

# Dissolution Profile in Relation to Initial Particle Distribution

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**Abstract** □ A general equation was derived describing the complete and exact dissolution profile of powders under sink conditions. It is applicable to powders having any initial particle-size distribution, with particles dissolving according to any explicit equation. It was applied to develop an equation for the dissolution of log-normal powders that is more generally applicable than previous approaches. The effect of change in initial particle-size distribution parameters on the dissolution profile is illustrated.

**Keyphrases** □ Dissolution profile—powders under sink conditions, general equation, relationship of initial particle-size distribution, applicability to dissolution of log-normal powders □ Particle-size distribution—effect on dissolution profile, general equation, applicability to dissolution of log-normal powders □ Powders—dissolution profile under sink conditions, general equation, relationship of initial particle-size distribution, applicability to dissolution of log-normal powders

Several investigators (1–4) considered the problem of exactly describing the dissolution profile of powders in relation to their particle-size distribution. These authors have been concerned with powders initially consisting of particles with log-normal size distribution. Earlier attempts made use of approximations (1) or computer simulations (2). More recently, Brooke (3) developed an equation that permits calculation of the dissolution profile of such powders without the aid of a computer. This equation was later presented in a form to account for truncated log-normal distributions (4), but in this paper it is shown not to be generally applicable for all timelengths.

A general equation that exactly describes the entire dissolution profile of powders under sink conditions would be of considerable value. Such an equation should be valid for particles having any initial size distribution and dissolving according to any explicit equation. In particular, it should be applicable to the dissolution of log-normal powders, which are frequently encountered.

## THEORY

Consider a powder consisting of particles which initially ( $t = 0$ ) has a weight density (probability) distribution  $f_0(w_0)$ . Let the particles dissolve independently of each other according to:

$$w = g(w_0, t, A) \quad (\text{Eq. 1})$$

where  $w$  and  $w_0$  are the particle weights at time  $t$  and  $t = 0$ , respectively; and  $A$  represents collectively the dissolution parameters such as solubility, particle density, and the particle shape factor. The inverse dissolution function is defined as:

$$w_0 = g^{-1}(w, t, A) \quad (\text{Eq. 2})$$

Using the rules of transformation of independent variables (5), the particle weight density function at time  $t$  becomes:

$$h(w) = f_0[g^{-1}(w, t, A)] \frac{d}{dw} g^{-1}(w, t, A) \quad (\text{Eq. 3})$$

For Eq. 3 to hold, the following conditions for  $g$  must be satisfied: (a)  $g^{-1}$  must be a strictly increasing function of  $w$  for all  $t$  values, (b)  $g$  must decrease strictly with time until equal to zero, and (c)  $g$  must remain equal to zero beyond that time. The latter two conditions ensure that the dissolution function reflects the actual physical conditions of the dissolution process. The first condition will rarely be violated because, in application,  $g$  is nearly always a strictly increasing function of  $w_0$  for all  $t$  values. It is obvious that the second condition must be met by any dissolution equation.

The third condition is not satisfied for most equations in the literature (1, 6, 7). To overcome this problem, it is necessary to redefine the particle weight density function such that it is generally applicable:

$$f(w) = \frac{h(w)}{\int_0^{\infty} h(w) dw} \quad \text{for } w > 0 \quad (\text{Eq. 4a})$$

$$f(w) = 0 \quad \text{for } w \leq 0 \quad (\text{Eq. 4b})$$

where division by the integral is necessary to satisfy the condition that the total integral (from  $-\infty$  to  $+\infty$ ) of  $f(w)$  must be equal to 1.

The weight of undissolved powder,  $W$ , at any time,  $t$ , is equal to the product of the number of particles remaining,  $N_t$ , and the mean particle weight, which for a large number of particles is the same as the expected value of  $w$ ,  $E_t(w)$ . Therefore, the following general equation can be written:

$$W = N_t E_t(w) \quad (\text{Eq. 5})$$

The number of particles remaining at time  $t$  is:

$$N_t = N_0 \int_0^{\infty} h(w) dw \quad (\text{Eq. 6})$$

where the initial number of particles,  $N_0$ , is equal to the initial powder weight,  $W_0$ , divided by the initial mean particle weight:

$$N_0 = \frac{W_0}{\int_0^{\infty} w_0 f_0(w_0) dw_0} \quad (\text{Eq. 7})$$

The mean particle weight at time  $t$  is given by:

$$E_t(w) = \int_{-\infty}^{\infty} w f(w) dw \quad (\text{Eq. 8})$$

which, according to Eq. 4a, can be written:

$$E_t(w) = \frac{\int_0^{\infty} w h(w) dw}{\int_0^{\infty} h(w) dw} \quad (\text{Eq. 9})$$

Substituting Eqs. 6, 7, and 9 into Eq. 5 yields:

$$\frac{W}{W_0} = \frac{\int_0^{\infty} w h(w) dw}{\int_0^{\infty} w_0 f_0(w_0) dw_0} \quad (\text{Eq. 10})$$

This equation relates to unbounded particle weight distributions. In practice, the distribution is always bound, so the limits of integration must be changed accordingly.

Let  $m_0$  and  $M_0$  denote the initial weights of the smallest and largest particle, respectively<sup>1</sup>. These values then represent the lower and upper boundaries, respectively, of  $f_0(w_0)$ ;  $f(w)$  will be correspondingly bounded by  $Pg(m_0, t, A)$  and  $Pg(M_0, t, A)$ . The operator  $P$  is introduced to ensure that the limits are never negative. Therefore, by definition,  $P$  is equal to 1 in the time period before the operand becomes zero and is equal to zero beyond that time. When these limits are introduced into Eq. 10 and  $h(w)$  is written according to Eq. 3, the following expression is obtained:

$$\frac{W}{W_0} = \frac{\int_{w=Pg(m_0, t, A)}^{w=Pg(M_0, t, A)} w f_0 [g^{-1}(w, t, A)] \frac{d}{dw} g^{-1}(w, t, A) dw}{\int_{m_0}^{M_0} w_0 f_0(w_0) dw_0} \quad (\text{Eq. 11})$$

If  $g^{-1}(w, t, A)$  and  $w_0$  in the integrals are considered as dummy variables and called  $x$ , Eq. 11 simplifies to:

$$\frac{W}{W_0} = \frac{\int_{L_1}^{L_2} g(x, t, A) f_0(x) dx}{\int_{m_0}^{M_0} x f_0(x) dx} \quad (\text{Eq. 12a})$$

Because of this transformation and the properties of the operator  $P$ , the limits of integration,  $L_1$  and  $L_2$ , have the following values:

$$L_1 = m_0 \quad \text{for } t \text{ such that } Pg(m_0, t, A) > 0 \quad (\text{Eq. 12b})$$

$$L_1 = g^{-1}(0, t, A) \quad \text{for } t \text{ such that } Pg(m_0, t, A) = 0 \quad (\text{Eq. 12c})$$

$$L_2 = M_0 \quad \text{for } t \text{ such that } Pg(M_0, t, A) > 0 \quad (\text{Eq. 12d})$$

$$L_2 = g^{-1}(0, t, A) \quad \text{for } t \text{ such that } Pg(M_0, t, A) = 0 \quad (\text{Eq. 12e})$$

The time at which  $g(m_0, t, A) = 0$  is the critical time, that is, the time when the dissolving particles begin to disappear. When  $g(M_0, t, A) = 0$ , all particles are dissolved. Beyond that time,  $L_1 = L_2$ , thus making  $W/W_0$  equal to zero.

Equation 12a requires knowledge of the initial weight distribution  $f_0(w_0)$ , but more often the initial size distribution is of greatest interest. Consider particles that are spherical and remain so during the dissolution; in this case,  $w = \rho \pi a^3/6$ , where  $\rho$  and  $a$  are the particle density and diameter, respectively<sup>2</sup>. Transformation in Eq. 11 from the initial weight distribution to the initial size distribution is then easily achieved; and by a similar procedure to that used to obtain Eq. 12a from Eq. 11, the following equation is derived:

$$\frac{W}{W_0} = \frac{\int_{R_1}^{R_2} g\left(\frac{\rho\pi}{6} x^3, t, A\right) l_0(x) dx}{\int_{d_0}^{D_0} \frac{\pi\rho}{6} x^3 l_0(x) dx} \quad (\text{Eq. 13a})$$

where:

$$R_1 = d_0 \quad \text{for } t \text{ such that } Pg\left(\frac{\rho\pi}{6} d_0^3, t, A\right) > 0 \quad (\text{Eq. 13b})$$

$$R_1 = \left[\frac{6}{\rho\pi} g^{-1}(0, t, A)\right]^{1/3} \quad \text{for } t \text{ such that } Pg\left(\frac{\rho\pi}{6} d_0^3, t, A\right) = 0 \quad (\text{Eq. 13c})$$

$$R_2 = D_0 \quad \text{for } t \text{ such that } Pg\left(\frac{\rho\pi}{6} D_0^3, t, A\right) > 0 \quad (\text{Eq. 13d})$$

$$R_2 = \left[\frac{6}{\rho\pi} g^{-1}(0, t, A)\right]^{1/3} \quad \text{for } t \text{ such that } Pg\left(\frac{\rho\pi}{6} D_0^3, t, A\right) = 0 \quad (\text{Eq. 13e})$$

<sup>1</sup> These values are not intended to be absolute but rather represent limits giving the best fit when the actual particle distribution is approximated by any particular function. Therefore, they also represent truncation limits of the function.

<sup>2</sup> The derivation is valid for particles of other shapes as long as they remain unchanged during dissolution and an appropriate shape factor is used in place of  $\pi/6$ .

In Eq. 13a,  $d_0$  and  $D_0$  are initial diameters of the smallest and largest particles, respectively<sup>1</sup>;  $l_0$  is the initial particle-size density function.

Equations 12a and 13a rigorously describe the entire dissolution profile of any powder if its initial particle weight density function,  $f_0$ , or initial particle-size density function,  $l_0$ , is known, together with the particle dissolution function, which can be any explicit expression. With appropriate choice of limits of integration, the equations are applicable to truncated as well as "ideal" distributions. The time-dependent integral in the numerator of Eqs. 12a and 13a reduces to the constant integral in the denominator at zero time, thus making the ratio  $W/W_0$  equal to 1 as expected.

## RESULTS AND DISCUSSION

The general mathematical models expressed by Eq. 12a or 13a require the use of a computer for numerical evaluation because they are in integral form. However, if the initial particle weight or particle-size distribution can be approximated by some simple function, then the model can often be solved in terms of an expression suitable for evaluation without the use of a computer.

Consider a powder consisting of spherical particles of initial diameters  $a_0$ , distributed such that  $\ln a_0$  approximates a normal distribution with mean  $\mu$  and standard deviation  $\sigma$ , truncated at  $\ln d_0 = \mu - i\sigma$  and  $\ln D_0 = \mu + j\sigma$ , where  $i$  and  $j$  are truncation parameters. The density function of  $\ln a_0$  is then given by:

$$u(\ln a_0) = \frac{N(\ln a_0, \mu, \sigma)}{\int_{\ln a_0 = \mu - i\sigma}^{\ln a_0 = \mu + j\sigma} N(\ln a_0, \mu, \sigma) d \ln a_0} \quad \mu - i\sigma \leq \ln a_0 \leq \mu + j\sigma \quad (\text{Eq. 14})$$

where the normal density function  $N$  is defined as  $N(x, \mu, \sigma) = [1/(\sigma\sqrt{2\pi})] \exp[-(x - \mu)^2/2\sigma^2]$ . Because the distribution is truncated, the integral in Eq. 14 is introduced to satisfy the requirement that the total integral of  $u(\ln a_0)$  must be equal to 1. By using standard transformation techniques (5), the initial particle-size density function,  $l_0$ , then becomes:

$$l_0(a_0) = \frac{a_0^{-1} N(\ln a_0, \mu, \sigma)}{\int_{d_0}^{D_0} a_0^{-1} N(\ln a_0, \mu, \sigma) da_0} \quad d_0 \leq a_0 \leq D_0 \quad (\text{Eq. 15})$$

Let the particles dissolve according to the Hixson-Crowell (6) cube root law:

$$w = (w_0^{1/3} - kt)^3 \quad (\text{Eq. 16})$$

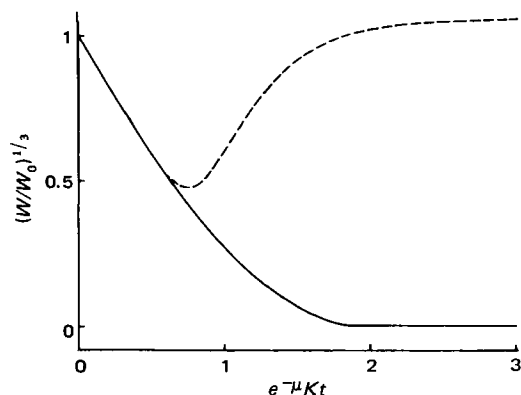
where  $k$  is a positive constant. The inverse dissolution function is then:

$$w_0 = (w^{1/3} + kt)^3 \quad (\text{Eq. 17})$$

After the initial particle-size distribution (Eq. 15) and the particle dissolution equation (Eq. 16 and its inverse Eq. 17) are defined, the relationship giving the dissolution profile can then be derived by means of Eq. 13a (for derivation, see Appendix):

$$\begin{aligned} W/W_0 = & \left[ \frac{F\left(\frac{T_2 - \mu}{\sigma} - 3\sigma\right) - F\left(\frac{T_1 - \mu}{\sigma} - 3\sigma\right)}{F(j - 3\sigma) - F(-i - 3\sigma)} \right] \\ & - 3(Kt) \left[ \frac{F\left(\frac{T_2 - \mu}{\sigma} - 2\sigma\right) - F\left(\frac{T_1 - \mu}{\sigma} - 2\sigma\right)}{F(j - 3\sigma) - F(-i - 3\sigma)} \right] e^{-\mu - 5\sigma^2/2} \\ & + 3(Kt)^2 \left[ \frac{F\left(\frac{T_2 - \mu}{\sigma} - \sigma\right) - F\left(\frac{T_1 - \mu}{\sigma} - \sigma\right)}{F(j - 3\sigma) - F(-i - 3\sigma)} \right] e^{-2\mu - 1\sigma^2} \\ & - (Kt)^3 \left[ \frac{F\left(\frac{T_2 - \mu}{\sigma}\right) - F\left(\frac{T_1 - \mu}{\sigma}\right)}{F(j - 3\sigma) - F(-i - 3\sigma)} \right] e^{-3\mu - 9\sigma^2/2} \quad (\text{Eq. 18a}) \end{aligned}$$

where:



**Figure 1**—Plot of the cube root of fraction undissolved versus  $e^{-\mu Kt}$  for hypothetical log-normal powder, with  $\sigma = 0.3$  and truncated at  $\mu \pm 2\sigma$  ( $i = j = 2$ ). The unbroken curve is calculated according to Eq. 18a, and the stippled curve is calculated according to an equation given by Brooke (4).

$$\begin{aligned}
 T_1 &= \mu - i\sigma & \text{for } \ln Kt \leq \mu - i\sigma & \quad (\text{Eq. 18b}) \\
 T_1 &= \ln Kt & \text{for } \ln Kt > \mu - i\sigma & \quad (\text{Eq. 18c}) \\
 T_2 &= \mu + j\sigma & \text{for } \ln Kt \leq \mu + j\sigma & \quad (\text{Eq. 18d}) \\
 T_2 &= \ln Kt & \text{for } \ln Kt > \mu + j\sigma & \quad (\text{Eq. 18e})
 \end{aligned}$$

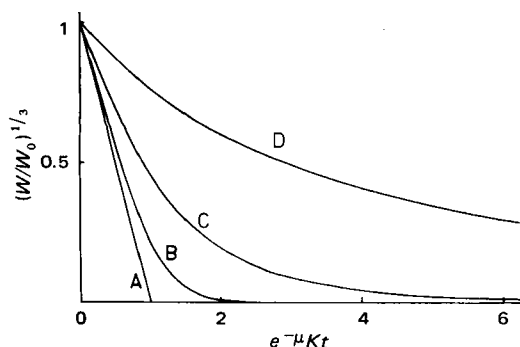
The function,  $F$ , is the commonly tabulated area under the standard normal curve function, defined by:

$$F(x) = \int_{-\infty}^x \frac{1}{\sqrt{2\pi}} e^{-x^2/2} dx \quad (\text{Eq. 19})$$

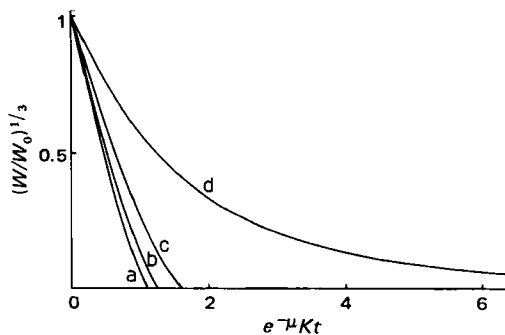
The positive constant,  $K$ , is used for simplification in place of the expression  $(6/\rho\pi)^{1/3}k$ . The change in  $T_1$  at timelength  $Kt = e^{\mu-i\sigma}$  (critical time) corresponds to the time when the smallest particles, initially having a diameter  $d_0 = e^{\mu-i\sigma}$ , begin to disappear. The change at  $Kt = e^{\mu+j\sigma}$  ( $= D_0$ ) signifies the end of the dissolution process, so  $W/W_0$  becomes zero after that timelength.

Equation 18a describes the complete dissolution profile of log-normal powders and any sieve fraction of such powders. It assumes that the particles dissolve according to the cube root law (Eq. 16), which also can be written in the form  $a = a_0 - (6/\rho\pi)^{1/3}kt$  or  $a = a_0 - Kt$  for spherical particles, where  $a_0$  and  $a$  are the particle diameters at times zero and  $t$ , respectively. This relationship is similar to the equation  $a = a_0 - \tau$  used previously (2-4) in which  $\tau$  denotes the timelength.

Brooke (4) derived an equation similar to Eq. 18a for log-normal powders. Directions were given for the changes required in the equation at the critical time. However, in his equation the first term is constant, equal to 1. Therefore, his equation is incorrect if applied to dissolution after the critical time. The error so intro-



**Figure 2**—Effect of the particle-size distribution parameter,  $\sigma$ , on plots of the cube root of fraction undissolved versus  $e^{-\mu Kt}$ , calculated according to Eq. 18a for hypothetical ideal ( $i = j = 10$ ) log-normal powders. Key: A,  $\sigma = 0$ ; B,  $\sigma = 0.2$ ; C,  $\sigma = 0.4$ ; and D,  $\sigma = 0.7$ .



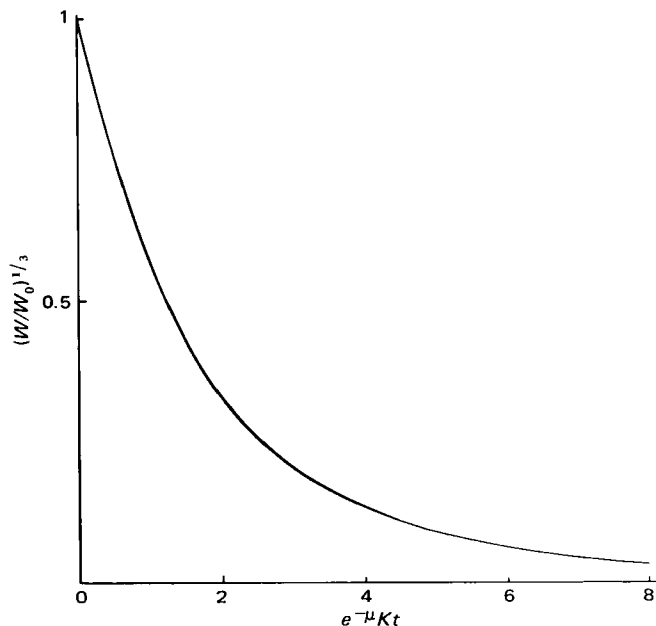
**Figure 3**—Effect of upper end truncation on the dissolution profile of powders having a log-particle diameter distribution that is normal, with  $\sigma = 0.5$ , and truncated at  $\mu - 10\sigma$  and  $\mu + j\sigma$ , where  $j = 0.25$  (a), 0.5 (b), 1 (c), and 10 (d).

duced becomes quite substantial for large timelengths and large values of  $\sigma$ .

Brooke calculated values of  $W/W_0$  for various values of  $\tau/e^\mu$  (the latter terminology corresponds to  $e^{-\mu Kt}$  used here). This procedure represents an ingenious method of "scaling time" (by the factor  $e^{-\mu K}$ ) so the dissolution profile becomes independent of the parameters  $\mu$  and  $k$  (Eq. 16) and only depends on  $\sigma$ , enabling the effect of  $\sigma$  alone to be assessed. In this work, however, cube root-type plots of  $(W/W_0)^{1/3}$  versus  $e^{-\mu Kt}$  are used for better comparison with the fundamental particle dissolution equation (Eq. 16), which obeys the cube root law.

Figure 1 shows such a plot for powders truncated at  $\mu \pm 2\sigma$  ( $i = j = 2$ ) and having  $\sigma = 0.3$ . The curvature of the unbroken line, calculated according to Eq. 18a, is logically expected. The stippled line represents the dissolution profile calculated according to Brooke's equation (Eq. 4 of Ref. 4)<sup>3</sup>. The two profiles are, as expected, identical until critical time ( $e^{-\mu Kt} = 0.5488$ ), but the later part clearly demonstrates the limitation of his equation.

Figure 2 demonstrates the effect of  $\sigma$  on the dissolution profile for a powder initially having an ideal distribution ( $i = j = 10$ ).



**Figure 4**—Effect of lower end truncation on the dissolution profile of powders having a log-particle diameter distribution that is normal, with  $\sigma = 0.5$ , and truncated at  $\mu - 10\sigma$  and  $\mu + 10\sigma$ , where  $i = 0.25, 0.5, 1$ , and 10. The four curves are essentially coincidental.

<sup>3</sup> A Cyber 76 digital computer equipped with Calcomp plotter was used for calculations and plots. Numerical evaluations were tested to six digits.

Powders of uniform particle size, *i.e.*,  $\sigma = 0$ , give linear cube root plots as expected, while the deviation from linearity is significant for larger  $\sigma$  values. An increase in  $\sigma$  results in a decrease in the initial slopes of the curves, which is consistent with calculations made by Brooke (4). Among powders having the same logarithmic mean diameter,  $\mu$ , those with broadest distribution will have the slowest initial release rate.

Figures 3 and 4 show the effect of truncation on the dissolution profile when the initial log (particle diameter) - distribution approximates a normal distribution ( $\sigma = 0.5$ ) with various degrees of upper (Fig. 3) and lower (Fig. 4) end truncation. Comparison of the two figures indicates that the effect of truncation at the low end is very small and considerably less than that of truncation at the upper end. The curves for  $i = 10, 1, 0.5$ , and  $0.25$  are so close that they are coincidental in the plot (Fig. 4), while they are clearly separate for  $j = 10, 1, 0.5$ , and  $0.25$  in Fig. 3. Figure 3 also shows that the magnitude of the slopes of the curves increases with increasing truncation. The most marked effect of truncation at the upper end is that the time for complete dissolution is drastically reduced.

## APPENDIX

After inserting Eqs. 15, 16, and 17 into Eq. 13a, the integral in the numerator,  $I_n$ , of Eq. 13a becomes:

$$I_n = \frac{\int_{R_1}^{R_2} \left[ \left( \frac{\rho\pi}{6} \right)^{1/3} w - kt \right]^3 w^{-1} N(\ln w, \mu, \sigma) dw}{\int_{d_0}^{D_0} w^{-1} N(\ln w, \mu, \sigma) dw} \quad (\text{Eq. A1})$$

It was indicated previously that  $W/W_0 = I_n/(I_n)_{t=0}$ . By using this fact,  $W/W_0$  can be written:

$$\frac{W}{W_0} = \frac{\int_{R_1}^{R_2} \left[ w - \left( \frac{6}{\rho\pi} \right)^{1/3} kt \right]^3 w^{-1} N(\ln w, \mu, \sigma) dw}{\int_{d_0}^{D_0} w^2 N(\ln w, \mu, \sigma) dw} \quad (\text{Eq. A2})$$

In Eq. A2, the time-independent integral in the denominator is equal to the time-dependent integral in the numerator evaluated

at zero time. To evaluate the numerator of Eq. A2, employing a technique similar to that used to derive the moment-generating function for a normal distribution (5), the following useful equation can be obtained, which is similar to Eq. 12 given by Brooke (3):

$$\int_q^r x^s N(\ln x, \mu, \sigma) dx = \left[ F\left(\frac{\ln r - \mu}{\sigma} - (s+1)\sigma\right) - F\left(\frac{\ln q - \mu}{\sigma} - (s+1)\sigma\right) \right] e^{s+1[\mu+(s+1)\sigma^2/2]} \quad (\text{Eq. A3})$$

where the function,  $F$ , is the area under the standard normal curve function given by Eq. 19. Thus, to evaluate the numerator,  $I$ , in Eq. A2,  $(w - Kt)^3 w^{-1}$  is expanded as  $w^2 - 3(Kt)w + 3(Kt)^2 - (Kt)^3 w^{-1}$  [letting  $K = (6/\rho\pi)^{1/3}k$  for simplicity]. The formula is then applied term by term by putting  $s = 2, 1, 0$ , and  $-1$ ;  $r = R_2$ ; and  $q = R_1$  and by treating  $t$  as a constant for purposes of integration. Equation 18a is then derived using  $W/W_0 = I/(I)_{t=0}$  and noting that  $\ln d_0 = \mu - i\sigma$  and  $\ln D_0 = \mu + j\sigma$ .

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