guished (on standing the color reappeared). The blanks required 13.40 ml. thiosulfate (theory = 13.29 ml.).

The activity parameter was determined as follows. A 5-ml. portion of the fraction was diluted to 60 ml., and a 0.1-ml. dose was given intraperitoneally twice daily for 10 days to eight mice starting 20 hr. after inoculation of 5×10^6 Ehrlich ascites tumor cells. At 30 days, the number of ascitic (abdominal distension) and nonascitic survivors was counted. The activity parameter is the sum of the nonascitic survivors and one-half the ascitic survivors out of the group of eight mice used for each bioassay. Only tubes 5–10 had any survivors at 30 days. The bioassays gave the results shown in Table V. The data on all of the parameters obtained are plotted in Fig. 2.

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ACKNOWLEDGMENTS AND ADDRESSES

Received January 15, 1973, from the *Department of Pharmacology, University of Hawaii, Leahi Hospital, Honolulu, HI 96816*

Accepted for publication April 10, 1973.

Supported by the Elsa U. Pardee Foundation, Midland, Mich.; the Juliette M. Atherton Trust and the F. C. Atherton Trust, Honolulu, Hawaii; and Public Health Service Grant CA-12623 from the National Cancer Institute.

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Nonsink Dissolution Rate Equation

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Abstract ☐ An equation was developed which describes the dissolution of monodisperse particles beyond the point where concentrations are small compared to solubility. If it is assumed that a stagnant layer model applies, the thickness of these layers is of the same order of magnitude as calculated *via* the Hixson–Crowell treatment but dissolution rate constants are 1.5–2 times as large. The application of the equation to dissolution of hydrocortisone, levodopa, and *p*-hydroxybenzoic acid is shown.

Keyphrases ☐ Dissolution rates, monodisperse particles—equation developed for nonsink conditions, applied to hydrocortisone, levodopa, and *p*-hydroxybenzoic acid ☐ Particles, monodisperse—nonsink dissolution rate equation developed, applied to hydrocortisone, levodopa, and *p*-hydroxybenzoic acid

The equation by Hixson and Crowell (1) has been employed for many years [*e.g.*, Wurster and Taylor (2)] for the purpose of describing the dissolution rates of monodisperse powders. Higuchi and Hiestand (3), Carstensen and Musa (4), and Brooke (5) extended its use to describe the dissolution kinetics of polydisperse powders. The treatment relies on an assumption of sink conditions, a condition that frequently—but not always (particularly for sparingly soluble compounds)—applies. Therefore, it was considered appropriate to seek a solution not relying on sink conditions.

THEORY

When Fick's law (6) is applied to dissolution of a spherical particle under laminar flow conditions, allowing for an adsorbed surface film, it takes the form:

$$dm/dt = (L)\, dC/dt = \frac{DO}{h}[S - C] = LkO[S - C] \quad \text{(Eq. 1)}$$

where m is the mass dissolved, L is the volume of the dissolution medium, C is the concentration in the dissolution medium, t is time, ρ is the density of the solid, D is the diffusion coefficient, O is the surface area, h is the thickness of the adsorbed liquid film, S is solubility, k is the dissolution rate constant[1], n is the number of particles, r is the diameter of each particle, and subscript zero denotes initial magnitudes.

The Hixson–Crowell treatment emanates from the Noyes–Whitney equation, where it is assumed that $C \ll S$; this leads to the well-known cube root equation:

$$m_0^{1/3} - m^{1/3} = Kt \quad \text{(Eq. 2)}$$

where:

$$K = 1.61LkS(n^{1/3})/(\rho^{2/3}) \quad \text{(Eq. 3)}$$

If sphericity is assumed as above, S is assumed to be independent of r, and sink conditions are not invoked, one has the following expression for the concentration in the medium at time t:

$$C = \frac{n\rho}{L}\frac{4\pi}{3}[r_0^3 - r^3] = \alpha[r_0^3 - r^3] \quad \text{(Eq. 4)}$$

where:

$$\alpha = \frac{n\rho}{L}\frac{4\pi}{3} \quad \text{(Eq. 5)}$$

Equations 1 and 4 may be combined in the form:

$$dC = -\frac{n\rho}{L}\frac{4\pi}{3}3r^2\, dr = k(n4\pi r^2)[S - \alpha(r_0^3 - r^3)]\, dt \quad \text{(Eq. 6)}$$

or:

$$-\frac{\rho}{L}\, dr = k[\beta + \alpha r^3]\, dt \quad \text{(Eq. 7)}$$

where:

$$\beta = S - (m_0/L) \quad \text{(Eq. 8)}$$

is positive when:

$$m_0 < SL \quad \text{(Eq. 9)}$$

The assumption is made in the following that the amount of

[1] The dimension of k is cm.$^{-2}$ sec.$^{-1}$. Some authors denote kL (cm./sec.) as the dissolution rate constant.

Table I—Data by Hussain (7) Fitted by Eqs. 2 and 13

Hydrocortisone: Time t, min.	$\psi_1(r)$, $\frac{cm.^4}{g.}$	$y_1 = \sqrt[3]{m_0} - \sqrt[3]{m}$	Levodopa: Time t, min.	$\psi_2(r)$, $\frac{cm.^4}{g.}$	$y_2 = \sqrt[3]{m_0} - \sqrt[3]{m}(g.^{1/3})$
0	42.44	0.00000	0	0.211	0.0000
8.5	42.24	0.00768	1	0.206	0.0191
23	40.25	0.02009	1.3	0.202	0.0252
26	39.31	0.02676	2	0.183	0.0406
40	35.93	0.04387	3	0.178	0.0635
49.6	32.12	0.05902	4	0.161	0.0926
70.1	30.15	0.06722			
Slope[a]	-0.197 ± 0.003[b]	0.00105 ± 0.00003[b]		-0.014 ± 0.004[b]	0.023 ± 0.003[b]
Intercept[a]	43.61 ± 0.07[b]			0.218 ± 0.009[b]	

[a] Least-square fits of the equations in the form $\psi(r) = -kt + \psi(r_0)$ and $y = Kt$. For goodness of fit, see text. [b] The 95% confidence values based on the stated equations.

Table II—Dissolution Rate Data for p-Hydroxybenzoic Acid in 0.1 N HCl

Time t, min.	C_1[a], mg./ml. Calculated	C_1[a], mg./ml. Found	$\Delta_1^2 = [C_1 - C_1]^2$	C_2[b], mg./ml., Calculated	$\Delta_2^2 = [C_2 - C_1]^2$
0	0.000	0.000	0.000	0.089	7.8×10^{-3}
2	0.179	0.511	0.110	0.479	1.6×10^{-3}
6	0.529	1.036	0.257	0.921	13.2×10^{-3}
10.4	0.901	1.533	0.400	1.573	1.5×10^{-3}
13	1.115	1.781	0.443	1.814	1.1×10^{-3}
16.5	1.398	2.074	0.457	2.127	2.9×10^{-3}
20	1.672	2.397	0.526	2.374	0.6×10^{-3}
55	4.026	4.633	0.368	4.705	5.2×10^{-3}
105	6.308	6.201	0.011	6.264	0.3×10^{-3}
120	6.782	6.562	0.049	6.551	0.1×10^{-3}
			$\frac{\Sigma\Delta^2}{9-1} = 0.328$		$\frac{\Sigma\Delta^2}{10-2} = 4.29 \times 10^{-3}$

[a] Calculated *via* cube root equation corresponding to $\sqrt[3]{m_0} - \sqrt[3]{m} = 0.0049t$. [b] Calculated *via* Eq. 13 corresponding to $\psi(r) = 3.136 - (5.714 \times 10^{-3}) \times t$ (where $q = 0.00683$ cm. and $\beta = 2.2173$ mg./ml.).

powder used is insufficient to saturate completely the dissolution medium or just suffices to do so. Since the term $(\beta + \alpha r^3)$ is positive, Eq. 7 may be rewritten:

$$\frac{dr}{\beta + \alpha r^3} = -\frac{kL}{\rho}\,dt \qquad \text{(Eq. 10)}$$

The integral of the left-hand side is:

$$\psi(r) = \frac{q}{6\beta}\ln\left[\frac{(r+q)^2}{r^2 - qr + q^2}\right] + \frac{q}{\beta\sqrt{3}}\,\text{arctg}\,\frac{r\sqrt{3}}{2q - r} \qquad \text{(Eq. 11)}$$

where:

$$q = (\beta/\alpha)^{1/3} \qquad \text{(Eq. 12)}$$

Equation 10, when integrated and subjected to initial conditions, therefore becomes:

$$\psi(r) = \psi(r_0) - \frac{kL}{\rho}t \qquad \text{(Eq. 13)}$$

$\psi(r)$, when plotted *versus* t, should then give a straight line with intercept $\psi(r_0)$ and slope $-kL/\rho = -(DL)/(h\rho)$.

RESULTS AND DISCUSSION

To test whether Eq. 13 gives results significantly different from Eq. 2 (and Eq. 3), the data reported by Hussain were plotted (7), primarily because the dissolution rates reported were carried into nonsink concentration ranges (30% saturation) and because Hussain rigorously reported all values of parameters necessary for computations of the cited nature.

Furthermore, the range of dissolution was extended in the following manner, using p-hydroxybenzoic acid as a test substance. p-Hydroxybenzoic acid was recrystallized from water, dried *in vacuo*, and screened. Material finer than 60 mesh but coarser than 80 mesh (USP) was used; this material had an average "diameter" of 212 μm., *i.e.*, $r = 106$ μm. The density of the material was determined pycnometrically to be 1.2626 g./ml. at 25 ± 0.1°. Three hundred milliliters of 0.1 N HCl was placed in a 1000-ml. conical flask and agitated by a magnetic stirrer at 58 r.p.m. The temperature was maintained at 25 ± 0.5°, and 2.485 g. of the p-hydroxybenzoic acid was added at zero time. Samples were withdrawn by pipet through glass wool at various time intervals and assayed at the UV absorption peak at 255 nm.

Results are listed in Tables I and II and shown graphically in Figs. 1–3. The calculated parameters in the tables are least squares fitted. It is noted from Figs. 1 and 2 that Eqs. 2 and 13 are adhered to well. How well can be estimated by the variances of the fits in

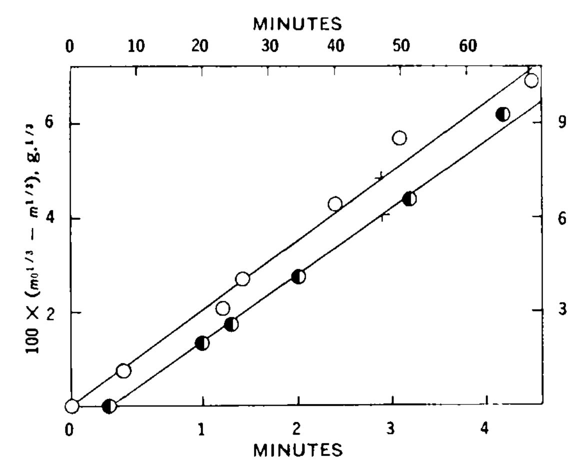

Figure 1—*Data by Hussain* (7) *plotted according to Eq. 2. The upper and left scales refer to hydrocortisone* (○) *and the lower and right scales refer to levodopa* (◐).

Table III—Dissolution Rate Constants (k) Calculated from Eqs. 2 and 13

	I, cm.$^{-2}$ sec.$^{-1}$, Eq. 2	k, cm.$^{-2}$ sec.$^{-1}$, Eq. 13	D, cm.^{2}/sec.	L, cm.^{3}	h, cm., Eq. 13
Hydrocortisone	4.4×10^{-6}	8.4×10^{-6}	2.47×10^{-6}	500	0.6×10^{-3}
Hydrocortisone	4.4×10^{-6}	8.4×10^{-6}	6×10^{-6} [a]	500	1.4×10^{-3}
Levodopa	4.1×10^{-6}	7.1×10^{-6}	4.6×10^{-6} [a]	500	1.3×10^{-3}
p-Hydroxybenzoic acid	0.19×10^{-6}	0.40×10^{-6}	6.21×10^{-6} [a]	300	5.2×10^{-3}

[a] By Wilke's method (8).

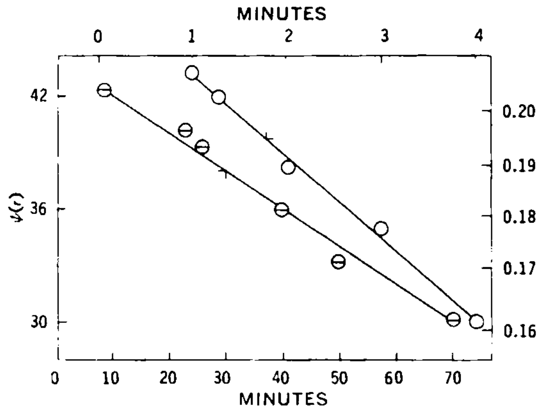

Figure 2—*Data by Hussain (7) plotted according to Eq. 13. The upper and right scales refer to levodopa (○) and the lower and left scales refer to hydrocortisone (⊖).*

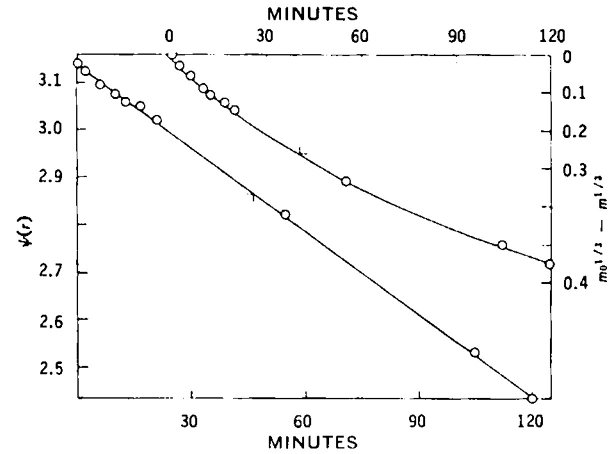

Figure 3—*Dissolution rate data of p-hydroxybenzoic acid plotted according to Eq. 13 (lower curve) and to Eq. 2 (upper curve).*

linear form, *i.e.*, $C = f(t)$. The variance is $\Sigma \Delta^2/\nu$, where $\Delta = \hat{C} - C$, ν denotes degrees of freedom, and $\hat{C}$ is the concentration calculated from the least-squares fit. For example, at time $t = 40$ in hydrocortisone dissolution (Table I), $\sqrt[3]{0.022} - \sqrt[3]{m} = 0.00105 \cdot 40$, so $m = 0.0135$ or $\hat{C} = 0.0135/500 = 27 \times 10^{-3}$ mg./ml. as compared to $C = 23 \times 10^{-3}$ mg./ml. found experimentally. The calculation of $\hat{C}$ corresponding to Eq. 13 is more cumbersome but can be done either graphically or by aid of a computer. It is noted from Table II (Fig. 3) that for p-hydroxybenzoic acid under nonsink conditions, Eq. 13 affords a significantly better fit than Eq. 2 [$F = 76$ as compared to $F_{0.01}$ (critical) = 5.5]. In the case of hydrocortisone and levodopa (where nonsink conditions were not so prevalent), both equations afford comparable fits.

Although statistical comparisons are worthwhile, the main point is that Eq. 13 gives a theoretically more correct solution than Eq. 2 under nonsink conditions and the data support this by exhibiting reasonable fits.

From the slope of the data plotted *via* Eq. 13, k can be found through knowledge of L and ρ. Similarly, knowledge of L, S, n, and ρ allows calculation of k from the slopes of data plotted *via* Eq. 2. These k values are listed in Table III. It is noted, as a general trend, that k values calculated from Eq. 2 are about half as large as those calculated from Eq. 13. Diffusion constants can be estimated *via* the Stokes-Einstein equation either *via* radius estimates from crystallographical parameters or *via* Wilke's method (8). The data by Haner and Norton (9) were used to obtain a diffusion coefficient for hydrocortisone of 2.47×10^{-6} cm.^{2}/sec.; by Wilke's method a value of 6×10^{-6} cm.^{2}/sec. results. By employing the relation $k = D/(hL)$, the value of h (the thickness of the adsorbed layer of liquid) can be estimated and is found to be 0.6×10^{-3} cm. = 60 μm. when using $D = 2.47 \times 10^{-6}$ cm.^{2}/sec. and 140 μm. when using $D = 6 \times 10^{-6}$ cm.^{2}/sec. Other values of this type are listed in Table III. The values are of the same order as those estimated by Hussain (7), Levy (10), and Cressman *et al.* (11).

The dimension of q is obtained from Eqs. 9 and 5 and was found to be $\{(g./ml.)/[g./(ml.)^2]\}^{1/3}$ = cm. The polynomial $r^2 - qr + q^2$ has no rational roots. The term in the denominator of the arctg function in Eq. 11 must be larger than zero; *i.e.*, cubing the inequality $2q > r$ (which is allowable since $\beta/\alpha > 0$), one gets: $(\beta/\alpha) = \{[S - (m_0/L)]/(n\pi 4\rho/3L)\} > (r^3/8)$ or $(LS - m_0) > (m/8)$, so that there is the added requirement that $LS > (9m_0/8)$ (since m can be at most m_0). This requirement is slightly more stringent than the one expressed in Eq. 9 and was adhered to in the experiment dealing with p-hydroxybenzoic acid (the initial amount being 80% of solubility). Not all of the p-hydroxybenzoic acid was dissolved at the end of the experiment, and the particle-size range was sufficiently narrow so that the number of particles had not decreased (4).

The arctg function is not single valued; $x = r\sqrt{3}/(2q - r)$ is here expressed in radians between 0 and $\pi/2$. Equation 11 could equally well have been expressed with values of x between 2π and $5\pi/2$, but this would simply increase both $\psi(r)$ and $\psi(r_0)$ by $2\pi q/(\beta\sqrt{3})$ and Eq. 13 would still apply. Hence, using $0 < x < \pi/2$ does not cause a loss in generality.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 5, 1973, from the *School of Pharmacy, University of Wisconsin, Madison, WI 53706*

Accepted for publication April 12, 1973.

Presented at the Arden House Conference, Columbia University School of Pharmacy, Harriman, N.Y., February 1973.

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