Topochemical Decomposition Patterns of Aspirin

ELWYN NELSON, DAVID EPPICH, and J. T. CARSTENSEN[x]

Abstract □ Aspirin in alkaline environment in a solid dosage form is shown to decompose by topochemical reaction patterns. At lower temperatures, the rate-determining step is diffusion controlled, whereas at higher temperatures it is kinetically controlled.

Keyphrases □ Aspirin—degradation in alkaline media, topochemical reactions □ Degradation, aspirin—in alkaline media, topochemical reactions

Some major reviews of solid substances have appeared in the past (1-4). The emphasis in general has been on stability prediction, although some work relating to mechanisms has also been considered (1, 3). In most reported specific cases, reaction orders were first (5) or zero (6) order; however, in a few cases (1, 7-10), broad, general (physical and chemical) bases for the degradations were arrived at.

Horikoshi and Himuro (11) reported the only topochemical reaction scheme in the pharmaceutical literature, although it was pointed out indirectly (3) that this type of reaction is probably the reason for most degradations in the solid state that appear to be first order. The purpose of the present study was to demonstrate the existence of topochemical reactions in competition with one another in the degradation of aspirin in an alkaline environment.

THEORY

If a cylinder nucleates on the curved surface but not on the ends, then the linear decomposition rate will be given by:

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

in which r and r_0 are the radii as illustrated in Fig. 1*a*, k is a rate constant, and t is time. By referring to Fig. 1*a*, it is easily seen that the mole fraction α decomposed at time t is given by:

$$1 - \alpha = \frac{h\pi r^2}{h\pi r_0^2} = [1 - (k/r_0)t]^2 \qquad \text{(Eq. 2)}$$

in which h is the height, or:

$$\sqrt{1 - \alpha} = 1 - (k/r_0)t \qquad \text{(Eq. 3)}$$

If a small amount of (spherical) material, B, is embedded in a matrix of A, and if $A + B \rightarrow C$ is the decomposition reaction, then at time t, A must diffuse through a layer of C which is equal to $r_0 - r$ in thickness. It is here assumed that A is the mobile species and that the reaction is diffusion controlled, *i.e.*, A reacts instantaneously with B, once it has diffused through the C layer. Loss of A causes a proportional increase in the C layer by a factor of γ, so one may write:

$$-\frac{dA}{dt} = \gamma\left(\frac{dl}{dt}\right) = \frac{q}{l} \qquad \text{(Eq. 4)}$$

in which $l = r_0 - r$ is the thickness of the C layer and q is a diffusional coefficient. The latter part of the equality in Eq. 4 is obtained from Fick's law.

Equation 4 may be integrated to:

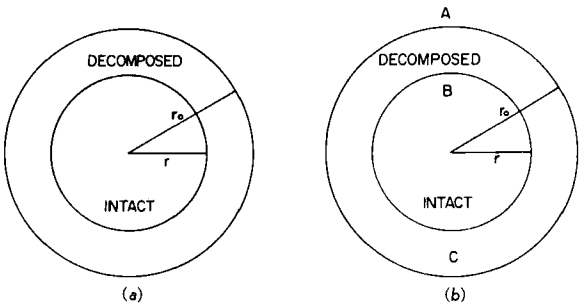

Figure 1—*Situation of* (a) *contracting cylinder and* (b) *contracting sphere, where* B *is intact drug separated from a catalyzing substance* (A) *by a layer of decomposition product.*

$$l^2 = (2q/\gamma)t = k't \qquad \text{(Eq. 5)}$$

or:

$$r_0 - r = \sqrt{k't} \qquad \text{(Eq. 6)}$$

It is seen that:

$$1 - \alpha = \frac{\pi r^3}{\pi r_0^3} = [1 - \sqrt{k''t}]^3 \qquad \text{(Eq. 7)}$$

the latter step being accomplished through Eq. 6. Here:

$$k'' = k'/r_0^2 = (2q)/(\gamma r_0^2) \qquad \text{(Eq. 8)}$$

Equation 7 is most conveniently written in the form:

$$[1 - \sqrt[3]{(1 - \alpha)}]^2 = kt \qquad \text{(Eq. 9)}$$

EXPERIMENTAL AND RESULTS

It is well known that aspirin decomposition is catalyzed by al-

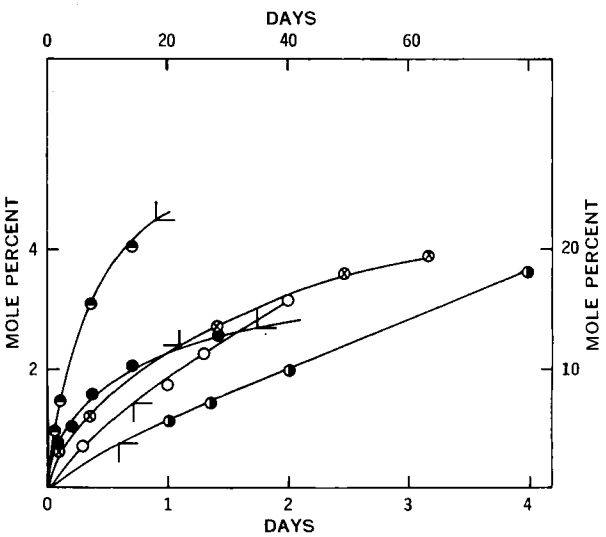

Figure 2—*Decomposition patterns of aspirin in alkaline environment. Key:* ○, *50°;* ◑, *47.5°;* ◓, *45°;* ●, *40°; and* ⊗, *25°.*

Table I—Salicylic Acid Content of Two Batches of Tablets

	2 Weeks of Storage at 40°		4 Weeks of Storage at 40°		12 Weeks of Storage at 25°	
	10.7	9.8	12.2	11.7	6.03	5.69
	10.9	9.5	12.3	12.3	6.54	5.23
	10.5	9.7	12.9	11.9	6.78	5.43
	11.2	9.9	12.8	11.7	6.21	5.66
	11.2	9.7	13.4	12.3	6.73	5.54
	11.0	9.7	12.6	12.3	6.03	5.58
Average	10.92	9.72	12.90	12.00	6.39	5.52
Standard deviation	0.28	0.13	0.40	0.30	0.34	0.17
$1 - \sqrt[3]{1 - \alpha}$	0.0378	0.0335	0.0449	0.0417	0.0217	0.0187
$\sqrt{t}$, $(\text{week})^{1/2}$	1.41	1.41	2	2	3.46	3.46
k	0.027	0.024	0.023	0.024	0.0062	0.0054

kali (12); therefore, tablets were made containing 324 mg of aspirin *(B)* in a total tablet weight of 3.5 g. The excipient was sodium bicarbonate *(A)*, pH 8.3 [0.1% (w/v) in water at 25°]. Five different batches of this composition were prepared.

Tablets were stored (four per container) in hermetically tight containers in stability ovens set at 25, 35, 40, 47.5, and 50°. Bottles were withdrawn from the ovens at the intervals indicated in Fig. 2. The four tablets were dissolved in 200 ml of water, the inside of the bottle was rinsed with water, and the volume was adjusted to 250 ml. The solution was then assayed for salicylic acid by UV absorption at 295 nm and adjusted for the contribution from aspirin at this wavelength. Prepared mixtures of salicylic acid and aspirin with 0.5–20 mole % of salicylic acid gave a standard deviation of 3–1 relative % when groups of four were assayed. Hence, the coefficient of variation of averages of four is of the order of 1.5–0.5 relative %. Six bottles from each batch were assayed from each stability point. The coefficient of variation of samples of four ranged from 1 to 2.5 relative % (Table I), the increase over the expected being the (expected) contribution of oven temperature variation (±0.5°) and tablet-to-tablet variation.

The data in Table II and in Fig. 2 are the stability patterns obtained. The figures are averages of five batches. If no batch-to-batch variation existed, one would expect the coefficient of variation to be $2.5/\sqrt{5}$–$1/\sqrt{5}$ or 1.1–0.45 relative %. In actuality, the data exhibit coefficients of variation from 1 to 2 relative % on the averages shown in the table, so that, for example, a salicylic acid content of 5.0% should have $\pm 2\sigma$ limits of about 0.2%.

DISCUSSION

The data in Fig. 2 at 47.5 and 50° adhere to Eq. 3 but not to Eq. 9 nor to a contracting sphere equation, derived in a fashion similar to the one leading to Eq. 3:

$$\sqrt[3]{1 - \alpha} = 1 - \left(\frac{k_0}{r_0}\right) \cdot t \qquad \text{(Eq. 10)}$$

The adherence to Eq. 3 is demonstrated in Fig. 3. On the other hand, the data in Fig. 2 at the lower temperatures adhere to Eq. 9 but not to Eq. 10 nor 3 (Fig. 4). The rate constants from Fig. 4 adhere well to an Arrhenius equation (Fig. 5).

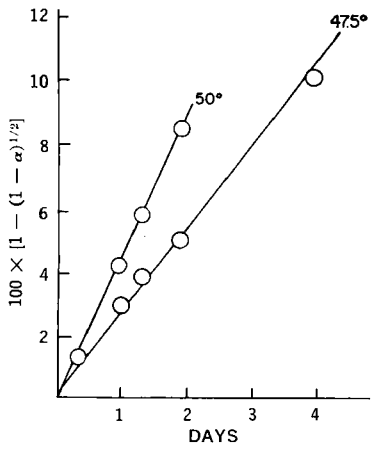

Figure 3—*Data from 50 and 47.5° treated according to Eq. 3.*

It has been pointed out (3) that topochemical reactions may *appear* first order. Figure 6 shows that the data in Fig. 2 can be made to fit an equilibrium scheme:

$$S = S_\infty(1 - e^{-Kt}) \qquad \text{(Eq. 11)}$$

As, however, the data are followed for longer times, S_∞ increases and, in essence, Eq. 11 only approximates Eq. 9 in a time interval up to $2 \times t'$, where t' is the largest time value in the study.

The inconsistency shows up in Arrhenius and Van't Hoff plots (which are only linear in fortuitous choices of t'). This is particularly important in the following context. Stability studies are usually thought of as a development tool in formulation choices and in the setting of ultimate overages in dosage forms. They are, however, *of great value in quality control as early warning systems, i.e.,* in monitoring whether a particular batch of a product has a suitable room temperature stability (*i.e.*, whether it falls into the limits projected from many other batches of the same product). For this purpose, a correlation test is usually necessary; in the cited case, *(a)* accelerated checks at temperatures above 45° would be meaningless and correlation to room temperature data would be unsound; and *(b)* in establishing correlation between behavior *at* 45° with patterns at room temperature, k and

Table II—Salicylic Acid Formation as a Function of Time at Various Temperatures

Temperature	Days (t)	Salicylic Acid, mole % (100)	$1 - \sqrt{1 - \alpha}$	$1 - \sqrt[3]{1 - \alpha}$	$\sqrt{t}$
25°	2	0.59	—	0.00197	1.41
	7	1.18	—	0.00394	2.65
	28	2.70	—	0.00908	5.29
	49	3.60	—	0.01214	7.00
	63	3.90	—	0.01317	7.94
35°	1	1.60	—	0.00536	1.00
	2	2.08	—	0.00698	1.41
	4	2.97	—	0.01002	2.00
40°	1	3.08	—	0.01037	1.00
	2	4.40	—	0.01489	1.41
	7	8.09	—	0.02772	2.65
	14	10.40	—	0.03594	3.74
	28	13.04	—	0.04550	5.29
45°	1	4.79	—	0.01622	1.00
	2	7.27	—	0.02484	1.41
	7	15.46	—	0.05444	2.65
	14	20.48	—	0.07354	3.74
47.5°	1	5.48	0.02778		
	1.33	7.26	0.03699		
	2	9.64	0.0443		
	4	18.08	0.09446		
50°	0.33	3.48	0.01755		
	1	8.7	0.04448		
	1.33	11.55	0.05952		
	2	16.93	0.08857		

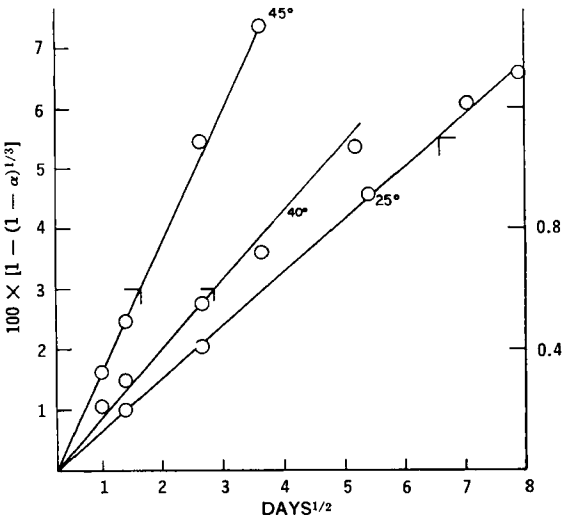

Figure 4—*Data from the remaining temperatures treated according to Eq. 10.*

E_a from Eq. 9 would be the parameters to use to get such correlations as "x days at 45° correspond to y days at 25°."

The explanation for the change in mechanism is fairly apparent. Let A = alkali, B = aspirin, and C = salicylic acid. Then $B \rightarrow C$ is catalyzed by A, so that:

$$-\frac{dB}{dt} = k_A[A] + k_B \qquad \text{(Eq. 12)}$$

where k_B is a spontaneous decomposition rate constant; $k_A \gg k_B$, but γ and k_B are such that at $T \geq 45°$ there is always A supplied to the interface between B and C, so that the first term in Eq. 12 is dominating. At $T > 47.5°$, k_B is sufficiently large so the interface proceeds more rapidly than the rate with which A can reach it. Hence, in the low temperature region the reaction is diffusion controlled, and in the higher temperature region it is kinetically controlled.

The considerations leading to Eqs. 3, 9, and 10 hold for a monodisperse powder. Carstensen and Musa (13) showed that if a cube root law (Eq. 10) holds for a monodisperse population, then it also holds for a log-normally distributed polydisperse population.

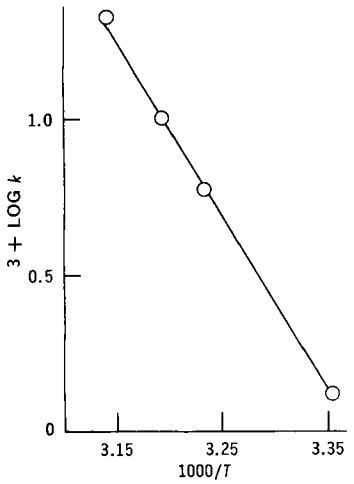

Figure 5—*Rate constants from Fig. 4 treated according to an Arrhenius equation.*

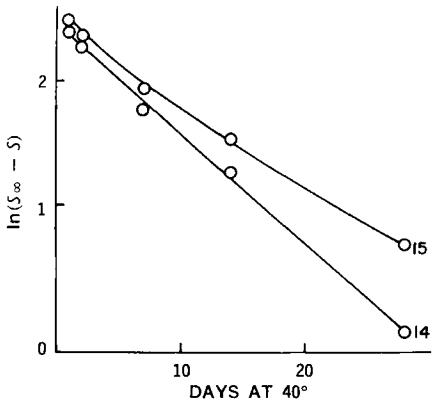

Figure 6—*Data for 40° treated by a pseudo-first-order scheme with equilibrium. Data seemingly linearize with an equilibrium level of 14 mole % salicylic acid. For limitations to this approach, see text.*

The value of slope k^*, however, would not be the same as k_0/r_0. The same type of consideration holds true for Eqs. 3 and 9 and k^* would be different from k/r_0 and k, respectively. This prohibits direct testing of the model *via* variation of r_0 (fineness of powder) in the actual situation where powders are polydisperse (as they are by necessity in tablet manufacture). Since the smallest particle decomposes completely before larger particles, it should be possible to see biphasic decompositions in cases such as these. However, in situations where the standard deviation of the particle-size distributions was not excessively large, these transitions would take place at times of high level of decomposition and were not observed in this study.

The effect of particle size on the decomposition was not a subject of systematic study in this investigation.

REFERENCES

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

(2) J. Carstensen, "Theory of Pharmaceutical Systems," vol. II, Academic, New York, N.Y., 1973, pp. 295–352.

(3) J. T. Carstensen, *J. Pharm. Sci.*, **63**, 1(1974).

(4) L. Lachman, *ibid.*, **54**, 1519(1965).

(5) J. T. Carstensen, J. J. Johnson, D. Spera, and M. Frank, *ibid.*, **57**, 23(1968).

(6) M. Nakanishi, T. Kuriyama, and M. Oda, *J. Pharm. Soc. Jap.*, **89**, 909(1969).

(7) L. Leeson and A. Mattocks, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 329(1958).

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

(9) K. Guillory and T. Higuchi, *ibid.*, **51**, 100(1962).

(10) J. T. Carstensen and N. M. Musa, *ibid.*, **61**, 1112(1972).

(11) I. Horikoshi and I. Himuro, *J. Pharm. Soc. Jap.*, **86**, 319(1966).

(12) L. J. Edwards, *Trans. Faraday Soc.*, **48**, 696(1952).

(13) J. T. Carstensen and N. M. Musa, *J. Pharm. Sci.*, **61**, 223(1972).

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[x] To whom inquiries should be directed. Present address: School of Pharmacy, University of Wisconsin, Madison, WI 53706