Correlation between Dissolution and Disintegration in Dissolution Apparatuses

Keyphrases □ Dissolution—disintegration, mathematical model linking dissolution and disintegration □ Disintegration—dissolution, mathematical model linking dissolution and distintegration

To the Editor:

El-Yazigi (1) in a recent article has proposed a model that links dissolution and disintegration in a dissolution apparatus. In deriving a convenient mathematical presentation mode, he assumes that the rate of appearance of dissolved material (A_s) is proportional to the mass of undissolved particles (A_p):

$$\frac{dA_s}{dt} = k_s A_p \qquad \text{(Eq. 1)}$$

where t is time and k_s is a dissolution rate constant (obviously in units of reciprocal time). He correctly cautions that this is not necessarily correct. The reason for using the mass dependence ($k_s A_p$ in Eq. 1) rather than a surface dependence:

$$\frac{dA_s}{dt} = k' \cdot \Gamma \cdot (A_p)^{2/3} \qquad \text{(Eq. 2)}$$

in which Γ is a shape factor (2), is presumably a mathematical convenience. It is an interesting approach, and it is the intent of this communication to compare the conclusion of El-Yazigi with those of previous investigators (3, 4). In the latter case the conditions of Eq. 2 and sink conditions were employed (*i.e.*, a cube root law was assumed) for the dissolution of drug from particles. The equations arrived at were for a basket apparatus, but a similar approach with similar conclusions can be arrived at for the simpler paddle apparatus.

The equations in the previous report (1) predict a biphasic exponential decay of undissolved mass, where the exponential term in the later phase depends on k_s. Several previously published treatments (3–6) have dealt with this problem. Carstensen *et al.* (3, 4) predicted (and demonstrated experimentally) that the undissolved mass should decay in a biphasic manner in the (often encountered) particular cases where disintegration (k_d in reciprocal time units) is rate determining. The latter phase is an exponential decay, but with the exponent dependent on k_d, *i.e.*, being a function of disintegration. This, however, is not universally applicable and only holds if the disintegration is rate limiting. A similar model has been developed (5) using (and demonstrating) a cube root dissolution model for the powder in a tablet, and for an established dissolution curve the disintegration curve was back calculated (6). This latter approach was found to be of a power exponential type [$\exp(-tb/a)$, where a and b are Weibull constants]. Other reports supporting surface dependent models have appeared in the literature (7).

In any event, the approach (1) is interesting and contains some supporting data which allow for some comparisons. Eq. 11 of Ref. 1 states:

$$DT_{calc} = 6 \cdot 0.693/k_d \qquad \text{(Eq. 3)}$$

where DT_{calc} is the calculated disintegration time obtained from the exponent of the initial phase of the dissolution plot. It is, as shown, based on the assumption that 1.56% of the tablet weight remaining (6 half-lives) constitutes complete disintegration. This is as good a conservative termination point as any, but it should be pointed out that there is nothing magical about it, and that, for instance, five half-lives would have been a good estimate as well. From a physical point of view, it might be rational to assume that the point where the tablet has been reduced to the size of a granule (8) (either the one used in producing the tablet or the one produced by disintegration) might be the cutoff point.

If, on the other hand, the number of half-lives, n, is assumed unknown than Eq. 3 takes the form:

$$DT = n\ 0.693/k_d \qquad \text{(Eq. 4)}$$

where DT stands for disintegration time. In logarithmic form this becomes:

$$\ln(DT) = \ln n + \ln 0.693 - \ln k_d \qquad \text{(Eq. 5)}$$

If this is equated to the experimentally determined disintegration time (DT), then $\ln(DT)$ should be linear in $\ln k_d$ with a slope of -1. The data from Table II of Ref. 1 are repeated in this form in Table I, and $\ln(DT)$ is shown as a functon of $\ln k_d$ in Fig. 1. It is seen that there is fair

Table I—Data from Table II of Reference 1

$\ln DT_{exp}$	$\ln k_d$
2.64	−1.136
2.34	−0.774
1.91	−0.785
2.43	−1.008
2.29	−0.884
3.20	−1.595
Slope[a]	−1.314
Intercept[a]	1.114
Correlation Coefficient[a]	−0.994

[a] Regression of $\ln DT$ on $\ln k$.

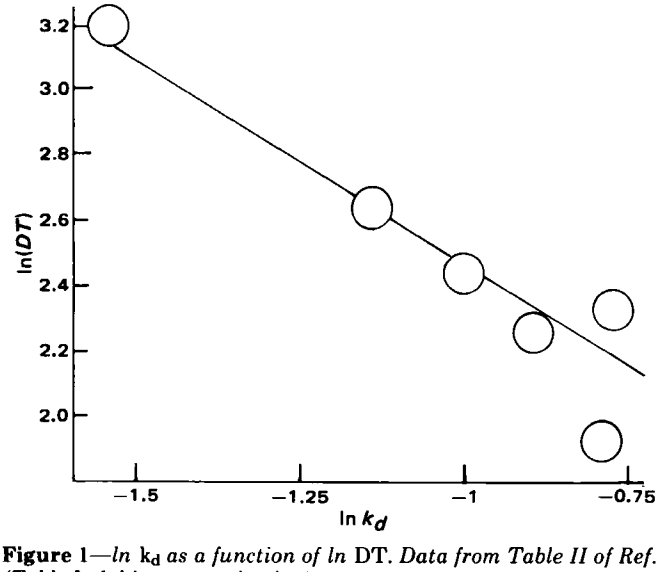

Figure 1—*ln* k_d *as a function of ln* DT. *Data from Table II of Ref. 1 (Table I of this communication).*

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linearity (the correlation coefficient being 0.994 as shown in Table I). The least-squares fit is:

$$\ln(DT) = -1.32 \ln k_d + 1.114 \qquad \text{(Eq. 6)}$$

Although the slope is (significantly) different from −1, it is of the same order of magnitude so that this fact in no way disproves the utility of the previous method[1]. From the intercept it can be concluded that $\ln(0.693n) = 1.114$, *i.e.*, $n = 3.0/0.693 = 4.4$ half lives.

It is seen that further analysis of the data (1) do not disprove the hypothesis put forth. Whether the model of El-Yazigi is more applicable than previously proposed models (3, 4) is a point for future experimentors to verify.

(1) Adnan El-Yazigi, *J. Pharm. Sci.*, **70**, 535 (1981).
(2) T. Y-F. Lai and J. T. Carstensen, *Int. J. Pharm.*, **1**, 33 (1978).
(3) J. T. Carstensen, J. L. Wright, K. W. Blessel, and J. Sheridan, *J. Pharm. Sci.*, **67**, 48 (1978).
(4) *Idem.*, **67**, 982 (1978).
(5) K. G. Nelson and L. Y. Wang, *J. Pharm. Sci.*, **67**, 1758 (1977).
(6) *Idem.*, **67**, 86 (1978).
(7) J. T. Carstensen, R. Kothari, and Z. T. Chowhan, *Drug. Dev. Ind. Pharm.*, **6**, 569 (1980).
(8) K. A. Khan and C. T. Rhodes, *J. Pharm. Sci.*, **64**, 166 (1975).

J. T. Carstensen[x]
School of Pharmacy
University of Wisconsin,
Madison, WI 53706

Ashok Mehta
Formby's Inc.
Olive Branch,
Miss. 38654

M. A. Zoglio
Merrell-Dow Laboratories
Cincinnati, OH 45215

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[1] Equation 6 is approximate in the sense that different formulations are being compared.

BOOKS

Annual Review of Pharmacology and Toxicology. Vol. 22. Edited by ROBERT GEORGE, RONALD OKUN, and ARTHUR K. CHO. Annual Reviews Inc., 4139 El Camino Way, Palo Alto, CA 94306. 1982. 739 pp. 16 × 23 cm. Price $22.00 ($25.00 outside USA).

Traditionally, the first chapter of each volume of this annual review has been devoted to a historical/philosophical/autobiographical topic. This year it is an autobiographical statement by Thomas H. Maren. Traditionally also, the last chapter has been reserved for Chauncey Leake's "Review of Reviews." Since Leake's death, that feature has been continued in a very creditable fashion by E. Leong Way, although with a somewhat narrower perspective. The remainder of the book consists of 23 reviews of the literature, which have been sorted into 13 sections with 1–4 chapters each.

The sections of this year's review are titled: Mechanisms of Action of Drugs and Chemicals; Perinatal Pharmacology; Antimicrobial, Antiviral, and Antiparasite Chemotherapy; Cardiovascular Pharmacology; Renal Pharmacology; Neuropharmacology and Neurochemistry; Behavioral and Psychopharmacology; Anesthetics, Analgesics, and Anti-Inflammatory Agents; Endocrine Pharmacology; Comparative Pharmacology; Environmental and Industrial Pharmacology and Toxicology; Clinical Pharmacology and Drug Interaction; and Techniques.

One would presume that the chapters within each section would be clumped together but, in actuality, they are randomly distributed among the chapters of other sections. Therefore, the practice of dividing the table of contents into sections seems to be an unnecessary gesture since the readers of this volume will be quite capable of grasping the general content of each chapter from the titles themselves.

Individuals in the pharmaceutical sciences will find the review by H. H. Szeto on "Pharmacokinetics in the Ovine Maternal–Fetal Unit" to be of interest and the review on "Food and Drug Interactions" by C. Jelleff Carr to be useful but rudimental. Especially effective literature reviews are M. J. Antonaccio's "Angiotensin Converting Enzyme (ACE) Inhibitors," J. Torretti's "Sympathetic Control of Renin Release," and H. E. Brezenoff and R. Giuliano's "Cardiovascular Control by Cholinergic Mechanisms in the Central Nervous System." Perhaps the most provocative review is "Neurochemical Basis of Acupuncture Analgesia" by J. S. Han and L. Terenius, while the most debatable offering is "Sociopharmacology" by M. T. McGuire, M. J. Raleigh, and G. L. Brammer.

This reviewer has a standing order for this series and considers it essential as a continuing education tool and as a quick reference source. The number of primary references per review ranges from 67 to 318 for this volume. Considering the current prices for technical books, this series is a bargain by any standard that might be applied.

Reviewed by Marvin H. Malone
Physiology and Pharmacology Unit
School of Pharmacy
University of the Pacific
Stockton, CA 95207

Topics in Pharmaceutical Sciences Edited by D. D. BREIMER and P. SPEISER. Elsivier/North Holland Biomedical Press, Amsterdam, The Netherlands 1981. 535 pp. 16 × 24 cm. Price $69.74 U.S., 150 Dfl.

The book, which contains over thirty chapters, is the proceedings of the 41st International Congress of FIP, held in Vienna, Austria, Sept. 1981. There chapters are divided into seven symposia which cover some of the major areas of thrust in the pharmaceutical sciences. The symposium titles are:

Advances in Pharmacokinetics;
Pharmaceutical Aspects of Anti-Cancer Drug Treatment;
Biopharmaceutics: Advances in Drug Delivery
Drug Stability *in vitro* and *in vivo;*
Analysis and Drug Metabolites in the 80s;
Pharmaceutical Technology;
Gene Manipulation, Cell Cultures, and Pharmaceutical Sciences.

An author index is provided but, unfortunately, there is no subject index. The price is rather high for a symposium proceeding produced from camera-ready copy.

Since *Topics in Pharmaceutical Sciences* covers a very broad spectrum of subjects, it cannot be recommended for anyone seeking an in-depth discussion on any particular subject. (It averages less than 80 pages per symposium.) It can, however, be recommended for those who want an overview of the current thinking in the subjects covered.

Reviewed by S. H. Yalkowsky
The Upjohn Co.
Kalamazoo, MI 49001