t = t'$] is downward convex by

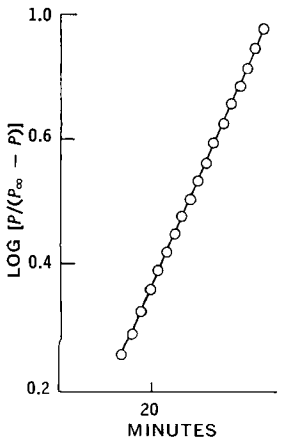

Figure 7—*Data from Fig. 6 plotted according to Eq. 18. Adapted, with permission, from Ref. 26.*

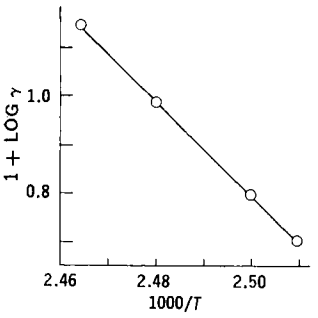

Figure 8—*Data from Fig. 7 plotted by Arrhenius plotting. Adapted, with permission, from Ref. 26.*

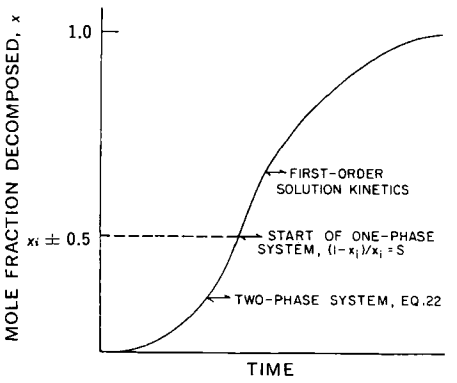

Figure 9—*Solid-state decomposition of aminobenzoic acid. Adapted, with permission, from Ref. 30.*

$$A_{solid} \longrightarrow B_{gas} + C_{liquid}$$

Scheme II

the equation:

$$(1 - x)/(1 - x') = e^{-k_s(t-t')} \qquad \text{(Eq. 23)}$$

The data by Carstensen and Musa (30) are indicative (although not proof) of the existence of an isokinetic point for solid reactions (31), as shown in Fig. 10.

The decomposition of a series of vitamin A derivatives was studied (32) and found to be zero order. The decomposition rate constants, k_A, were found to be related to the melting point, T_m, of the compounds by the equation (Fig. 11):

$$\log k_A = \theta\frac{1}{T_m} + \sigma \qquad \text{(Eq. 24)}$$

The results are rationalized *via* the assumption of a liquid layer theory; similar theories have been proposed (33–43). Gluzman and coworkers (34–43) showed evidence of pseudoliquid layers at temperatures far below the melting temperature of the compounds studied. Carstensen and Musa (30) also found that a series of *p*-substituted benzoic acids adhered to the Guillory–Higuchi (32) equation (Eq. 24) (Fig. 11).

DECOMPOSITION OF ONE-COMPONENT PHARMACEUTICAL SYSTEMS

There are two main purposes for conducting studies of solid decomposition in pharmaceutics: (*a*) to elucidate the mechanism of a reaction, and (*b*) to predict stability. In general, pharmaceutical systems do not lend themselves to studies through many half-lives, so fractional order assignment is not possible in most cases. Distinction between first and zero order is, however, both possible and important; in extrapolatory techniques, wrong conclusions can be drawn by wrong order assignments. Statistical methods for these purposes have been described (1, 44).

Zero-order patterns are explained by being either the initial part of curves such as the ones shown in Fig. 2 or the induction period of curves such as the ones shown in Fig. 6. There are, of course, times where first and zero order cannot be distinguished in

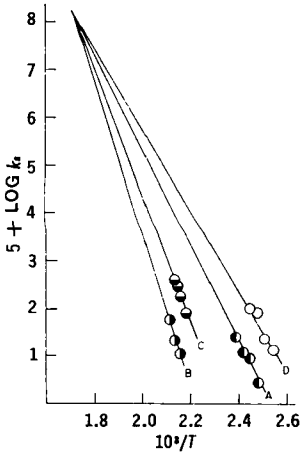

Figure 10—*Plot showing possible isokinetic point in solid-state decomposition of* p-*substituted benzoic acids. Key: A, amino; B, dimethylamino; C, hydroxy; and D, methylamino.*

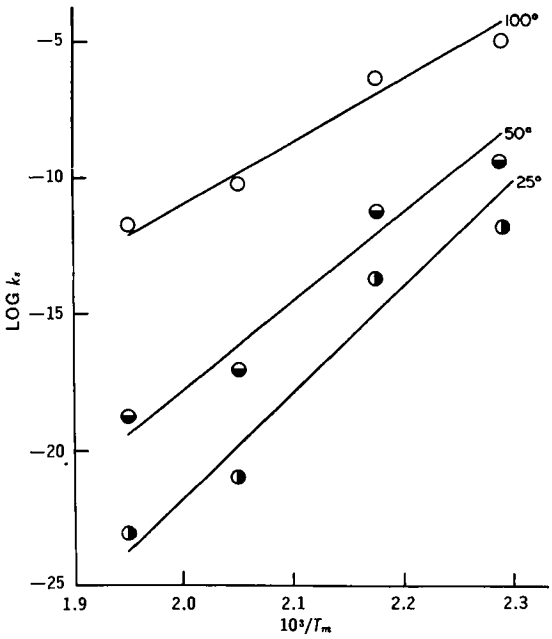

Figure 11—*Decomposition rate constants in solid state* (k_s) *as a function of melting point* (T_m). *Reprinted, with permission, from Ref. 30.*

any way: in general, when $x < 0.15$, $\ln(1 - x) \sim -x$ (45). An example is the work by Brownley and Lachman (46) where the formation of hydroxymethylfuraldehyde from lactose was studied. Another case is the bacitracin study by Gross *et al.* (47, 48) (Fig. 12). Neither plotting of decomposition-time curves nor Arrhenius plotting will reveal the actual order. Adherence to Arrhenius plotting was reported by Garrett (49) in the case of fumagillin decomposition; the case of vitamin A derivatives reported by Guillory and Higuchi (32) was already mentioned. Nakanishi *et al.* (50) found aluminum aspirin to decompose by zero-order kinetics and found good Arrhenius correlation.

First-order cases can be explained by inspection of

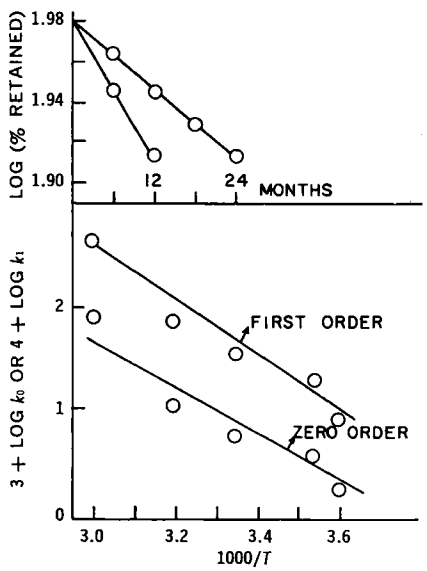

Figure 12—*Bacitracin decomposition. Adapted, with permission, from Refs. 47 and 48.*

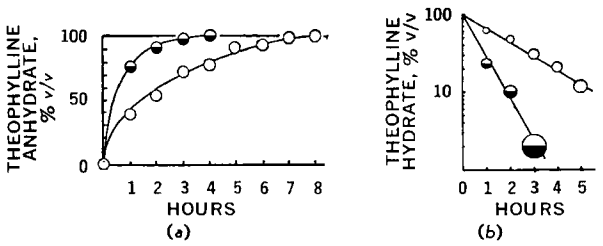

Figure 13—*Dehydration kinetics of theophylline hydrate.* (a) *Anhydrate formation at 40°* (◒) *and theophylline hydrate at 40°* (○). (b) *Logarithmic plotting of the data. Reprinted, with permission, from Ref. 53.*

Fig. 2. If the reaction goes to completion, any of the curves corresponding to Eq. 3*a*, 6*a*, or 7 may be approximated by Eq. 8; in particular, at higher temperatures where thermal lag may be operative, an apparent first-order scheme is perfectly sound. The same applies to decompositions following Prout-Tompkins kinetics (Eq. 18) as long as lag times are short. Carstensen and Pothisiri (51) found the decomposition of aminosalicylic acid *in vacuo* [as opposed to atmospheric decomposition (27)] to be first order and amenable to Arrhenius plotting.

The approach to equilibrium reported by Takahashi and Yamamoto (52) in the case of isomerization of vitamin D_2 to isocalciferol and isotachysterol is the consequence of the chemistry of reaction, as is the high temperature equilibrium approached by fumagillin reported by Garrett (49). In other cases, there are *apparent* approaches to equilibrium that may be of either chemical or physical origin, as will be discussed later. The bacitracin work by Gross *et al.* (47, 48) can be viewed in this light. Again, any of the curves in Fig. 2 may be approximated by an equation such as:

$$x = x_\infty[1 - e^{-kt}] \qquad \text{(Eq. 25)}$$

where x_∞ is an apparent equilibrium level; if analytical methods have a coefficient of variation of more than 5%, distinction between this and the particular topochemical scheme may be difficult to establish.

DEHYDRATION KINETICS

Although loss of water of crystallization is not a clearcut "chemical decomposition," it is of pharmaceutical importance. The case of dehydration of some glucuronic acid derivatives was reported by Horikoshi and Himuro (18) and their results are tabulated in Table II. Shefter and Kmack (53) reported on the dehydration kinetics of theophylline hydrate, and their results are shown in Fig. 13.

Shefter and Kiral[1] showed that the thermal decomposition of sodium bicarbonate is an $A \rightarrow B \rightarrow C$ reaction (Scheme III), in that twice the appearance rate of sodium carbonate (Na_2CO_3), followed by X-ray techniques, does not equal the disappearance rate of sodium bicarbonate ($NaHCO_3$), except at the beginning and at the end; the intermediate $[NaHCO_3]^+$ is not detectable by X-ray techniques.

[1] E. Shefter and R. Kiral, to be published.

$$2NaHCO_3 \longrightarrow 2[NaHCO_3]^+ \longrightarrow Na_2CO_3 + H_2O + CO_2$$

Scheme III

$$A_{solid} + B_{solid} \longrightarrow 2C_{solid}$$

Scheme IV

In the case of dehydration of hydrates, Garner (54) suggested that water in coordination complexes is more strongly held than "structural" water (*i.e.*, interstitial water) and that the surface may dehydrate first and that the formed interface serves as a barrier through which subsequent water must diffuse. Kohlschütter and Nitschmann (55) showed by X-ray techniques that cupric sulfate pentahydrate, when dehydrated *in vacuo*, forms a dehydrated product with no apparent crystalline structure, whereas dehydration at (low) water vapor pressure produces a crystalline end-product. It is assumed that *in vacuo* the evaporation of water molecules leaves a surface of ionic network, which is stable in only a few cases (zeolites); it will mostly rearrange to a phase of ill-defined crystalline structure.

Zawadski (56) and Garner (54) showed interfaces of the same type to be important in carbon dioxide loss from carbonates as well.

TWO-COMPONENT SYSTEMS

When two compounds are involved in a decomposition reaction, Scheme IV, a "reaction layer" of thickness ζ forms between A and B. A molecules must diffuse through this layer to reach and react with B molecules if it is assumed that the B molecules are the less mobile. This diffusion is governed by Fick's first law, *i.e.*, the rate of A diffusion is:

$$\frac{dA}{dt} = \frac{\pi([A] - 0)}{\zeta} \qquad \text{(Eq. 26)}$$

where π is the permeability and the reaction rate is assumed to be much greater than the diffusion rate. A loss of an A molecule means an increase of the thickness of the layer by:

$$dA = ad\zeta \qquad \text{(Eq. 27)}$$

so:

$$\frac{d\zeta}{dt} = \frac{q}{\zeta} \qquad \text{(Eq. 28)}$$

which is integrated to:

$$\zeta^2 = 2qt \qquad \text{(Eq. 29)}$$

This is comparable to Eq. 7. In actuality, a is not independent of ζ. The complete expression was derived by Cohn (57) and Rastogi and coworkers (58–61) and is:

$$\zeta^2 = Qte^{-\alpha\zeta} \qquad \text{(Eq. 30)}$$

They studied the reaction of trinitrophenol (picric acid) and α-naphthol; their data, plotted *via* Eq. 30, are shown in Fig. 14. It is seen from the figure that the temperature relationship is akin to an Arrhenius relationship. The factor Q, of course, is related to

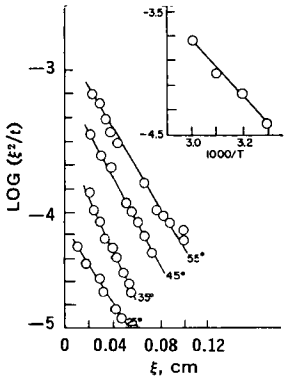

Figure 14—*Solid-state reaction between trinitrophenol and α-naphthol, according to Eq. 30. Adapted, with permission, from Ref. 58.*

diffusion, so that activation energy may be different from that usually encountered in chemical reactions, as indeed it is (60 kcal/mole).

Interactions of solids with oxygen were reported by Garrett (49) and Tingstad and Garrett (62), who established (Scheme V) that fumagillin (A) oxidized *via* a steady-state intermediate (AO_2) which reacted with A to form AO:

$$A + O_2 \underset{k_-}{\overset{k_+}{\rightleftharpoons}} AO_2 \xrightarrow[k_2]{+A} 2AO$$

Scheme V

If $k_2[A] \gg k_- \gg k_+[A]$, then:

$$\frac{d[AO]}{dt} = -2\frac{d[A]}{dt} = \frac{k_2[O_2]}{k_-}[A]^2 \qquad \text{(Eq. 31)}$$

so that the reaction should be second order and follow:

$$\frac{1}{[A]} = \frac{1}{[A]_0} - kt \qquad \text{(Eq. 32)}$$

The data are plotted in this way in Fig. 15, and Fig. 16 shows that the rate constants follow an Arrhenius relation.

DECOMPOSITIONS INVOLVING MOISTURE

The work by Kornblum (63) and by Kornblum and Sciarrone (27) included a study of the effect of atmospheric moisture. Figure 17 shows that added

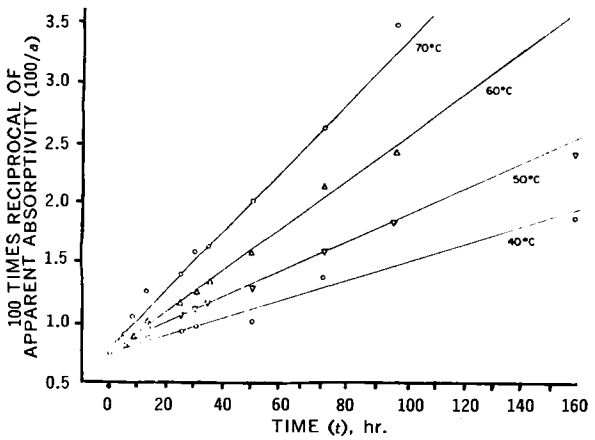

Figure 15—*Second-order decomposition of fumagillin in presence of oxygen. See Eq. 32. Reprinted, with permission, from Ref. 49.*

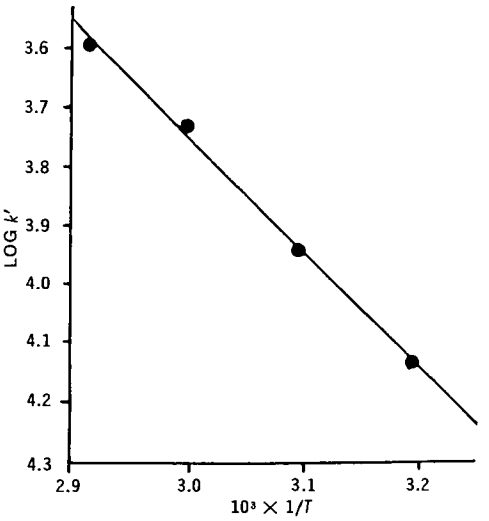

Figure 16—*Arrhenius plot of the data in Fig. 15. Reprinted, with permission, from Ref. 49.*

moisture decreases the lag time and increases the zero-order rate constant. Leeson and Mattocks (64) showed that in the presence of abundant moisture, the decomposition of aspirin can be accounted for by considering the moisture adsorbed, being saturated by aspirin, and the sole source of decomposition. They took into account that the "solution" gets more acid as the reaction progresses. Denoting by k_H the hydrogen-catalyzed hydrolysis rate constant and by K the ionization constant of acetic acid, and assuming that the volume, V, of moisture adsorbed follows a Freundlich isotherm:

$$V = k'p^n \qquad \text{(Eq. 33)}$$

they arrived at the following expression for decomposition at time t:

$$\log[a_0(\sqrt{d} - \sqrt{c_0})/\{a(\sqrt{a} + \sqrt{c})\}] = ([\sqrt{d_0}kp^{3n/2}]/2.3)t \qquad \text{(Eq. 34)}$$

where a denotes aspirin content, c is salicylic acid content, $d = a + c = a_0 + c_0$, p is water vapor pressure, and $k = k_H k'\sqrt{Kk'}$. Figure 18 shows that Eq. 34 was followed well. The slopes of the lines α are given by:

$$\log \alpha = (3n/2) \log p + \log[\sqrt{d_0}k/2.3] \qquad \text{(Eq. 35)}$$

and Fig. 19 shows that this relation held well at all temperatures. From the intercept it is possible to

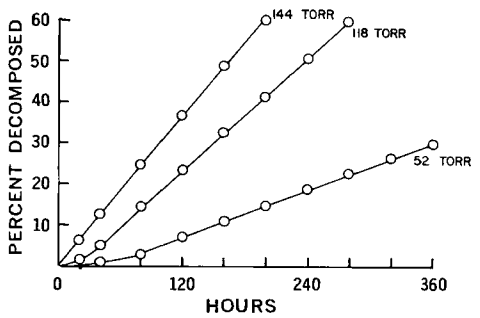

Figure 17—*Decomposition* versus *time curves for aminosalicylic acid in atmospheres containing moisture: 144, 118.4, and 52.3 torr. Adapted, with permission, from Ref. 27.*

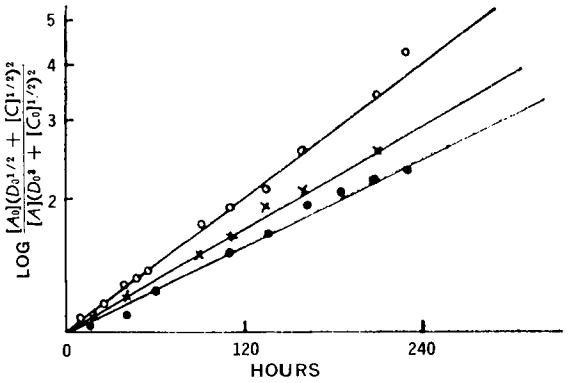

Figure 18—*Decomposition of aspirin at different vapor pressures. Key: ○, 233 torr; ×, 200 torr; and ●, 181 torr. See Eq. 34. Reprinted, with permission, from Ref. 64.*

calculate $k_H k'^{3/2}$ (knowing the value of K). This value should depend on temperature *via* the following equation:

$$\log k_H + 1.5 \log k' = \frac{-E}{2.3R}\frac{1}{T} + q \qquad \text{(Eq. 36)}$$

where E is the sum of activation and adsorption energies. The latter is negligible if the water is not chemisorbed. The value of E found (15 kcal) is indeed close to the 15.6 kcal found by Edwards (65) for aspirin decomposition in solution. In this manner, the Leeson-Mattocks (64) study provides complete accounting of the decomposition *via* solution kinetics in a saturated, sorbed moisture layer.

Kornblum (63) and Kornblum and Sciarrone (27) found that the lag time disappeared for the aminosalicylic acid system and that the rate constant increased with increasing moisture; they, however, could not quantitatively account for the decomposition as occurring in a saturated, sorbed moisture layer. They suggested that the layer was "stagnant" and might not be completely saturated; *i.e.*, the decomposition might be diffusion controlled. Carstensen (66) showed that, in such a case, the saturation term (S) should be replaced by:

$$C = S[1 - e^{-\alpha l}]/\alpha \qquad \text{(Eq. 37)}$$

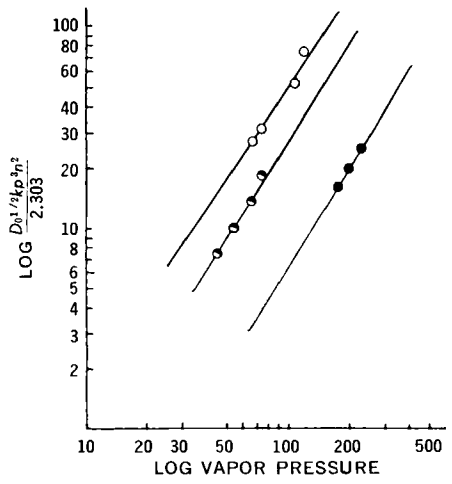

Figure 19—*Aspirin data in Fig. 18 plotted according to Eq. 35 at different vapor pressures. Key: ○, 233 torr; ◒, 200 torr; and ●, 181 torr. Reprinted, with permission, from Ref. 64.*

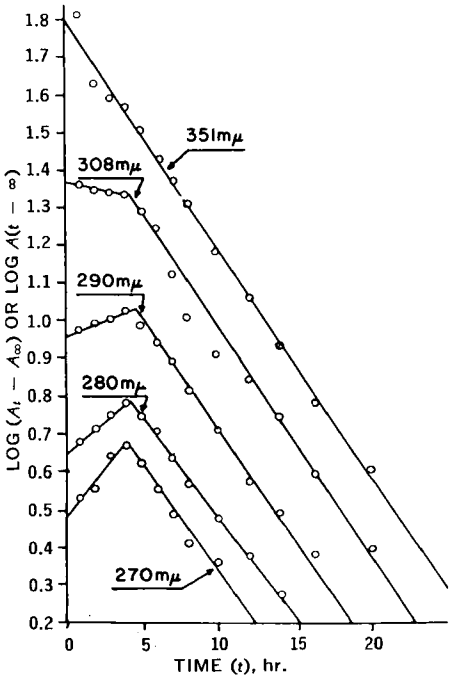

Figure 20—*Pseudo-first-order photolysis of fumagillin. Reprinted, with permission, from Ref. 67.*

where $\alpha = k/D$, l is the layer thickness, k is the rate constant, and D is the diffusion coefficient.

PHOTOLYSIS

There are a few examples of photolysis of pharmaceutical compounds, notably the work by Eble and Garrett (67). From their work shown in Fig. 20, it can be seen that the decomposition is first order; although no general statement can be made to this effect, it is frequently true. DeMerre and Wilson (68) found the photodecomposition of cyanocobalamin to be first order, and Carstensen (69) found that vitamin A in gelatin-coated beadlets decomposed in a first-order type of reaction. Savard *et al.* (70) reported on photodecomposition of steroids.

DECOMPOSITION OF SOLID DOSAGE FORMS

From what has been stated regarding pure compounds, it would appear that both zero- and first-order patterns of decomposition might be expected in solid dosage forms. The theories relating to decomposition in sorbed moisture layers should be particularly attractive for solid dosage forms since moisture is always present to some extent. This would lead one to expect that zero-order patterns would predominate. The development pharmacist and chemist need to establish the order with which a dosage form decomposes and whether or not Arrhenius plotting is possible. A large number of one- and two-component systems have already been quoted where this was possible.

Haynes *et al.* (71) reported on first-order decomposition of chlortetracycline capsules. Carstensen (72) reported on the first-order decomposition of vitamin A in tablets, and Tardif (73) reported on first-

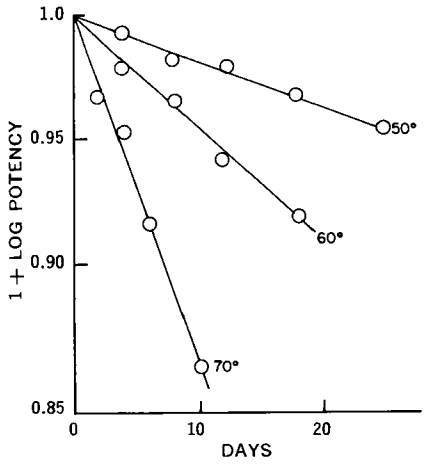

Figure 21—*Pseudo-first-order plots of thermal decomposition of ascorbic acid in a solid dosage form. Adapted, with permission, from Ref. 73.*

order decomposition of vitamins B_1, C, and A in tablets. In the latter two studies, there was adherence to an Arrhenius equation. The data by Tardif are shown in Figs. 21 and 22.

Enezian (74) showed that aspirin in tablets made in a microcrystalline cellulose base decomposed by a first-order pattern and that the rate constants adhered to an Arrhenius equation. The data by Leyden *et al.* (75) regarding reserpine also imply first-order decomposition. In fact, there is a general tendency to expect first-order decomposition; nomograms and stability designs assuming first-order decomposition have been constructed (76, 77), although these are not necessarily restricted to solid dosage forms.

In some cases, it is (as mentioned) difficult to distinguish between first and zero order. The decomposition of lactose, aside from the quoted work of Brownley and Lachman (46), was also reported (78–80) with much the same conclusions. Distinction between orders is also difficult in the decomposition of thiamine, riboflavin, and niacinamide (81–83), thiamine mononitrate (84), and ascorbic acid (85), all decompositions relating to solid dosage forms. On the other hand, the data relating to decomposition in tablets of vitamin A, cyanocobalamin, ascorbic acid, and pantothenic acid (81–83) are first order. In the case of cyanocobalamin, Macek and Feller (86) showed that the decomposition at higher temperatures is catalyzed by thiamine decomposition products and, hence, is complicated.

EQUILIBRIA IN SOLID DOSAGE FORM STABILITY

The earlier quoted bacitracin work (47) also covered stability of troches containing bacitracin. From the data (Table III and Fig. 23), it appears that equilibrium at 65% retained is implied. Equilibria are much more common in solid dosage forms than in solutions or pure solids, and there are several reasons why this is the case. It may only be an apparent equilibrium (and, indeed, dictated by a more correct topochemical relation) but frequently it offers a sound procedure for extrapolation in predictive work.

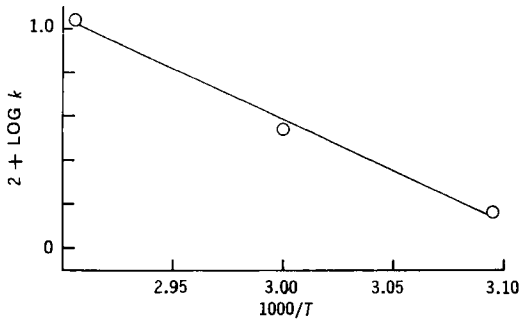

Figure 22—*Arrhenius plots of the slopes from Fig. 21. Adapted, with permission, from Ref. 73.*

Actual reasons for equilibria in solid dosage forms may be chemical, as shown earlier for vitamin D_2 (52). Takahashi and Yamamoto (52) found that various excipients (dicalcium phosphate and talc) accelerated the approach to equilibrium and tied this in with surface acid on the excipients; experiments in hexane solution showed this to be the case in solution as well. Other compounds (ascorbic acid, folic acid, thiamine hydrochloride, and pyridoxine hydrochloride), having a pKa in the dry state of 2–4, also catalyzed the isomerization; but calcium pantothenate and niacinamide, having a "dry pKa" of 4.8–6.8, did not catalyze the isomerization. Carstensen *et al.* (87) showed that vitamin A in gelatin beadlets and vitamin E succinate (deesterification) approach equilibria in solid dosage forms and that the data can be plotted *via* a Van't Hoff (rather than an Arrhenius) plot (Fig. 24). In this case, two kinetic parameters (rate constant and equilibrium level) are sought. Simple procedures for attaining them have been published (87).

Some equilibria are predicated on competitive adsorption on a carrier [thiamine on microcrystalline cellulose (88)] (Fig. 25).

Kornblum and Zoglio (89) demonstrated that impurities present on the surface of solid excipients could give rise to equilibrium kinetics in solid dosage forms and described a suspension technique whereby the effect of particular batches of calcium stearate on the stability of aspirin could be predicted. It is assumed that there are surface impurities in an excipient and that they go into solution in the sorbed moisture layer where they can react with the active ingredient, *A*; the reaction continues until the impurity (*I*) is exhausted (Scheme VI):

$$A + I \longrightarrow C$$

Scheme VI

so:

$$-dC/dt = dI/dt = -kIA = -k'I \qquad \text{(Eq. 38)}$$

where the amount of active ingredient dissolved in the moisture layer, *A*, is the saturation concentration and hence constant. Equation 38 can be integrated to:

$$I = I_0 e^{-k't} \qquad \text{(Eq. 39)}$$

The amount of active compound lost is equivalent to

Table III—Potency of Bacitracin Troches

Number of Months Stored	Potency Retained, A		A − 65, 25°	log(A − 65), 25°
	40°	25°		
0	100	100	35	1.544
3	69	93	23	1.447
6	67	80	15	1.177
12	66	78	13	1.114
18	64	75	10	1.000
24	63	69	4	0.610

the amount of impurity lost (*i.e.*, $V[I_0 - I]$, where V is the volume of the sorbed layer). If the active component only degrades *via* Scheme VI, then the maximum loss is VI_0, so that $A_\infty = A_0 - VI_0$, and mass balance then dictates:

$$A - A_\infty = VI_0 e^{-k't} \qquad \text{(Eq. 40)}$$

The equilibrium level is *independent of temperature* whereas, of course, k' is temperature dependent. If this type, as is often the case, is superimposed on a regular decomposition, then time–potency curves will intersect the potency axis at lower than initial (and theoretical) potency; this is then referred to as "manufacturing loss," although it may truly be a "raw material loss."

If a limited amount of moisture is present, then Eq. 40 may still apply where now I_0 is the limited amount of moisture present. This can be superimposed on a first- or zero-order reaction to give a less than 100% intercept at time zero. The bend in the curve in this case would be a measure of the amount of water present (and would be temperature independent). To this end, it is important to be able to distinguish between free and bound moisture; Armstrong and Griffiths (90) published a method for such a differentiation.

DECOMPOSITIONS INVOLVING MOISTURE

Aspirin tableted in a microcrystalline cellulose base degrades by a first-order reaction as shown by Enezian (74). Other published data (91–93) imply that the trend reverts to a zero-order pattern with higher moisture contents. As pointed out earlier, the nature of a raw material can greatly influence the stability of a dosage form. Table IV, taken from the

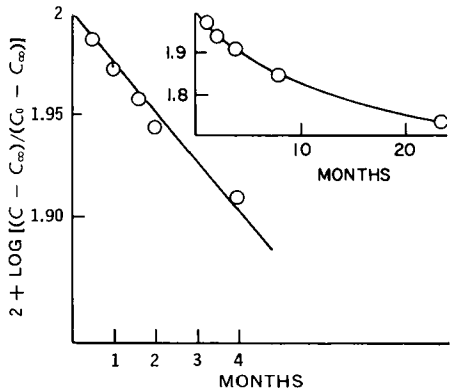

Figure 23—*Equilibrium treatment of data by Gross* et al. *(47).*

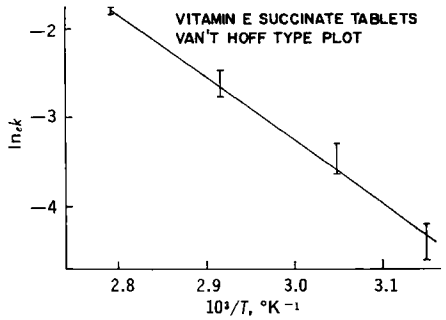

Figure 24—*Van't Hoff plot of vitamin E succinate decomposition in a solid dosage form. Adapted, with permission, from Ref. 87.*

work of Gold and Campbell (93), shows the effect of different talcs on the stability of aspirin tablets. Carstensen *et al.* (94) showed that vitamin A beadlets compressed in lactose degrade with rate constants that are proportional to the third power of the water content. *Stability programs should always include samples that have artificially been stressed by moisture addition. One purpose of a stability program should be to define the stability of the dosage form as a function of moisture content.*

SOLID-SOLID INTERACTIONS IN DOSAGE FORMS

There are only a few implied cases of solid-solid interactions as such in pharmaceutical dosage forms, although such interactions apparently would occur in many instances. The work by Troup and Mitchner (95) is classical and is illustrated in Fig. 27. It was concluded that in solid dosage forms containing aspirin and phenylephrine, there is a correlation between loss rates of both compounds. Chromatography proved the existence of acetylated phenylephrine in the dosage form, so that the acetic acid liberated in the aspirin decomposition resulted in acetylation of the phenylephrine; this is borne out by Fig. 27. Jacobs *et al.* (96) showed that a similar phenomenon takes place in aspirin-codeine combinations in solid

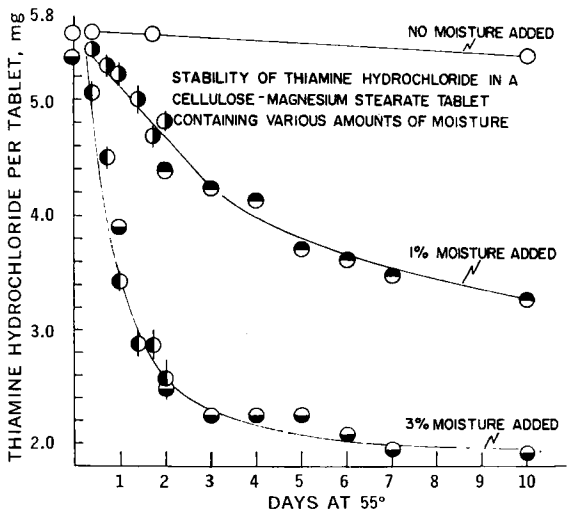

Figure 25—*Equilibrium attained in adsorption process in solid dosage form. Adapted, with permission, from Ref. 88.*

Table IV—Free Salicylic Acid (Percent) in Aspirin Tablets with Various Sources of Talc (93)

Weeks	Talc A	Talc B	Talc C	Talc D
0	0.1	0.1	0.1	0.1
1	0.13	0.30	0.93	0.28
2	0.23	0.69	2.61	0.57
4	0.41	1.07	5.85	1.12
8	0.32	2.05	13.00	1.46
12	0.80	3.35	25.80	2.96

dosage forms. Eppich *et al.* (97) showed that aspirin in alkaline environment degrades by a topochemical relation that adheres to Eq. 3*a* above 46° and to Eq. 7 below 46°.

The detection of solid–solid interactions in drug dosage form development programs is of great importance. By detecting so-called *incompatibilities* early in a development program, it is possible to formulate dosage forms with ingredients that are least likely to interact; this type of screening program is usually referred to as a "compatibility program" or a "preformulation screening program." A detailed, simple program was described by Carstensen *et al.* (98), and Table V shows the "general performance" of several excipients in 3 years of program performance.

The test simply consists of mixing drug and excipients in the stated amounts in a sealed vial and storing for 14 days at 55°. Half of the vials have moisture (5%) added to them, so that there is a dry and a "wet" rating. The appearance is gauged visually but, in later years, TLC has been employed as well to detect chemical interactions. Although the method provides a good preformulation screen, it is crude in quantitative aspects.

Lach and coworkers (99–107) developed methods for screening by using diffuse reflectance spectroscopy. In most of these investigations, *solutions* of drug were exposed to the adsorbent and equilibrated (often for 24 hr.) at 30°. These solutions were then vacuum dried (often at 40°). These "incompatibilities" are hence solvent mediated; they are an excellent quantitative refinement of the "wet" ratings referred to above but do not throw light on the dry ratings.

Compatibility tests give information about the chemical and physical stability that might result from storage of a dosage form containing the tested combination; one cannot necessarily draw conclusions regarding therapeutic availability from such tests. For instance, Su (108) showed that certain adsorbates on montmorillonite are of an ion-dipole nature and, hence, are not chemisorbed. They nevertheless cause shifts in diffuse reflectance spectroscopy spectra. The alleged interaction between silica gel and ascorbic acid (99–101) was shown (109) to be an interaction with moisture in that the ascorbic acid loss is directly proportional to the unbound moisture in the system. Bioassays furthermore showed that the bioavailability of ascorbic acid is unaffected by the presence of silica gel.

Blaug and Huang (110) demonstrated the interaction between dextroamphetamine sulfate and spray-dried lactose in a quantitative fashion by use of a (ethanol-mediated) diffuse reflectance spectroscopy technique.

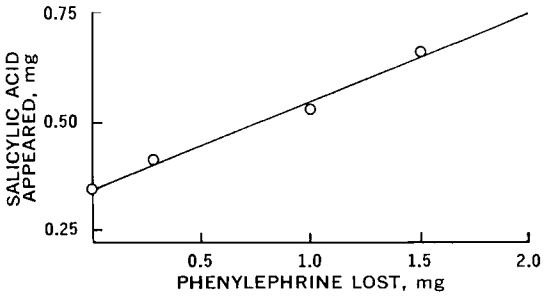

Figure 27—*Correlation between aspirin and phenylephrine stability (4 weeks, 70°) in solid dosage forms. Adapted, with permission, from Ref. 95.*

LIGHT SENSITIVITY OF SOLID DOSAGE FORMS

It was shown (111) that photolysis of surface molecules should give rise to first-order decay; free radicals were shown (112) to be of importance in this type of reaction. Other reports (113–120) established that the decay pattern consists of three consecutive first-order decays (Fig. 28) and stressed that the fad-

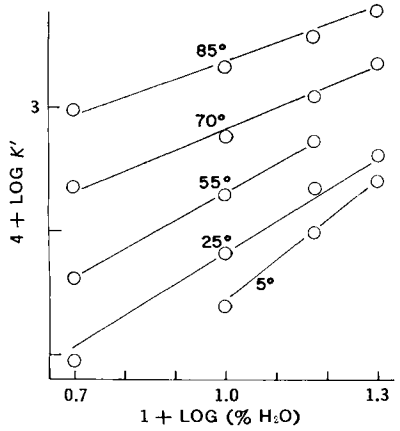

Figure 26—*Effect of moisture on vitamin A beadlet stability. Adapted, with permission, from Ref. 94.*

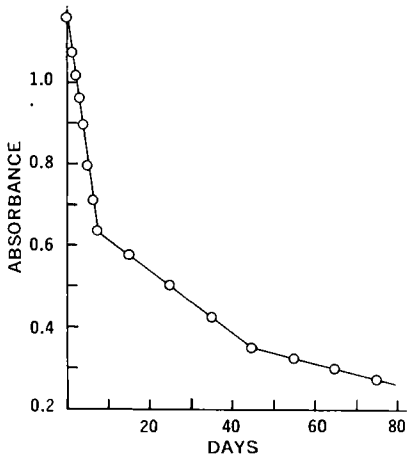

Figure 28—*Fading of the surface of tablets colored with FD&C Blue No. 1. Adapted, with permission, from Ref. 114.*

Table V—Categories for Two-Component Systems[a] (98)

		Identical	17–27 Months at 25° Worse	10 Days at 55° Worse	Total Score 25°	Total Score 55°
Drug *per se*	Dry	15	4	1	38	31
	5% water	9	8	3	49	38
Drug + magnesium stearate	Dry	16	3	1	34	30
	5% water	15	4	1	43	35
Drug + calcium stearate	Dry	13	4	3	37	32
	5% water	12	5	3	38	35
Drug + stearic acid	Dry	15	5	0	42	31
	5% water	7	11	2	60	38
Drug + talc	Dry	14	5	1	38	30
	5% water	10	8	2	45	34
Drug + acid-washed talc	Dry	12	8	0	44	31
	5% water	10	9	1	49	35
Drug + lactose	Dry	12	5	3	38	32
	5% water	9	7	4	65	56
Drug + calcium phosphate, dibasic, anhydrous	Dry	12	6	2	46	36
	5% water	9	8	3	66	53
Drug + starch	Dry	12	5	3	39	34
	5% water	10	5	5	40	37
Drug + mannitol	Dry	10	7	3	39	31
	5% water	8	7	5	47	45
Drug + terra alba	Dry	14	6	0	41	28
	5% water	11	6	3	50	45
Drug + sugar 4x	Dry	12	6	2	41	34
	5% water	9	7	4	63	61

[a] Values in fourth and fifth columns represent scoring from 1 to 6 for degree of color change (1 = unchanged, 6 = substantially changed) and from 1 to 6 for degree of fineness change.

ing is not necessarily three different mechanisms with different rates but that the probable causes are alteration in tablet surface and fading of subsequent layers. The photolysis is a *surface phenomenon* and, in most cases, the interior of the tablet will be unaffected.

It has been established (113–118) that when the fading has penetrated to a depth of 0.03 cm, the tablet surface appears white and that the faded layer does not become thicker upon further light exposure. This has also been demonstrated for plastics (121–123). The ratio of absorbed to scattered light, θ, relates to the fraction, R, absorbed to reflected light by the relation (124):

$$\theta = [1 - R^2]/2R \qquad \text{(Eq. 41)}$$

By use of this relation, Everhard and Goodhart (125) and Goodhart *et al.* (126, 127) showed that a suitable presentation of data consists of using "color difference" as the ordinate and "footcandle hours" as the abscissa.

APPEARANCE STABILITY

Appearance can be quantitated by reflectance measurements (98); tristimulus tests (which give percent reflectance X, Y, and Z at three wavelength bands) can be performed on tablet surfaces, and the parameter x, y, or z, where $x = 100X/(X + Y + Z)$, can be used for plotting. Plots such as the one shown in Fig. 29 result. After evaluation of the asymptote, plotting of log $[x/x_\infty]$/log $[x_0/x]$ usually gives a straight line (Fig. 30). The slopes of these lines are a type reaction constant k, and these can be plotted in Arrhenius plots; constants at 25° can be calculated from accelerated data (Fig. 31).

SUMMARY

It has been shown that solids *per se* decompose ei-

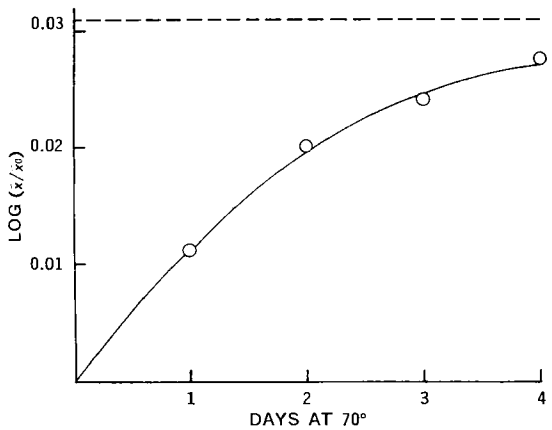

Figure 29—*Reflectance meter readings as a function of age of tablet. Adapted, with permission, from Ref. 98.*

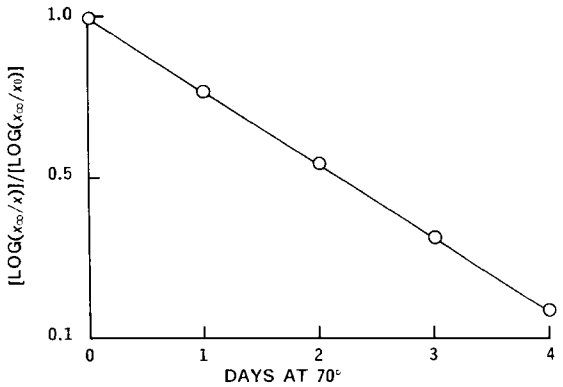

Figure 30—*Data in Fig. 29 plotted after adjustment for infinity value. Adapted, with permission, from Ref. 98.*

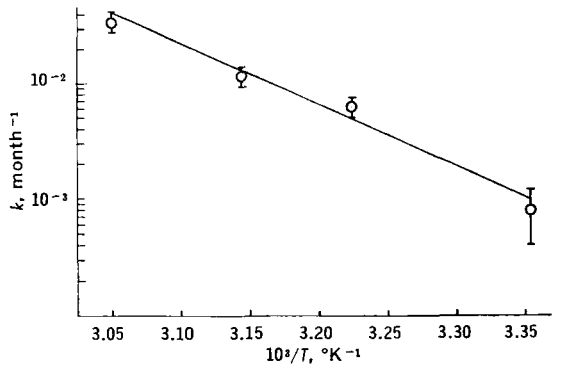

Figure 31—*Data from plots of the type shown in Fig. 30, plotted in formal Arrhenius fashion. Adapted, with permission, from Ref. 98.*

ther topochemically, in which case the decomposition appears *first order*, or by Prout-Tompkins kinetics, in which case *S-shaped curves* result. The logarithm of rate constants is, in a homologous series, often proportional to the reciprocal of the absolute melting temperature. When moisture is present, decomposition is often accounted for by solution kinetics of a saturated, sorbed solution, in which case, barring complications, the decomposition is *zero order*. If the decomposition is diffusion controlled, then it still appears zero order, but the solubility term is replaced by a smaller, constant concentration. In either event, the rate constants are amenable to *Arrhenius plotting*. In the case of interacting substances, the equation $[1 - (1 - x)^{1/3}]^2 = kt$ often holds.

These considerations often apply to solid dosage forms, with the one added feature that *equilibria* frequently occur. If these are of strictly chemical nature, then a *Van't Hoff plot* can be used for prediction of shelflife. Equilibria due to limited moisture content and limited impurity content have equilibrium levels that are temperature independent. Equilibria may also be due to competitive adsorption. The outlined principles allow meaningful prediction by accelerated testing methods when reaction patterns have been elucidated.

REFERENCES

(1) E. R. Garrett, *J. Pharm. Sci.*, **51**, 811(1962).

(2) E. R. Garrett, *Advan. Pharm. Sci.*, **2**, 1(1967).

(3) L. Lachman, *J. Pharm. Sci.*, **54**, 1519(1965).

(4) J. T. Carstensen, "Theory of Pharmaceutical Systems," vol. II, Academic, New York, N. Y., 1973, p. 295.

(5) W. McKeehan, *J. Pharm. Sci.*, **52**, 613(1963).

(6) W. McKeehan and L. Lappas, *ibid.*, **53**, 695, 847(1964).

(7) L. Lappas and R. Dempski, *ibid.*, **54**, 931(1965).

(8) R. Dempski and G. Polli, *ibid.*, **55**, 645(1966).

(9) P. D. Barnardo and E. J. Russo, *ibid.*, **58**, 777(1969).

(10) E. J. Russo and T. L. Benney, *ibid.*, **59**, 883(1970).

(11) T. L. Benney and W. E. Hamlin, *ibid.*, **60**, 959(1971).

(12) W. E. Hamlin and A. C. Shah, *ibid.*, **61**, 989(1972).

(13) D. A. Young, "Solid and Surface Kinetics," Pergamon Press, Oxford, England, 1966, p. 37.

(14) I. Langmuir, *J. Amer. Chem. Soc.*, **38**, 2263(1916).

(15) P. W. M. Jacobs and F. C. Tompkins, in "Chemistry of the Solid State," W. E. Garner, Ed., Butterworths, London, England, 1955, p. 201.

(16) S. Roginski and E. Schul'tz, *Z. Phys. Chem.*, **A138**, 21(1928).

(17) W. Jander, *Z. Anorg. Chem.*, **163**, 1(1927).

(18) I. Horikoshi and I. Himuro, *J. Pharm. Soc. Jap.*, **86**, 319, 324, 353, 356(1966).

(19) E. Prout and F. Tompkins, *Trans. Faraday Soc.*, **40**, 448(1944).

(20) V. Kohlschütter, *Kolloid-Z.*, **56**, 1169(1927).

(21) J. Coppeck, J. Colvin, and J. Hume, *Trans. Faraday Soc.*, **27**, 283(1931).

(22) W. Garner and W. Southon, *J. Chem. Soc.*, **1935**, 1705.

(23) W. Garner and H. Pike, *ibid.*, **1937**, 1565.

(24) J. Coppet and W. Garner, *Trans. Faraday Soc.*, **32**, 1739(1936).

(25) A. Wischin, *Proc. Roy. Soc.*, **A172**, 314(1939).

(26) M. Goldstein and T. Flanagan, *J. Chem. Ed.*, **41**, 276(1964).

(27) S. Kornblum and B. Sciarrone, *J. Pharm. Sci.*, **53**, 935(1964).

(28) E. R. Garrett, E. Schumann, and M. Grostic, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 684(1959).

(29) S. Eriksen, J. Pauls, and J. Swintosky, *ibid.*, **47**, 697(1958).

(30) J. Carstensen and M. Musa, *J. Pharm. Sci.*, **61**, 1112(1972).

(31) J. Carstensen, "Theory of Pharmaceutical Systems," vol. II, Academic, New York, N. Y., 1973, p. 303.

(32) K. Guillory and T. Higuchi, *J. Pharm. Sci.*, **51**, 100(1962).

(33) C. Bawn, in "Chemistry of the Solid State," W. E. Garner, Ed., Butterworths, London, England, 1955, p. 254.

(34) M. Gluzman, *Uch. Zap. Khar'kov Gos., Univ. A. M. Gor-'kogo*, **71**; *Tr. Khim. Fak. Nauch.-Issled. Inst. Khim.*, **14**, 177(1956).

(35) M. Gluzman, *Uch. Zap. Khar'kov Univ.*, **54**; *Tr. Khim. Fak. Nauch.-Issled. Inst. Khim.*, **12**, 333(1956).

(36) M. Gluzman, *Tr. Khim. Fak. Nauch.-Issled. Inst. Khim.*, **14**, 197(1956).

(37) M. Gluzman, *Zh. Fiz. Khim.*, **32**, 388(1958).

(38) M. Gluzman and D. Arlozorov, *Zh. Prik. Khim.*, **31**, 657(1958).

(39) M. Gluzman and I. Levitskaya, *ibid.*, **31**, 807(1958).

(40) M. Gluzman and R. Mil'ner, *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.*, **3**, 305(1956).

(41) *Ibid.*, **3**, 684(1960).

(42) M. Gluzman and D. Plotkina, *Tr. Khim. Fak. Nauch.-Issled. Inst. Khim.*, **14**, 187(1956).

(43) M. Gluzman, A. Gershuns, S. Polatnik, D. Plotkina, and R. Mil'ner, *Zh. Fiz. Khim.*, **27**, 1304(1955).

(44) J. Carstensen, "Theory of Pharmaceutical Systems," vol. I, Academic, New York, N. Y., 1973, p. 22.

(45) J. Carstensen and K. Su, *Bull. Parenteral Drug Ass.*, **25**, 287(1971).

(46) C. Brownley and L. Lachman, *J. Pharm. Sci.*, **53**, 452(1964).

(47) H. Gross, W. Johnson, and G. Lafferty, *J. Amer. Pharm. Ass., Sci. Ed.*, **45**, 447(1956).

(48) H. Gross, *ibid.*, **44**, 700, 705(1955).

(49) E. R. Garrett, *ibid.*, **43**, 539(1954).

(50) M. Nakanishi, T. Kuriyama, and M. Oda, *J. Pharm. Soc. Jap.*, **87**, 1(1967).

(51) J. Carstensen and P. Pothisiri, *J. Pharm. Sci.*, in press.

(52) T. Takahashi and R. Yamamoto, *J. Pharm. Soc. Jap.*, **89**, 909(1969).

(53) E. Shefter and G. Kmack, *J. Pharm. Sci.*, **56**, 1028(1967).

(54) W. E. Garner, in "Chemistry of the Solid State," W. E. Garner, Ed., Butterworths, London, England, 1955, pp. 213, 227.

(55) V. Kohlschütter and N. Nitschmann, *Z. Phys. Chem., Bodenstein Festband*, **1931**, 494.

(56) A. Zawadski, *Z. Elektrochem.*, **41**, 221(1935).

(57) G. Cohn, *Chem. Rev.*, **47**, 527(1947).

(58) R. P. Rastogi and N. B. Singh, *J. Phys. Chem.*, **70**, 3315(1966).

(59) *Ibid.*, **72**, 4446(1968).

(60) R. P. Rastogi, P. S. Bassi, and S. L. Chadha, *J. Phys.*

Chem., **66**, 2707(1962).
(61) *Ibid.*, **67**, 2569(1963).
(62) J. Tingstad and E. R. Garrett, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 352(1960).
(63) S. Kornblum, *Diss. Abstr.*, **24**, 1410(1963).
(64) L. Leeson and A. Mattocks, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 329(1958).
(65) L. J. Edwards, *Trans. Faraday Soc.*, **48**, 696(1962).
(66) J. T. Carstensen, "Theory of Pharmaceutical Systems," vol. II, Academic, New York, N. Y., 1973, p. 319.
(67) T. Eble and E. R. Garrett, *J. Amer. Pharm. Ass., Sci. Ed.*, **43**, 536(1954).
(68) L. J. DeMerre and C. Wilson, *ibid.*, **45**, 129(1956).
(69) J. T. Carstensen, "Theory of Pharmaceutical Systems," vol. II, Academic, New York, N. Y., 1973, p. 324.
(70) K. Savard, H. Wotis, P. Marcus, and H. Lemon, *J. Amer. Chem. Soc.*, **75**, 6327(1953).
(71) J. Haynes, J. Carstensen, J. Calahan, and R. Card, *Stevens Symp. Statist. Methods Chem. Ind.*, **3**, 1(1959).
(72) J. Carstensen, *J. Pharm. Sci.*, **53**, 839(1964).
(73) R. Tardif, *ibid.*, **54**, 281(1965).
(74) G. Enezian, *Rev. Prod. Probl. Pharm.*, **23**, 1(1968).
(75) A. Leyden, E. Pomerantz, and E. Bouchard, *J. Amer. Pharm. Ass., Sci. Ed.*, **45**, 771(1956).
(76) N. Lordi and M. Scott, *J. Pharm. Sci.*, **54**, 531(1965).
(77) L. Kennon, *ibid.*, **53**, 815(1964).
(78) K. Koshy, R. Duvall, A. Troup, and J. Pyles, *ibid.*, **54**, 549(1965).
(79) R. Duvall, K. Koshy, and R. Dashiell, *ibid.*, **54**, 1196(1965).
(80) N. Batuyios, *ibid.*, **55**, 727(1966).
(81) J. Campbell, *Can. Med. Ass. J.*, **68**, 103(1953).
(82) J. Campbell, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 598(1955).
(83) J. Campbell and H. Mcleod, *ibid.*, **44**, 263(1955).
(84) J. Bird and R. Shelton, *ibid.*, **39**, 500(1950).
(85) S. Seth and H. Mital, *Indian J. Pharm.*, **27**, 119(1965).
(86) T. Macek and B. Feller, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 662(1955).
(87) J. Carstensen, J. Johnson, D. Spera, and M. Frank, *J. Pharm. Sci.*, **57**, 23(1968).
(88) J. Carstensen, M. Osadca, and S. Rubin, *ibid.*, **58**, 549(1969).
(89) S. Kornblum and M. Zoglio, *ibid.*, **56**, 1569(1967).
(90) N. A. Armstrong and R. V. Griffiths, *Powder Technol.*, **1**, 374(1967/68).
(91) S. Lee, G. DeKay, and G. Banker, *J. Pharm. Sci.*, **54**, 1153(1965).
(92) M. Nazareth and C. Huyck, *ibid.*, **50**, 620(1961).
(93) G. Gold and J. Campbell, *ibid.*, **53**, 52(1964).
(94) J. Carstensen, E. Aron, D. Spera, and J. Vance, *ibid.*, **55**, 561(1966).
(95) A. Troup and H. Mitchner, *ibid.*, **53**, 375(1964).
(96) A. L. Jacobs, A. E. Dilatush, S. Weinstein, and J. J. Windheuser, *ibid.*, **55**, 893(1966).
(97) D. Eppich, E. Nelson, and J. Carstensen, *ibid.*, in press.
(98) J. Carstensen, J. Johnson, W. Valentine, and J. Vance, *ibid.*, **53**, 1050(1964).
(99) J. L. Lach and M. Bornstein, *ibid.*, **54**, 1731(1965).
(100) M. Bornstein and J. L. Lach, *ibid.*, **55**, 1033(1966).
(101) J. L. Lach and M. Bornstein, *ibid.*, **55**, 1040(1966).
(102) M. Bornstein, J. P. Walsh, B. J. Munden, and J. L. Lach, *ibid.*, **56**, 1410(1967).
(103) M. Bornstein, J. L. Lach, and B. J. Munden, *ibid.*, **57**, 1653(1968).
(104) W. Wu, T. Chin, and J. L. Lach, *ibid.*, **59**, 1122(1970).
(105) *Ibid.*, **59**, 1234(1970).
(106) J. L. Lach and L. D. Bighley, *J. Pharm. Sci.*, **59**, 1261(1970).
(107) J. D. McCallister, T. Chin, and J. L. Lach, *ibid.*, **59**, 1286(1970).
(108) K. Su, Ph.D. thesis, University of Wisconsin, Madison, Wis., 1971, p. 115.
(109) E. DeRitter, M. Osadca, L. Magid, and S. H. Rubin, *J. Pharm. Sci.*, **59**, 229(1970).
(110) S. M. Blaug and V. Huang, *ibid.*, **61**, 1770(1972).
(111) P. Kubelka, *J. Opt. Soc. Amer.*, **38**, 448(1948).
(112) J. Weiss, *J. Soc. Dyers Colour.*, **65**, 719(1949).
(113) L. Lachman, C. Swartz, and J. Cooper, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 213(1960).
(114) L. Lachman, S. Weinstein, C. Swartz, T. Urbanyi, and J. Cooper, *J. Pharm. Sci.*, **50**, 141(1961).
(115) L. Lachman, T. Urbanyi, S. Weinstein, J. Cooper, and C. Swartz, *ibid.*, **51**, 321(1962).
(116) R. Kuramoto, L. Lachman, and J. Cooper, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 175(1958).
(117) C. Swartz, L. Lachman, T. Urbanyi, and J. Cooper, *J. Pharm. Sci.*, **50**, 145(1961).
(118) C. Swartz, L. Lachman, T. Urbanyi, S. Weinstein, and J. Cooper, *ibid.*, **51**, 326(1962).
(119) C. Swartz and J. Cooper, *ibid.*, **51**, 89(1962).
(120) T. Urbanyi, C. Swartz, and L. Lachman, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 163(1960).
(121) N. Desai and C. Giles, *J. Soc. Dyers Colour.*, **65**, 635(1949).
(122) E. Atherton and I. Seltzer, *ibid.*, **65**, 585(1949).
(123) A. Taylor and W. Pracejus, *Illum. Eng.*, **45**, 149(1950).
(124) P. Kubelka and F. Munk, *Z. Tech. Phys.*, **12**, 593(1931).
(125) M. Everhard and F. Goodhart, *J. Pharm. Sci.*, **52**, 281(1963).
(126) F. Goodhart, M. Everhard, and D. Dickcius, *ibid.*, **53**, 388(1964).
(127) F. Goodhart, H. Lieberman, D. Mody, and F. Ninger, *ibid.*, **56**, 63(1967).

ACKNOWLEDGMENTS AND ADDRESSES

Received from the *Center for Health Sciences, School of Pharmacy, University of Wisconsin, Madison, WI 53706*