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x To whom inquiries should be directed

Dissolution Profile of Log-Normal Powders II: Dissolution before Critical Time

DANA BROOKE

Abstract □ The dissolution of log-normal powders, particularly in that period before the smallest particles disappear, was examined. An approximation for the slope of a cube-root law plot was developed for the dissolution before the critical time of ideally distributed powders. Such an approximation does not hold, however, for severely truncated log-normal distributions. The work of previous investigators in this area appears to be incorrect and is discussed.

Keyphrases □ Dissolution profiles—log-normal powders, dissolution before critical time, cube-root law plot approximation □ Powders, dissolution—log-normal distribution profile, dissolution before critical time, cube-root law plot approximation □ Particle dissolution—log-normally distributed powders, dissolution before critical time, cube-root law plot approximation

In their paper on the dissolution of powders that follow the log-normal distribution, Carstensen and Musa (1) attempted to find correlations between the well-known "cube-root law" (2) and their computer-generated dissolution patterns. They offered two approximations to the cube-root law wherein the slopes were stated as functions of the means and standard deviations of the log-normal distributions. One equation dealt with dissolution before the time when the smallest particles disappeared, *i.e.*, before the "critical time." Another equation dealt with dissolution after the critical time.

Brooke (3), in a discussion of exactly calculated dissolution profiles for log-normally distributed powders, reported that the Carstensen and Musa approximation for dissolution before the critical time gave excellent results. Further examination of this subject, however, shows that the approximation is incorrect. The test of the approximation (3) was, in fact, inconclusive.

The present paper examines the time course of dissolution, particularly in that period before a significant number of particles disappear, for log-normally distributed powders varying in standard deviation and extent of truncation. As expected, for narrow distributions the cube-root law holds for dissolution before the critical time. However, one approximation of the cube-root law slope will not apply for all log-normal distributions. An approximation is offered that does hold for powders obeying the ideal log-normal distribution.

THEORETICAL AND CALCULATIONS

The complete derivation of an expression that exactly describes the dissolution of log-normal powders was given by Brooke (3). Briefly, if there is a powder containing spherical particles of diameters a_0 which are distributed, on a numbers basis, so that $\ln a_0$ is normal with mean μ and standard deviation σ, then the probability frequency f of log diameters is:

$$f = (1/\sigma\sqrt{2\pi})e^{-(\ln a_0 - \mu)^2/2\sigma^2} \qquad \text{(Eq. 1)}$$

If such particles dissolve isotropically under sink conditions and if the solubility C_s is independent of particle size, then the diameters a_τ of particles at some function τ of time can be written (1) as:

$$a_\tau = a_0 - \tau \qquad \text{(Eq. 2)}$$

Here τ is $2kC_st/\rho$, where k is a proportionality constant, ρ is particle density, and t is time. The weight w_τ of a powder remaining at any τ is found by the integration:

$$w_\tau = \int(\pi\rho N/6)(a_0 - \tau)^3 f \, d \ln a_0 \qquad \text{(Eq. 3)}$$

where N is the number of particles at time zero. This is somewhat different from the integral in Eq. 6 of the Carstensen and Musa (1) paper.

The limits of integration in Eq. 3 depend on τ and on the original powder distribution. Let i and j be numbers that reflect the extent of truncation at the small particle end and the large particle end, respectively. If the powder is such that all $\ln a_0$ are found between $\mu - i\sigma$ and $\mu + j\sigma$, then for $\ln \tau \leq \mu - i\sigma$, the integration would be from $\mu - i\sigma$ to $\mu + j\sigma$. For $\ln \tau > \mu - i\sigma$, the integration would be from $\ln \tau$ to $\mu + j\sigma$. If $i = j = \infty$, the solution to Eq. 3 becomes Eq. 13 of the previous paper (3).

Table I—Exactly Calculated Dissolution Profiles for Various Log-Normal Powders[a]

		Ideal Distributions, $i = 10, j = 10$							Truncated Distributions: $i = 2, j = 10$			Truncated Distributions: $i = 1, j = 10$		Truncated Distributions: $i = 2, j = 2$		
τ/M	$\sigma = 0$	0.03	0.05	0.1	0.2	0.3	0.5	0.7	0.03	0.1	0.3	0.1	0.3	0.03	0.1	0.3
0.1	72.9	73.0	73.1	73.5	75.3	78.1	85.0	91.6	73.0	73.6	78.1	74.0	78.6	72.9	73.4	76.8
0.2	51.2	51.3	51.5	52.2	55.3	59.9	72.0	84.0	51.3	52.4	60.0	53.0	60.7	51.3	52.0	57.8
0.3	34.3	34.4	34.6	35.6	39.3	45.2	60.9	77.1	34.5	35.7	45.2	36.4	46.0	34.4	35.3	42.4
0.4	21.6	21.7	21.9	23.0	27.0	33.4	51.4	70.8	21.8	23.1	33.5	23.8	34.2	21.7	22.6	30.3
0.5	12.5	12.6	12.8	13.8	17.7	24.2	43.3	65.2	12.7	13.9	24.3	14.5	24.9	12.6	13.5	21.1
0.6	6.4	6.5	6.7	7.6	11.1	17.3	36.6	60.1	6.5	7.6	17.3	8.1	17.7	6.5	7.3	14.2
0.7	—	—	—	—	6.7	12.2	31.0	55.6	—	—	12.2	—	12.4	—	—	9.4
0.8	—	—	—	—	—	8.7	26.5	51.5	—	—	8.7	—	8.7	—	—	—
1.0	—	—	—	—	—	—	19.6	44.5	—	—	—	—	—	—	—	—
1.5	—	—	—	—	—	—	10.5	32.3	—	—	—	—	—	—	—	—
2.0	—	—	—	—	—	—	—	24.8	—	—	—	—	—	—	—	—
3.0	—	—	—	—	—	—	—	16.5	—	—	—	—	—	—	—	—
4.0	—	—	—	—	—	—	—	12.2	—	—	—	—	—	—	—	—

[a] The tabled values are ($w_\tau \times 100/w_0$).

Table II—Slopes (β) for the Cube-Root Law, Eq. 6, for Various Log-Normal Distributions[a]

σ	i 10 j 10	2 10	1 10	2 2	10 2	10 3	3 3
0.03	0.997	0.996	0.989	0.998	0.999	0.997	0.997
0.05	0.993	0.991	0.981	0.994	0.997	0.993	0.993
0.1	0.974	0.971	0.954	0.980	0.983	0.975	0.974
0.2	0.901	0.898	0.877	0.924	0.927	0.904	0.904
0.3	0.792	0.790	0.772	0.841	0.843	0.800	0.800
0.5	0.526	0.526	0.519	0.643	0.643	0.552	0.552
0.7	0.288	0.288	0.286	0.456	0.456	0.334	0.334

[a] The values of the table are β; i and j indicate extent of truncation.

The general expression for weight fraction undissolved, w_τ/w_0, is based on the derivations of the previous report (3) and the above discussion. If it is remembered (3) that $\mu = \ln M$, where M is the geometric mean diameter, then it can be shown that w_τ/w_0 is:

$$1 - 3(\tau/M)e^{-5\sigma^2/2}\left[\frac{F(j-2\sigma) - F((T-\mu-2\sigma^2)/\sigma)}{F(j-3\sigma) - F(-i-3\sigma)}\right] + 3(\tau/M)^2 e^{-4\sigma^2}\left[\frac{F(j-\sigma) - F((T-\mu-\sigma^2)/\sigma)}{F(j-3\sigma) - F(-i-3\sigma)}\right] - (\tau/M)^3 e^{-9\sigma^2/2}\left[\frac{F(j) - F((T-\mu)/\sigma)}{F(j-3\sigma) - F(-i-3\sigma)}\right] \quad \text{(Eq. 4)}$$

where $F(\ )$ is the area under a standard normal curve from $-\infty$ to the stated argument, and T is defined by $T = \mu - i\sigma$ when $\ln \tau \leq \mu - i\sigma$, or $T = \ln \tau$ when $\ln \tau > \mu - i\sigma$.

For any set σ, i, and j, all dissolution profiles will be identical if considered on a w_τ/w_0 *versus* τ/M basis. When T in Eq. 4 is $\mu - i\sigma$ the term μ disappears from the equation. When $T = \ln \tau$, then every $T - \mu$ can be expressed as $\ln(\tau/M)$.

Dissolution profiles for different log-normally distributed powders were calculated according to Eq. 4 using a computer[1]. Each $F(\ )$ term was evaluated by numerical methods. Values so calculated compared with tabled values for the standard normal distribution to the fourth significant figure. Several computer results for w_τ/w_0 were checked for correctness by independent calculations. All values w_τ/w_0 were calculated to four significant figures and rounded to three figures in this report to conserve space.

RESULTS AND DISCUSSION

Exactly calculated dissolution profiles for hypothetical log-normal powders variously truncated and having standard deviations ranging from 0.03 to 0.7 are presented in Table I as weight percent undissolved ($100 \times w_\tau/w_0$) *versus* τ/M. In the strictest sense, no profiles were calculated for "ideal" distributions, *i.e.*, where $-\infty < \ln a_0 < +\infty$. Practically speaking, however, profiles for distributions where $i = j = 10$ should be considered ideal.

[1] IBM 1800.

In the previous paper (3), Brooke indicated how to calculate w_τ/w_0 for distributions truncated at the large particle end. Instead of treating a truncation at the small particle end, Brooke suggested that truncation effects at the small end could, in many cases, be ignored without introducing large errors. Comparisons of dissolution patterns (Table I) of distributions that are "ideal" at the small end ($i = 10$) with those for similar distributions truncated at the small end ($i = 1, 2, \ldots$) show that this is generally true. The difference between values of w_τ/w_0 for an ideal distribution and for a truncated ($i = 2$) distribution is less than 1% through 95% of the profile. The differences between w_τ/w_0 for an ideal *versus* a truncated distribution with $i = 1$ runs to about 6.6%. For $\sigma \geq 0.3$, differences tend to be negligible. Distributions truncated so that $i = 3$ could be treated as ideal at the small end with errors much smaller than 1%.

The dissolution pattern for a log-normal distribution with $\sigma = 0$ is given in Table I. For $\sigma = 0$, Eq. 4 becomes:

$$w_\tau/w_0 = [1 - (\tau/M)]^3 \quad \text{(Eq. 5)}$$

which is the equation for a monosized distribution of particles of diameter M. The profile so calculated comes close to, but slightly underestimates, the weight fraction remaining through 80 or 90% of the profile for powders having standard deviations as large as 0.1. Thus, for many log-normal distributions with small σ, including all of those treated by Carstensen and Musa (1), it may be more desirable to approximate dissolution patterns quickly by Eq. 5 and to accept the generally modest errors that result than to calculate tediously such profiles exactly.

To treat the dissolution before the critical time of log-normal powders, the initial portions of profiles like those of Table I were fitted to a modified cube-root law equation given by:

$$1 - (w_\tau/w_0)^{1/3} = \beta(\tau/M) \quad \text{(Eq. 6)}$$

Here β is the slope of a linear plot of $1 - (w_\tau/w_0)^{1/3}$ *versus* (τ/M). Carstensen and Musa (1) used the more classical form of the cube-root law shown below:

$$w_0^{1/3} - w_\tau^{1/3} = \alpha\tau \quad \text{(Eq. 7)}$$

Table III—Least-Squares Regression Data for Plots of ln β *versus* σ^2 Based on Values in Table II[a]

	i 10 j 10	2 10	1 10	2 2	10 2	10 3	3 3
−slope	2.539	2.533	2.519	1.610	1.616	2.244	2.244
−intercept	0.0023	0.0047	0.0210	0.0119	0.0100	0.0095	0.0095
r^2	0.99997	0.99997	0.9996	0.9970	0.9970	0.9990	0.9990

[a] Extent of truncation is indicated by i and j.

where $w_0 = 100$ and α is a constant. It is seen that α and β are related by $\alpha = (w_0^{1/3}\beta/\mathrm{M})$. Equations 6 and 7 really apply only for the narrowest of distributions (4).

Values for β for numerous distributions are given in Table II. In every case, the value was calculated from the portion of the profile given for $0 < \tau/\mathrm{M} < 0.1$. If the critical time τ_c is taken as that τ when the smallest particles disappear, then no such time exists for ideal distributions since $0 \leq a_0 \leq \infty$. However, if one defines the critical time by $\ln \tau_c = \mu - 3\sigma$, then only small errors are introduced into the calculations. Every β in Table II was calculated for a time shorter than that defined by $\ln \tau_c = \mu - 3\sigma$.

By the following reasoning, it was found that, for ideal or nearly ideal distributions, a good approximation for β would have the form $e^{-c\sigma^2}$. For ideal distributions or for not severely truncated distributions (*e.g.*, where $j - 3\sigma$ and $i + \sigma$ are greater than about 3), Eq. 4 for $\tau < \tau_c$ can be approximated by:

$$w_\tau/w_0 = 1 - 3(\tau/\mathrm{M})e^{-5\sigma^2/2} + 3(\tau/\mathrm{M})^2e^{-4\sigma^2} - (\tau/\mathrm{M})^3e^{-9\sigma^2/2} \quad \text{(Eq. 8)}$$

Although the right side of the equation is not a perfect cube, it can be treated as a cubic of the form:

$$w_\tau/w_0 = [1 - (\tau/\mathrm{M})e^{-c\sigma^2}]^3 \quad \text{(Eq. 9)}$$

since the terms $3(\tau/\mathrm{M})^2e^{-4\sigma^2}$ and $(\tau/\mathrm{M})^3e^{-9\sigma^2/2}$ for small (τ/M) are relatively unimportant and can be manipulated without seriously affecting the equation. If this is true, then a plot of ln β *versus* σ^2 will be a straight line with a slope of $-c$ and an intercept of zero. Figure 1 shows such a plot for a series of ideal ($i = j = 10$) distributions and for a series of truncated ($i = j = 2$) distributions.

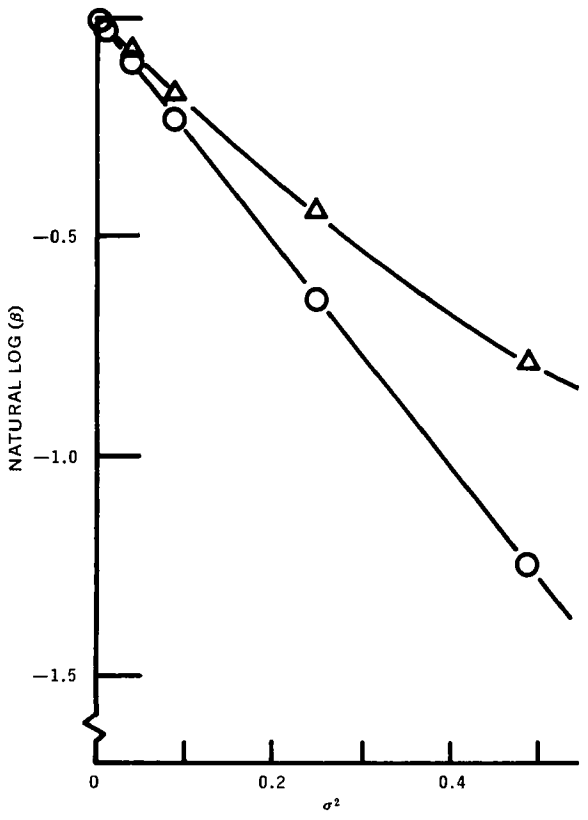

Figure 1—*Plot of ln* β versus σ^2 *for a series of ideal* (i = j = *10) distributions* (○) *and for a series of truncated* (i = j = *2) distributions* (△). *The symbols refer to calculated slopes given in Table II.*

The plot in Fig. 1 for the ideal distributions appears to be straight. Linear regression techniques (Table III) indicate a slope of −2.54 and a near zero intercept. The linearity, as judged by a coefficient of determination (r^2) of 0.99997, is excellent. Thus, for ideal or nearly ideal distributions, β can be approximated by $e^{-2.54\sigma^2}$ and the dissolution before the critical time can be approximated by:

$$1 - (w_\tau/w_0)^{1/3} = e^{-2.54\sigma^2}(\tau/\mathrm{M}) \quad \text{(Eq. 10)}$$

For distributions like those where $i = j = 2$, the effect of truncation becomes more and more important as σ is increased. A convenient approximation such as Eq. 10 is not acceptable with severely truncated distributions.

It is intuitively satisfying that in the approximation $\beta = e^{-2.54\sigma^2}$ the coefficient of σ^2 is close to −2.5. It is also satisfying that as $\sigma \to 0$, $\beta \to 1$, a result required by Eq. 5. Furthermore, it is satisfying that the approximation holds over a wide range of σ, although this might not have been expected since the cube-root law is to be applied only for narrow distributions.

In contrast, the Carstensen and Musa (1) approximation, given in the notation of this report by $\alpha = 50/\mathrm{M}(\sigma/2.303)^{1.05}$, predicts that as $\sigma \to 0$, $\alpha \to \infty$. Furthermore, the form of the approximation does not hold over a wide range of σ. In addition, the slopes of cube-root plots for times before the critical time presented in the Carstensen and Musa table cannot be calculated by their approximation. The tabled slopes do appear to be correct and are calculable by the approximation used in Eq. 10. By using the slopes in the Carstensen and Musa (1) paper and linear regression techniques, it can be determined that α should be given by:

$$\alpha = 4.26/\mathrm{M}(\sigma/2.303)^{0.0195} \quad \text{(Eq. 11)}$$

In the previous paper, Brooke (3) calculated α from the incorrect approximation, chose a point $(\tau^*, w_\tau^*/w_0)$ from the exactly calculated profile, and then calculated a $w_0^{1/3}$ to fit the following expression:

$$w_\tau^*/w_0 = [1 - (\alpha/w_0^{1/3})\tau^*]^3 \quad \text{(Eq. 12)}$$

Obviously, the ratio $\alpha/w_0^{1/3}$ obtained was correct, even though the separate values α and $w_0^{1/3}$ were not. Thus, the test of the approximation α offered by Brooke was inconclusive.

This report has dealt with approximations for the slopes of cube-root law plots for the dissolution of log-normal powders before the critical time. Although such approximations may seem useful, a convenient approximation for all log-normal distributions has not been found. To apply an approximation like that of Eq. 10 for the dissolution of ideal log-normal powders before the critical time, one must know all of the parameters that would allow exact calculations to be made. Such approximations might, however, be useful in curve-fitting experimental data to determine one or several basic parameters of dissolution profiles.

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Colorimetric Determination of Guanazole in Plasma and Blood

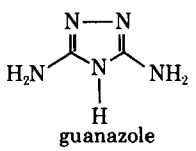
C. DAVE[x] and L. CABALLES

Abstract □ A simple colorimetric procedure is described for determination of guanazole (3,5-diamino-1,2,4-triazole), a new antileukemic drug. The test is based upon diazotizing guanazole in water or in trichloroacetic acid extract obtained from plasma or serum, coupling the diazonium salt with diphenylamine, and extracting the azo dye with isopentyl alcohol. The product has a λ_{max} at 485 nm, is stable for several days, and obeys Beer's law over a wide concentration range. An amount as low as 5 nmoles in 2 ml can be determined under the conditions described. Under the same condition, 3-amino-1,2,4-triazole gave a yellow product in isopentyl alcohol (λ_{max} 450 nm) with a sensitivity 20 times less than that with guanazole, whereas 1*H*-1,2,4-triazole gave no color at all. Recoveries of guanazole added to fetal calf serum and dog plasma were within 95–105%. Following a single intravenous dose to a rat, blood levels of guanazole, evaluated by the colorimetric procedure, were comparable to those obtained measuring concurrently administered ^{14}C-labeled compound by standard tracer techniques. A half-life of 68 min was thus observed by both methods. The sensitivity and reproducibility of the assay, together with the relative lack of interference from other substances like urea and amino acids, make the procedure suitable for the determination of plasma levels of drug in small samples.

Keyphrases □ Guanazole in plasma and blood—colorimetric analysis □ Colorimetry—analysis, guanazole in plasma and blood

Guanazole (3,5-diamino-1,2,4-triazole, NSC-1895, mol. wt. 99.1), reportedly synthesized by Pellizzari in 1894 (1), is a new antileukemic agent which is therapeutically effective against mouse leukemia L-1210 (2) and human acute myelocytic leukemia (3, 4). Its antileukemic actions appear to be related to its ability to inhibit ribonucleoside diphosphate reductase, a key enzyme involved in deoxynucleotide synthesis during the DNA-synthetic phase of the cell cycle (5).

A sensitive colorimetric procedure was developed to study the pharmacokinetics of guanazole in patients with acute myelocytic leukemia (6). The rationale for the present methodology is based upon the fact that the primary amino groups of 1,2,4-triazole are diazotizable (7). The diazotized product in the case of guanazole was coupled with diphenylamine, resulting in the formation of a red dye which could be readily extracted with isopentyl alcohol.



guanazole

EXPERIMENTAL

Chemicals and Reagents[1]—The purity of labeled and unlabeled guanazole was determined by TLC on silica gel precoated plastic sheets without fluorescent indicator[2] using the following three solvent systems (v/v): (*a*) methanol–dioxane (2:1), (*b*) water–dioxane (1:10), and (*c*) water–methanol (1:10).

Chromatograms were developed in a TLC chamber[3] for 30–45 min. Spots were visualized by placing the dried chromatogram in iodine vapors, and the R_f values for guanazole were found to be 0.31, 0.73, and 0.61. Both labeled and unlabeled compounds migrated as a single spot on the chromatogram with each solvent system.

For a standard colorimetric assay, the following reagents were prepared: (*a*) acid mixture, 1.5% (v/v) sulfuric acid in acetic acid; (*b*) nitrite reagent, 1% (w/v) $NaNO_2$ in water; and (*c*) diphenylamine reagent, 10% (w/v) diphenylamine in the acid mixture reagent.

Protein Precipitation—Blood plasma or serum samples were generally diluted five- to 10-fold with 5% (w/v) trichloroacetic acid, mixed, and allowed to stand on ice for 10 min. The precipitates were centrifuged and the supernate was used for analysis. In samples with low guanazole content, plasma was diluted only with an equal volume of 10% trichloroacetic acid, the precipitate was washed once with one volume of 5% trichloroacetic acid, and the supernates were combined.

Standard Colorimetric Procedure—To a 2-ml aliquot containing 0.5–50 μg guanazole, 0.1 ml of the acid mixture reagent was added and cooled in ice. Nitrite reagent (0.1 ml) was added and mixed rapidly, and the mixture was kept in ice for 10 min for optimal diazotization. Diphenylamine reagent (0.1 ml) was added and mixed rapidly, and the mixture was left for 15 min at room temperature for maximum color development. The azo dye was extracted with 3.0 ml of isopentyl alcohol by gently inverting the tube several times. Centrifugation, although not required in the authors' experience, may be carried out if an emulsion forms. The organic solvent phase was transferred to another test tube containing about 1 g of anhydrous sodium sulfate, mixed, and allowed to stand for 5 min. The absorbance of the solvent layer was then read[4] in a 1-cm cell at 485 nm.

Since trichloroacetic acid extracts from control plasma samples

[1] Guanazole, as well as guanazole uniformly labeled with ^{14}C (51 μCi/mg), was generously provided by Dr. J. F. Holland, Mount Sinai Hospital, New York, N.Y. 3-Amino-1,2,4-triazole and 1*H*-1,2,4-triazole were obtained from Eastman Kodak, Rochester, N.Y. Fetal calf serum was purchased from Grand Island Biologicals, Grand Island, N.Y. All other chemicals were analytical grade from Fischer Chemical Co.

[2] Eastman Kodak, Rochester, N.Y.

[3] Gelman.

[4] Beckman model DB-G spectrophotometer.