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Short Communication

Rate equation for solid state decomposition of aspirin in the presence of moisture

Wu-Huang Yang ** and Dana Brooke *

Pharmaceutical Product Development Department, Mead Johnson Pharmaceutical Division, Evansville, IN 47721 (U.S.A.)

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There are, in the literature, two approaches to describing the solid state decomposition of acetylsalicyclic acid (I) in the presence of water vapor. The earliest was published in 1958 by Leeson and Mattocks. They proposed a model in which a thin film of water was adsorbed onto the surface of the crystals. The small volume of moisture was assumed to be saturated by instantaneously dissolved I. Hydrolysis of I then occurred in a system which was conceptually that of a suspension with an extremely high concentration of solids. Studies at temperatures of 50–80°C and various partial pressures of water vapor indicated that the rate of decomposition of I increased markedly in the early part of the drug vs time profile. This accelerated phase was explained on the basis that acetic acid from the hydrolysis of I made the moisture layer progressively more acidic. This, in turn, accelerated the decomposition of I due to the well-known specific-acid catalysis (Edwards, 1950) of acetylsalicylic acid hydrolysis.

The other approach to the decomposition of solid I is typified by the papers of Hasegawa et al. (1975) and Okamura et al. (1980). Here, the decomposition of I or its derivatives is treated from the standpoint of formation and growth of reaction nuclei on the crystal surfaces. This approach satisfactorily explains the acceleratory phase in the profile but leads to expressions which are empirical and difficult to relate to processes at the molecular level (e.g. bond breaking). This approach does, nevertheless, represent the current thinking of many workers in the field of solid state reactions (Ng, 1975).

The Leeson and Mattocks paper (1958), because of the elegance of the proposed model, undoubtedly contributed much to the conceptualization of solid state reac-

* To whom correspondence should be addressed.
** Present address: Quality Control Department, Allergan, Irvine, CA, U.S.A.

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tions in the presence of water vapor. It is not surprising that it has been cited in a number of discussions on solid state reactions (Carstensen et al., 1969; Carstensen, 1974; Nelson et al., 1974; Carstensen and Pothisiri, 1975; Hasegawa et al., 1975; Byrn, 1976; Yoshioka et al., 1979; Okamura et al., 1980). Nevertheless, in spite of the elegance of the sorbed-moisture model, we have eschewed the Leeson and Mattocks (1958) derivation[1] of a rate equation. Instead, we wish to report a different, straightforward mathematical analysis of the sorbed-moisture model for the degradation of aspirin in the solid state.

The rate law for the proposed model is:

$$\frac{dn_{II}}{dt} = kn_H n_{I,s} \tag{1}$$

where n_{II} is the number of moles of salicylic acid (II) formed from the hydrolysis of I, k is a rate constant, n_H is the number of moles of hydrogen ion in the liquid phase and $n_{I,s}$ is the number of moles of I dissolved in the liquid film. If the volume (V) of the sorbed moisture layer is constant, and S is the solubility of I in mol/liter, then:

$$\frac{dn_{II}}{dt} = kn_H VS \tag{2}$$

The number of moles of II and of acetic acid from the hydrolysis of I are equal. Thus, if all of the hydrogen ion is assumed to be from the dissociation of acetic acid, then n_H can be approximated by:

$$n_H = (n_{II} K_a V)^{1/2} \tag{3}$$

where K_a is the dissociation constant of acetic acid. Thus, Eqn. 2 becomes:

$$\frac{dn_{II}}{dt} = kSK_a^{1/2} V^{3/2} n_{II}^{1/2} \tag{4}$$

Integrating Eqn. 4 with an initial condition of $n_{II} = 0$ at $t = 0$ leads to:

$$n_{II}^{1/2} = \tfrac{1}{2} kSK_a^{1/2} V^{3/2} t \tag{5}$$

Since $n_{II} = n_{I,o} - n_I$, where $n_{I,o}$ is the initial number of moles of I present, and if N is the total number of moles of salicyclate[2] in the sample, Eqn. 5 becomes:

$$\left(\frac{n_{I,o} - n_I}{N} \right)^{1/2} = \tfrac{1}{2} kSK_a^{1/2} N^{-1/2} V^{3/2} t \tag{6}$$

[1] We believe that the step in the Leeson and Mattocks (1958) derivation from Eqn. 3 ($K = (H^+)^2/(C)$) to Eqn. 4 ($KV = (H^+)^2/(C)$) is invalid. A similar situation occurs in going from Eqn. 6 to Eqn. 7. From Eqn. 4 onward, the units on the left and right sides of the equations are inconsistent. (Please see the referenced paper for definitions.)

[2] The term N accounts for the presence of salicylic acid in the sample initially. However, n_{II} is defined as amount of salicylic acid formed *during* the hydrolysis reaction and is necessarily zero at zero time.

TABLE I

SLOPES OF THE DECOMPOSITION EQUATION OF ASPIRIN (EQN. 8)

Temp. (°C)	Vapor pressure (mm Hg)	Slope $= \frac{1}{2}kk'^{3/2}SK_a^{1/2}N^{-1/2}P^{3/2n}$	r^2
80	181.0	1.810×10^{-3} h^{-1}	0.98
	199.5	2.370×10^{-3} h^{-1}	0.97
	232.5	2.704×10^{-3} h^{-1}	0.99
60	68.41	2.967×10^{-3} day^{-1}	0.99
	74.50	3.347×10^{-3} day^{-1}	0.99
	111.9	5.145×10^{-3} day^{-1}	0.98
	120.3	6.595×10^{-3} day^{-1}	0.96
50	46.02	9.807×10^{-4} day^{-1}	0.96
	54.50	1.206×10^{-3} day^{-1}	0.96
	68.30	1.513×10^{-3} day^{-1}	0.97
	74.20	2.059×10^{-3} day^{-1}	0.98

Eqn. 6 is in a convenient form for the use of the Leeson and Mattocks data.

The adsorption of moisture onto the aspirin crystal surface is assumed to follow the Freundlich adsorption isotherm equation:

$$V = k'P^{1/n} \tag{7}$$

where k′ and n are constants and P is the partial pressure of water vapor. Substituting Eqn. 7 into Eqn. 6, we obtain:

$$\left(\frac{n_{I,o} - n_I}{N}\right)^{1/2} = \tfrac{1}{2}kk'^{3/2}SK_a^{1/2}N^{-1/2}P^{3/2n}t \tag{8}$$

Where P is constant, a plot of the left hand side of Eqn. 8 vs time should be a straight line. Data generated by Leeson and Mattocks[3] (1958) were treated in this manner using a least-squares regression method. Excellent r^2 values (Table I) were obtained. Typical data are presented in Fig. 1. The values of the slopes are shown in Table I.

According to Eqn. 8, when log (slope) is plotted against log P at constant temperature, a straight line should be obtained with an intercept of $\log(\frac{1}{2}kk'^{3/2}SK_a^{1/2}N^{-1/2})$ and a slope of 3/2n. Data from Table I were treated in this fashion and are graphically represented in Fig. 2. Table 2 shows the values of the parameters obtained from Fig. 2 using a least-squares regression method. Further separation to deduce k is difficult and complicated by not knowing N and the values

[3] We consider the Leeson and Mattocks data to be reliable because of their statement that no salicylic acid was lost due to volatilization and the original amount of I could always be accounted for by a summation of I and II found. Gore et al. (1968) have found that loss of salicylic acid by volatilization could affect the reliability of similar studies. Byrn (1976) has expressed a similar concern in his review on the solid state reactions.

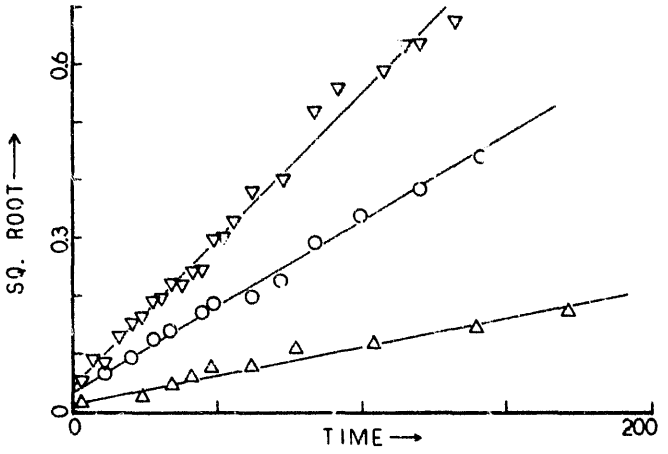

Fig. 1. A plot of typical data from Leeson and Mattocks according to Eqn. 8. The ordinate is the left hand side of the equation, the abscissa is time in days. The data represented are: 50°C at 46.02 mm Hg (△); 60°C at 68.41 mm Hg (○); and 60°C at 111.9 mm Hg partial pressure of water (▽). The lines drawn are least-squares lines.

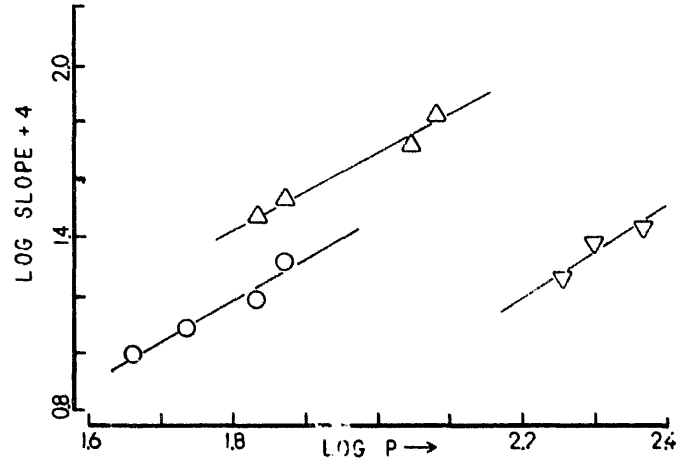

Fig. 2. A plot illustrating the dependence of the slope obtained from Eqn. 8 on the partial pressure of water vapor. The temperatures were: 50°C (○), 60°C (△) and 80°C (▽). The lines drawn are least-squares line. See text.

TABLE 2

VALUES OF PARAMETERS OBTAINED FROM THE PLOT OF log(SLOPE) VS log P

Temp. (°C)	3/2n	$\frac{1}{2}kk'^{3/2}SK_a^{1/2}N^{-1/2}$	r^2
80	1.54	6.422×10^{-7} h^{-1} mm Hg$^{-3/2n}$	0.90
60	1.29	1.268×10^{-5} day^{-1} mm Hg$^{-3/2n}$	0.97
50	1.42	4.197×10^{-6} day^{-1} mm Hg$^{-3/2n}$	0.94

of S, K and k' at the temperatures studied. Reducing the data to $kk'^{3/2}$ and treating $\log(kk'^{3/2})$ vs $1/T$ in the Arrhenius fashion (Leeson and Mattocks, 1958) seems unproductive because the temperature-dependence of k' is unknown.

The mechanism proposed by Leeson and Mattocks is not without challenge. The role of formed acetic acid in further accelerating the decomposition of I was questioned by Okamura et al. (1980) after they vacuum-dried 'pre-decomposed' samples of I and then returned the samples to their humid-high temperature condition. The degradation rate of those dried samples was equal to that of the samples not vacuum-dried. Okamura et al. argued that the vacuum-drying would have removed acetic acid and that the rate should be low (equivalent to that of a fresh sample of I) if an autocatalytic effect for acetic acid were important. This result may be difficult to accept in view of what is known about the solution-phase degradation of I.

There may be other weaknesses in the Leeson-Mattocks model. For example, as degradation occurs, acetic acid would become a significant fraction of the adsorbed liquid film. This, in turn, could change the solubility of I as well as the degradation rate. In addition, the accumulation of crystalline II, as well as acetic acid, could alter the distribution of water in the sample. Moreover, as suggested by Okamura et al. (1980), greater strains in the crystal due to the reaction could cause fracturing accompanied by creation of new surface. On the other hand, degradation of I would lead to reduction of crystal volume and, therefore, reduction of surface. Finally, the attractive assumption of instantaneous dissolution of I to replace drug which has decomposed may bear closer scrutiny. Nevertheless, the sorbed-moisture model is helpful in visualizing the possible events in solid state aspirin degradation. If the rate equation derived herein is applied to data cautiously, with due regard for the limitations discussed, it should prove useful.

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