On the Variability of Dissolution Data

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Purpose. To investigate dissolution data variability and its origins.
Methods. The Weibull function with four parameters, t_0 (dissolution lag-time), K (the rate parameter), β (the shape parameter) and D (the fraction dissolved as $t \rightarrow \infty$), is used to describe the dissolution curve. The variance of the dissolution data is expressed in terms of these parameters and their individual variances $\sigma^2_{t_0}$, σ^2_K, σ^2_β, and σ^2_D. These four variances originate from variable physical properties of the dosage units and from a variable dissolution environment. Therefore, dissolution data variability depends on both, the functional form of the curve and on the variance of the physical conditions. The use of this method enables the elucidation of the sources of dissolution data variability.
Results. In the case of a sigmoidal dissolution curve ($\beta > 1$), data variance is zero as dissolution begins (following dissolution lag-time). This initial variance diverges when the dissolution curve is non-sigmoidal (with $\beta < 1$) but assumes a finite value, proportional to the dissolution lag-time variance ($\sigma^2_{t_0}$) when the data fits a regular first order rate curve ($\beta = 1$). Following a long dissolution time, data variance attains a constant value equal to the dissolution extent variance, σ^2_D. When the dissolution curve is sigmoidal and the variability related to the dissolution extent is sufficiently small ($\sigma_D/D << 1$), a maximum in the variance is expected at some intermediate time point (corresponding to the curve inflection point, when the main source of variability is dissolution lag-time t_0, or around $t = 1/K + t_0$, when the main sources of variability are the rate parameter K or the shape parameter β). When the curve is sigmoidal ($\beta > 1$) and the main source of variability relates to the dissolution extent, the overall variance grows with time all the way to the plateau of the dissolution curve. With a non-sigmoidal dissolution curve ($\beta \leq 1$), data variability decreases with time soon after dissolution begins. In that case, if the main source of variability is the dissolution lag-time (t_0), the variance decreases all the way to the plateau of the dissolution curve. If the dissolution extent, D, is the main source of variability, a minimum in the variance is expected at some intermediate time point. The dissolution *relative* variance, on the other hand, diverges as dissolution begins and decreases with time at least until 63% of the drug is released, irrespective to the Weibull parameter values. Later, it may decrease or increase, attaining a fixed value (σ^2_D/D^2) at the plateau of the dissolution curve.
Conclusions. The particular time dependence of dissolution data variance is well defined in terms of the Weibull shape parameters and their individual variances. Dissolution data variability may decrease or increase with time along the curve. It may attain a maximum or a minimum value at some intermediate time point. It may converge or diverge as dissolution begins. When the dissolution data is well fitted to the Weibull function, the sources of data variability (in terms of the Weibull parameters) may be elucidated. The variability of dissolution data originates from physical sources but is also dependent on the functional form of the curve.

KEY WORDS: dissolution variability; Weibull function.

INTRODUCTION

Variability of dissolution data originates from non-homogenous physical characteristics of the dosage units and from temporal variability in the dissolution vessel environment, to which these units are exposed. This variability of the dissolution environment is affected by many factors; two of the most common being mechanical instabilities in the agitation system (vibration effects) and improper deaeration of the dissolution medium. Other sources of variability are: irregularly shaped vessels, careless filtering, inaccurately prepared buffers as well as wear of the paddles and baskets (1). In addition, the orientation of the tablet on the bottom of the vessel may result in variable hydrodynamic conditions which, in turn, may lead to nonreproducible results (2). The formation of a cone of disintegrated material under the paddle may lead to instability of the dissolving system and, hence, to variable dissolution data (3). It was also demonstrated that a certain degree of turbulence always exists in the boundary layer of a dissolving solid (4).

Wagner (5) cautioned that the inherent variability in the dissolution method should be less than the inherent variability that can be tolerated in the product. Calibration of the dissolution apparatus by the use of calibrator tablets and calibration criteria is intended for this purpose. However, a calibrated dissolution apparatus may, still, produce variable data following the use of a test product which is more sensitive to the dissolution conditions than the standard calibrator tablets.

The purpose of this work is to investigate dissolution data variability and its origins. An assessment of the time dependence of the variance may be important in the determination of the dissolution specifications. Furthermore, prior detection of a divergence in the variance is important since the determination of a mean value (for the percent dissolved) is impossible at the time interval where divergence is expected.

It is also important to locate a maximum or a minimum in the variance as a function of time. An evaluation of dissolution data should be avoided in the vicinity of the time where a maximum in the variance is expected while, on the other hand, evaluation of dissolution data is preferable in the vicinity of time correlating to a minimum value of the variance. The attribution of dissolution data variability to specific physical properties of the dosage units is helpful in the search for an improved production process which may lead to a better uniformity among the dosage units. All of these issues are addressed in the present work, where the "absolute" variance (or simply "the variance") and the relative variance are discussed separately.

It must be pointed out that dissolution apparatus (environmental) variability cannot be distinguished from product variability by mathematical analysis alone. This goal may be reached however, by the combination of mathematical analysis and dissolution experiments, when the effects of both dissolution conditions and product formulation, are investigated separately.

THE VARIANCE

The Weibull function, F(t), is commonly used for the approximation of dissolution data (6):

$$F(t) = D(1 - e^{-x^\beta}) \quad (1)$$

where

$$X = K(t - t_0)$$

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D is the dose fraction dissolved as $t \to \infty$, t_0 is the dissolution lag-time, K is a first order rate constant (the rate parameter) and β is the shape parameter. When $\beta = 1$, K is identical to the dissolution rate constant. However, in the general case when $\beta \neq 1$, K cannot be simply related to the dissolution rate. As a matter of fact, K may present a pseudo (time dependent) first order rate constant even though dissolution is a true first order process (see App. A).

When the four parameters of the Weibull function, t_0, K, β and D, are independent of each other, the variance of F(t), σ^2, can be expressed as a linear combination of variances related to each parameter (7):

$$\sigma^2 = \left(\frac{\partial F}{\partial K}\right)^2 \sigma_K^2 + \left(\frac{\partial F}{\partial t_0}\right)^2 \sigma_{t_0}^2 + \left(\frac{\partial F}{\partial \beta}\right)^2 \sigma_\beta^2 + \left(\frac{\partial F}{\partial D}\right)^2 \sigma_D^2 \quad (2)$$

Differentiation of F(t) with respect to t and with respect to each of the four parameters (App B) yields:

$$\frac{\partial F}{\partial t} = KDe^{-x^\beta}\beta X^{\beta-1} \quad (3)$$

$$\sigma^2 = [F'(t)]^2 \frac{X^2}{K^2}\left[\frac{\sigma_K^2}{K^2} + \frac{K^2\sigma_{t_0}^2}{X^2} + \ln^2 X \frac{\sigma_\beta^2}{\beta^2}\right] + F^2(t)\frac{\sigma_D^2}{D^2} \quad (4)$$

where

$$F'(t) = \frac{\partial F}{\partial t}$$

It is instructive to examine σ^2 following very long or very short dissolution times.

Following a long dissolution time, as $X \to \infty$:

$$\lim_{X\to\infty} F(t) = D \quad (5)$$

$$\lim_{X\to\infty} F'(t) = 0 \quad (6)$$

Then, by eq. 3

$$\lim_{X\to\infty} \sigma^2 = \sigma_D^2 \quad (7)$$

It may be stated that following a very long dissolution time, the variance of F is equal to variance of D (the dissolution extent variance, which may originate from a poor content uniformity of the dosage units).

Following a very short dissolution time, as $X \to 0$:

$$\lim_{X\to 0} F'(t) = \lim_{X\to 0} DK\beta(1 - X^\beta)X^{\beta-1} = \lim_{X\to 0} DK\beta X^{\beta-1} \quad (8)$$

$$\lim_{X\to 0} F(t) = \lim_{X\to 0} DX^\beta \quad (9)$$

By comparing eq. 8 and eq. 9 it follows that:

$$\lim_{X\to 0} F(t) = \lim_{X\to 0} \frac{F'(t)X}{K\beta} \quad (10)$$

letting X approach zero in eq. 4, provides:

$$\lim_{X\to 0} \sigma^2 = \lim_{X\to 0} [F'(t)]^2 \sigma_{t_0}^2 \quad (11)$$

where eq. 10 has been used. Introducing eq. 8 into eq. 11 yields:

$$\lim_{X\to 0} \sigma^2 = \lim_{X\to 0} D^2K^2\beta^2 X^{2\beta-2}\sigma_{t_0}^2 \quad (12)$$

It follows that the variance of F(t) at the very short dissolution time intervals is proportional to the lag-time variance.

By eq. 12:

$$\lim_{X\to 0} \sigma^2 = 0 \qquad \text{when } \beta > 1 \quad (13)$$

$$\lim_{X\to 0} \sigma^2 = \infty \qquad \text{when } \beta < 1 \ (\sigma_{t_0} \neq 0) \quad (14)$$

$$\lim_{X\to 0} \sigma^2 = D^2K^2\sigma_{t_0}^2 \quad \text{when } \beta = 1 \quad (15)$$

It should be noted that F acquires an inflection point (a sigmoid shape) whenever $\beta > 1$. This can be shown by differentiating F(t) twice with respect to t:

$$F''(t) = \frac{\partial^2 F}{\partial t^2} = (\beta - 1 - \beta X^\beta) D\beta K^2 e^{-x^\beta} X^{\beta-2} \quad (16)$$

or, by the use of eq. 3:

$$F''(t) = (\beta - 1 - \beta X^\beta)F'(t)K\,X^{-1} \quad (17)$$

an inflection point in F is defined by the condition:

$$\beta - 1 - \beta X^\beta = 0 \quad (18)$$

which may hold only when $\beta > 1$.

The time dependence of σ^2 is examined by differentiation of σ^2 with respect to t (App. C):

$$\frac{\partial(\sigma^2)}{\partial t} = \frac{2(F')^2X}{K}\left[\beta(1 - X^\beta)\frac{\sigma_K^2}{K^2} + (\beta - 1 - \beta X^\beta)\frac{K^2}{X^2}\sigma_{t_0}^2 + \{\beta(1 - X^\beta)\ln^2 X + \ln X\}\frac{\sigma_\beta^2}{\beta^2}\right] + 2F'F\frac{\sigma_D^2}{D^2} \quad (19)$$

In the limit as X approaches zero ($\beta \neq 1$):

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = \lim_{X\to 0}\left[\frac{2(F')^2X}{K}(\beta - 1)\frac{K^2}{X^2}\sigma_{t_0}^2 + 2F'F\frac{\sigma_D^2}{D^2}\right] \quad (20)$$

where only the leading terms in eq. 19 have been left (assuming $\beta \neq 1$).

By the use of eq. 10 in eq. 20, we get:

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = \lim_{X\to 0} 2(F')^2\left[\frac{(\beta - 1)K}{X}\sigma_{t_0}^2 + \frac{X}{K\beta D^2}\sigma_D^2\right] \quad (21)$$

Keeping only the leading term in eq. 21 and using expression 8 for F', provides:

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = \lim_{X\to 0} 2(\beta - 1)D^2\beta^2K^3X^{2\beta-3}\sigma_{t_0}^2 \text{ when } \beta \neq 1 \quad (22)$$

It follows that the time derivative of the variance of F at very short time intervals is proportional to the lag-time variance.

From eq. 22, when $\sigma_{t_0} \neq 0$:

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = -\infty \qquad \text{when } \beta < 1 \tag{23}$$

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = +\infty \qquad \text{when } 1 < \beta < 1.5 \tag{24}$$

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = D^2\beta^2K^3\sigma_{t_0}^2 \qquad \text{when } \beta = 1.5 \tag{25}$$

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = +0 \qquad \text{when } \beta > 1.5 \tag{26}$$

By App. D:

$$\lim_{X\to 0} \frac{\partial(\sigma^2)}{\partial t} = -2D^2\beta^2K^3\sigma_{t_0}^2 \quad \text{when } \beta = 1 \tag{27}$$

To summarize the implementation of eqs. 13–15 and 23–27 for the short time variability of dissolution data:

When dissolution data fits a Weibull function *with* an inflection point ($\beta > 1$), data variability is zero at t_0 and grows with t ($\sigma_{t_0} \neq 0$) for short time intervals.

When dissolution data fits a Weibull function *without* an inflection point ($\beta \leq 1$) two cases should be distinguished:

For $\beta < 1$, the variability of the data diverges at t_0 ($\sigma_{t_0} \neq 0$) and decreases sharply with t in the vicinity of this time point.

For $\beta = 1$ (a regular first order dissolution curve) the variance of the data assumes a finite value at t_0 (proportional to $\sigma_{t_0}^2$). The variance decreases with t, close to t_0.

Eq. 19 at $X = 1$ yields:

$$\left[\frac{\partial(\sigma^2)}{\partial t}\right]_{x=1} = \left[-2(F')^2K\sigma_{t_0}^2 + 2F'F\frac{\sigma_D^2}{D^2}\right]_{x=1}$$

$$= 2KDe^{-1}\beta[-K^2De^{-1}\beta\sigma_{t_0}^2 + (1 - e^{-1})\sigma_D^2D^{-1}] \tag{28}$$

When $K^2D^2\beta\sigma_{t_0}^2/[(e - 1)\sigma_D^2] > 1$, then:

$$\left[\frac{\partial(\sigma^2)}{\partial t}\right]_{x=1} < 0 \tag{29}$$

Eq. 19 when $X << 1$, (see "Discussion and Conclusions") yields:

$$\left[\frac{\partial(\sigma^2)}{\partial t}\right]_{x<<1} > 0 \qquad \text{when } \beta > 1 \tag{30}$$

Therefore (assuming continuity of the derivative with respect to t), when $\beta > 1$ and $K^2D^2\beta\sigma_{t_0}^2/[(e - 1)\sigma_D^2] > 1$, there is a time point t_I corresponding to value $X = X_I$ ($X_I < 1$) such that:

$$\left[\frac{\partial(\sigma^2)}{\partial t}\right]_{X_I} = 0 \quad ; \quad \beta > 1, \quad K^2D^2\beta\sigma_{t_0}^2/[(e - 1)\sigma_D^2] > 1 \tag{31}$$

which corresponds to a maximum value for σ^2.

In other words: for $\beta > 1$ (a sigmoid shaped curve) the variability of dissolution data assumes a maximum value at X_I (<1) if $K^2D^2\beta\sigma_{t_0}^2/[(e - 1)\sigma_D^2] > 1$.

If $K^2D^2\beta\sigma_{t_0}^2/[(e - 1)\sigma_D^2] < 1$, maximum value for σ^2 is attained at $\infty > X > 1$ (see "Discussion and Conclusions").

THE RELATIVE VARIANCE

Consider the relative variance σ^2/F^2. Applying eqs. 4 and 1 at the limit as X approaches zero, provides:

$$\lim_{X\to 0} \frac{\sigma^2}{F^2} = \lim_{X\to 0} K^2\beta^2X^{-2}\sigma_{t_0}^2 \tag{32}$$

This expression diverges in the limit as X approaches zero, irrespective of the value of β (provided that $\sigma_{t_0} \neq 0$).

Following a very long dissolution time:

$$\lim_{X\to\infty} \frac{\sigma^2}{F^2} = \frac{\sigma_D^2}{D^2} \tag{33}$$

The derivative of the relative variance with respect to t yields (App. E):

$$\frac{\partial}{\partial t}\left(\frac{\sigma^2}{F^2}\right) = \frac{2(F')^2X}{F^2K}\left[\left\{\beta(1 - X^\beta) - \frac{F'X}{FK}\right\}\frac{\sigma_K^2}{K^2} + \left\{\beta - 1 - \beta X^\beta - \frac{F'X}{FK}\right\}\frac{K^2\sigma_{t_0}^2}{X^2} + \left\{\beta(1 - X^\beta)\ln^2X - \ln X - \frac{F'X}{FK}\ln^2X\right\}\frac{\sigma_\beta^2}{\beta^2}\right] \tag{34}$$

Consider eq. 34 in the limit as X approaches zero.

By the use of eqs. 1 and 3:

$$\lim_{X\to 0} \frac{F'X}{FK} = \lim_{X\to 0} \beta(1 - X^\beta) = \beta \tag{35}$$

Letting X approach zero, in eq. 34, while keeping only the leading terms, provides:

$$\lim_{X\to 0} \frac{\partial}{\partial t}\left(\frac{\sigma^2}{F^2}\right) = \lim_{X\to 0} (-2\beta^2K^3X^{-3}\sigma_{t_0}^2) \tag{36}$$

were eq. 35 has been used. Hence:

$$\lim_{X\to 0} \frac{\partial}{\partial t}\left(\frac{\sigma^2}{F^2}\right) = -\infty \quad (\sigma_{t_0} \neq 0) \tag{37}$$

The use of expression 3 for $F'(t)$ in eq. 34, while letting $X \to \infty$, leads to:

$$\lim_{X\to\infty} \frac{\partial}{\partial t}\left(\frac{\sigma^2}{F^2}\right) = 0 \tag{38}$$

By the use of eqs. 1 and 3:

$$\beta(1 - X^\beta) - \frac{F'X}{FK} = \frac{\beta(1 - e^{-x^\beta} - X^\beta)}{(1 - e^{-x^\beta})} \tag{39}$$

It can be proven (App. F) that:

$$1 - e^{-x^\beta} - X^\beta < 0 \quad \text{for} \quad 0 < X < 1 \tag{40}$$

It is also true that:

$$0 < 1 - e^{-x^\beta} < 1 \text{ when } X > 0 \tag{41}$$

and

$$X^{\beta} \geq \text{when } X \geq 1 \tag{42}$$

Hence:

$$1 - e^{-x^{\beta}} - X^{\beta} < 0 \text{ when } X \geq 1 \tag{43}$$

Combining eq. (40) and (43):

$$1 - e^{-x^{\beta}} - X^{\beta} < 0 \text{ when } X > 0 \tag{44}$$

By eqs. 41, 44 and 39:

$$\beta(1 - X^{\beta}) - \frac{F'X}{FK} < 0 \text{ when } X > 0 \tag{45}$$

This means that the σ_K^2 and $\sigma_{t_0}^2$ terms in eq. 34 are negative irrespective of the X value.

The σ_β^2 terms may be written as:

$$\left[\beta(1 - X^{\beta}) - \frac{F'X}{FK} + \frac{1}{\ln X}\right] \ln^2 X \frac{\sigma_\beta^2}{\beta^2} \tag{46}$$

When $X < 1$, ln X is negative and expression 46 assumes a negative value.

When $X > e$ and $\beta > 1$, 1/lnX is smaller than 1 while the absolute value of expression 39 is larger than 1, therefore expression 46 is negative (but has a very small absolute value). When X is close to unity, 1/lnX becomes a dominant term in expression 46 and the expression is positive. However, under this condition ($X \cong +1$) the (positive) σ_β^2 term is negligible with respect to the (negative) σ_K^2 and $\sigma_{t_0}^2$ terms.

Therefore, under these conditions, eq. 34 assumes a negative value. On the other hand, when $1 < X < e$ ($X \neq 1$) irrespective of the β value, expression 46 may attain a positive non-negligible values. For $\beta_\beta < 1$, this statement is true also when $X > e$. If, in addition, $\sigma_\beta/\beta >> \{\sigma_K/K, K\sigma_{t_0}\}$, a positive value for eq. 34 may be observed. Under these conditions the relative variance is increasing with t.

DISCUSSION AND CONCLUSIONS

By eqs. 1, 3 and 4:

$$\frac{\sigma^2}{D^2} = (e^{-x^{\beta}} \cdot \beta X^{\beta})^2 \left[\frac{\sigma_K^2}{K^2} + \frac{K^2\sigma_{t_0}^2}{X^2} + \ln^2 X \frac{\sigma_\beta^2}{\beta^2}\right] + (1 - e^{-x^{\beta}})^2 \frac{\sigma_D^2}{D^2} \tag{47}$$

Hence, the dimensionless quality σ^2/D^2 is a function of five dimensionless constants: β, σ_K/K, $K\sigma_{t_0}$, σ_β/β, σ_D/D and one dimensionless variable: X. These dimensionless parameters are used for data presentation in the relevant figures of this work.

Eq. 4 enables an estimation of each of the Weibull parameter variances. By a best fit of the mean dissolution data to the Weibull function (eq. 1), the four parameters may be estimated. These values are then introduced into eq. 4. Next, eq. 4 is fitted to the experimental variance in F (as a function of time), using σ_K, σ_{t_0}, σ_β and σ_D as the fitting variables. This procedure is demonstrated in Figs. 1a and 1b using the data relating to particular entero-coated tablets.

As dissolution begins ($t = t_0$), dissolution data variability originates from the lag-time variance $\sigma_{t_0}^2$ (eq. 12), whereas,

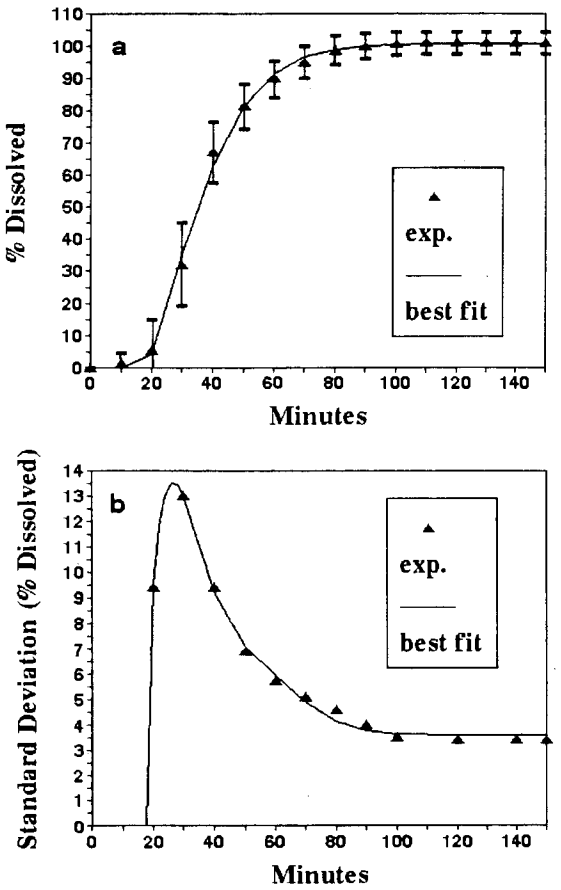

Fig. 1. (a) A best fit of eq. 1 to mean dissolution data of an entero-coated tablet. The fit was assessed by the use of MINSQ, a minimum squares nonlinear fitting procedure (MicroMath, Scientific Software, Salt Lake City Utah). The best-fitted values are: D = 100.65%, β = 1.3891 K = 0.044346 min^{-1} and t_0 = 17.694 min (b) A best fit of eq. 4 to the experimental standard deviation presented in fig. 1a. The fit was assessed by the use of the MINSQ fitting procedure. The best values for t_0 D, β and K, obtained by fitting the mean dissolution data to eq. 1 (see fig. 1a), were used as constants. σ_K, σ_{t_0}, σ_β and σ_D were used as the fitting variables. The best-fitted values are: σ_K = 0.002126 min^{-1}, σ_{t_0} = 3.7209 min, σ_β = 0.2852, σ_D = 3.583%.

after a long period of dissolution, variability originates from the dissolution extent variance σ_D^2 (eq. 7).

Following the dissolution lag-time, a divergence in the variability may be observed only with non-sigmoidal dissolution curves ($\beta < 1$) (eq. 14). However, significant changes in σ^2 are expected for sigmoidal curves as dissolution begins, when $1 < \beta < 1.5$, $\sigma_{t_0} \neq 0$ (eq. 24).

Consider the variability change as a function of time (eq. 19): the signs of the σ_K and the σ_β terms are time dependent: they are positive for low values of X (or low values of t) and negative for high values of X (or high values of t).

The above is also true for the σ_{t_0} term when $\beta > 1$. When $\beta < 1$ this term is negative for any value of X (or t). The σ_D term, on the other hand, is positive for any X value (F′ and F assume only positive values). Therefore, with a sigmoidal dissolution curve ($\beta > 1$), the variability increases with t as dissolution begins ($t = t_0$).

With a sigmoidal dissolution curve ($\beta > 1$) and when the variability related to the dissolution extent is sufficiently small

($\sigma_D/D << 1$), a maximum in the overall variance may be observed at some intermediate time point. Otherwise, the variability may grow all the way up to the plateau of the dissolution curve. Typically, a maximum in the variance is observed around the time corresponding to the inflection point of the curve, or around $t = 1/K + t_0$ ($X = 1$). In order to understand this, consider eq. 28: when both σ_D/D and $K\sigma_{t_0}$ are null, a maximum in the variance is observed at $X = 1$. If both terms are sufficiently small a maximum in the variance occurs around $X = 1$.

Therefore, with a sigmoidal dissolution profile ($\beta > 1$), a maximum in the variance is expected around $t = 1/K + t_0$ when both the dissolution extent variability and the dissolution lag-time variability are low enough such that $\{\sigma_D/D, K\sigma_t\} << 1$ (Fig. 2).

On the other hand, consider the variance at the inflection point. Using eq. 18 in eq. 19 provides

$$\left[\frac{\partial(\sigma^2)}{\partial t}\right]_{i.p.} = \frac{2(F')^2X}{K}\left[\frac{\sigma_K^2}{K^2} + (\ln^2 X + \ln X)\frac{\sigma_\beta^2}{\beta^2}\right] + 2F'F\frac{\sigma_D^2}{D^2} \quad (48)$$

where i.p. stands for "inflection point". F, F', and X in eq. 47 should be evaluated at the time corresponding to the inflection point. Eq. 48 is independent of σ_{t_0}. If the variability in the data originates mainly from lag-time variability (σ_{t_0}), as in the case of entero-coated tablets, eq. 28 has a negative sign (meaning a negative slope for σ^2 at $X = 1$) while all terms in eq. 48 are relatively small. This leads to a maximum in the variance around the time corresponding to the inflection point in the curve. Therefore, with a sigmoidal dissolution profile, a maximum in the overall variance is expected around the inflection point when the variabilities related to the dissolution extent and to the rate and shape parameters are low enough such that $\{\sigma_D/D, \sigma_K/K, \sigma_\beta/\beta\} << 1$, while the dissolution lag-time variability is high enough such that $K\sigma_{t_0}$ is not much smaller than 1 (Fig. 3).

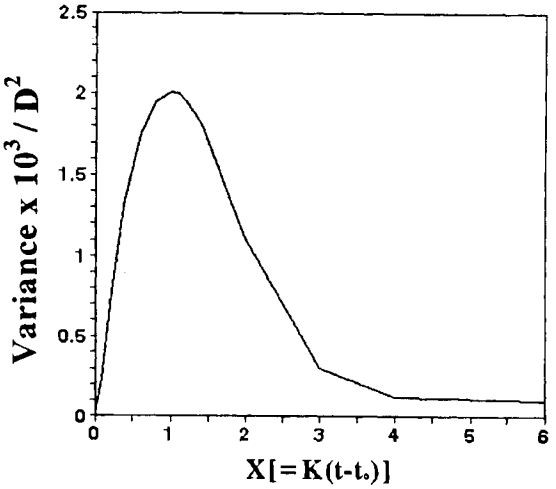

Fig. 2. With a sigmoidal dissolution profile ($\beta > 1$), a maximum in the variance is expected around $t = 1/K + t_0$ ($X = 1$), when both the dissolution extent variability and dissolution lag-time variability are low enough such that $\sigma_D/D << 1$ and $K\sigma_{t_0} << 1$. As an example, σ^2/D^2 was evaluated by eq. 47 using: $\beta = 1.2$, $\sigma_D/D = 0.01$, $\sigma_\beta/\beta = 0.0833$, $\sigma_K/K = 0.1$ and $K\sigma_{t_0} = 0.01$.

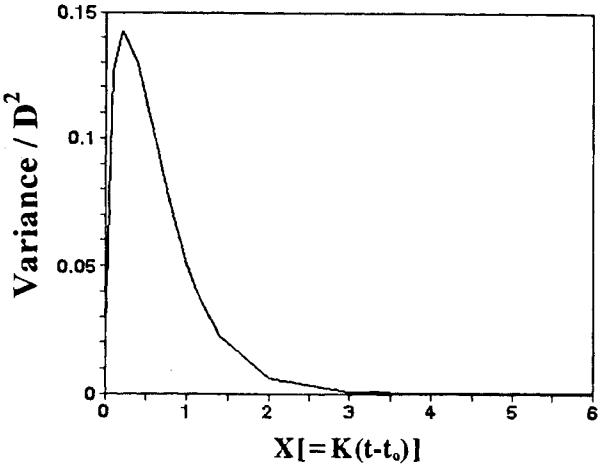

Fig. 3. With a sigmoidal dissolution profile ($\beta > 1$), a maximum in the variance is expected around the inflection point when the variabilities related to the dissolution extent and to the rate and shape parameters are low enough, such that: $\{\sigma_D/D, \sigma_K/K, \sigma_\beta/\beta\} << 1$, while the dissolution lag-time variability is high enough such that $K\sigma_{t_0}$ is not much smaller than 1. This, for instance, would be the case in a system where the main source of variability is dissolution lag-time, where variabilities from all other sonices are extremely low, where the K value is not too low and where the dissolution curve is sigmoidal. As an example, σ^2/D^2 has been evaluated by eq. 47 using: $\beta = 1.2$, $\sigma_D/D = 0.01$, $\sigma_\beta/\beta = 0.0833$, $\sigma_K/K = 0.1$ and $K\sigma_{t_0} = 0.5$. For $\beta = 1.2$, an inflection point is defined at $X = 0.2246$. The maximum variance is observe exactly at that X value.

Using eq. 19, when σ_D/D is relatively large, the variance time derivative is positive for any value of X. Hence with a sigmoidal dissolution profile ($\beta > 1$) and when the main source of variability is related to the dissolution extent, the overall variance grows all the way to the plateau (fig. 4). When the main sources of variability are related to both the dissolution extent and the dissolution lag-time (with $\beta > 1$), and intermediate situation between the ones presented in Fig. 3 and in Fig. 4 is observed (Fig. 5).

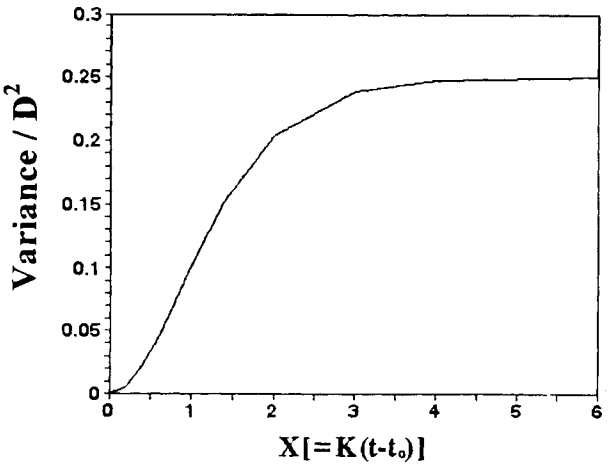

Fig. 4. With a sigmoidal dissolution profile ($\beta > 1$) and when the main source of variability is related to the dissolution extent, the overall variance grows all the way to the plateau. For example, σ^2/D^2 has been evaluated by eq. 47 using: $\beta = 1.2$, $\sigma_D/D = 0.5$, $\sigma_\beta/\beta = 0.0833$, $\sigma_K/K = 0.1$ and $K\sigma_{t_0} = 0.01$.

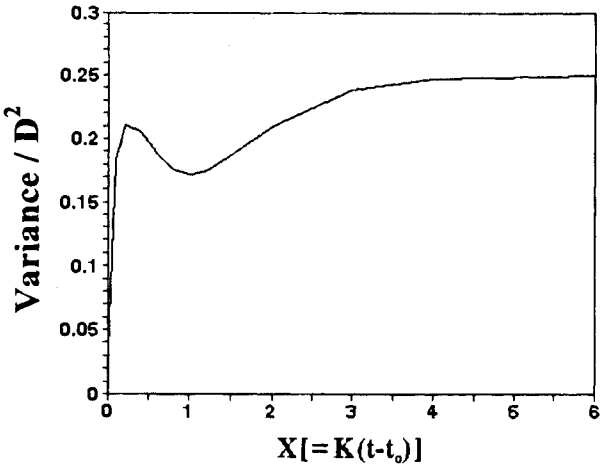

Fig. 5. With a sigmoidal dissolution profile ($\beta > 1$) and when the main sources of variability are related to the dissolution extent and to the dissolution lag-time, an intermediate situation between the ones presented in figs. 3 and 4 is observed. For example, σ^2/D^2 has been evaluated by eq. 47 using $\beta = 1.2$, $\sigma_D/D = 0.5$, $\sigma_\beta/\beta = 0.0833$, $\sigma_K/K = 0.1$ and $K\sigma_{t_0} = 0.6$.

With a non-sigmoidal dissolution profile ($\beta \leq 1$) and when the variability related to the dissolution lag-time is non-zero ($\sigma_{t_0} \neq 0$), the overall variance attains a maximum value as dissolution begins ($t = t_0$). Under these conditions, if dissolution lag-time variability is large enough while the variabilities related to all other sources are small enough such that $K\sigma_{t_0} >> \{\sigma_K/K, \sigma_\beta\beta, \sigma_D/D\}$, then, the overall variance decreases all the way to the plateau (Fig. 6). If, instead, the variabilities related to both, the dissolution lag-time and the dissolution extent are large enough while the variabilities related to the two other sources are small enough such that $\{K\sigma_{t_0}, \sigma_D/D\} >> \{\sigma_K/K, \sigma_\beta/\beta\}$, then the overall variance reaches a minimum before it grows with t (Fig. 7).

The Weibull function does not originate from a physical model. Therefore, two of the function parameters (K and β) cannot be simply related to some definite physical properties of the dosage units or the dissolution set. However, a functional form, similar to the Weibull function, may be derived by use of a modelistic approach (to be presented in a future publication). With such an approach, the physical interpretation of the functional parameters is more straightforward.

It may be concluded that although variability of dissolution data originates from the variability of some physical properties of the dosage units and from a variable dissolution environment, this data variability is also dependent on the functional form of the dissolution curve. Divergence of the data immediately following dissolution lag-time is not necessarily a result of a poor formulation: for a non-sigmoidal dissolution curve (excluding the simple first order case when $\beta = 1$) and for a sigmoidal curve with $1 < \beta < 1.5$, this divergence is a property of the function. Data variance may decrease or increase with time along the curve; it may attain a maximum or a minimum value at some intermediate time point along the curve. Addressing the *relative* variability: it has been proven that irrespective of the curve shape (β value), the relative variance diverges as dissolution begins at $t = t_0$ when $\sigma_{t_0} \neq 0$. It decreases as t increases at least up to $t = 1/K + t_0$ ($X = 1$). Using this value of $X = 1$ in eq. 1, leads to the conclusion that the relative variance must decrease with t until (at least) 63% of the drug is released, independently of the curve shape. Following this time point, if the shape parameter variability is much larger than both the rate parameter and the dissolution lag-time variabilities such that $\sigma_\beta/\beta >> \{\sigma_K/K, K\sigma_{t_0}\}$, the

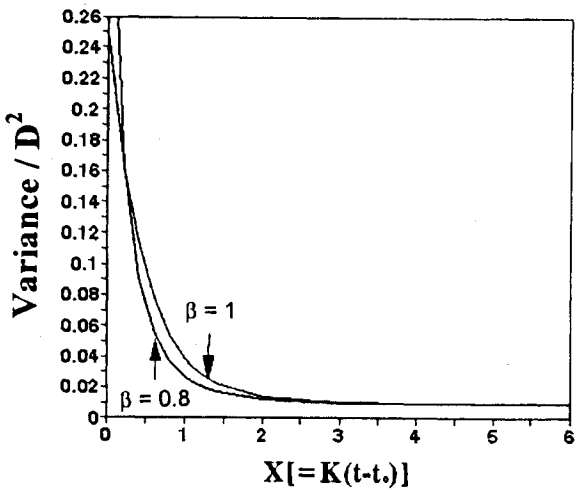

Fig. 6. With a non-sigmoidal dissolution profile ($\beta \leq 1$) and when the variability related to dissolution lag-time in non-zero ($\sigma_{t_0} \neq 0$), the overall variance attains a maximum value as dissolution begins at $t = t_0$ ($X = 0$). Under these conditions, if dissolution lag-time variability is large enough while the variabilities related to other sources are small enough such that $K\sigma_{t_0} >> \{\beta_K/K, \sigma_\beta/\beta, \sigma_D/D\}$, then the overall variance decreases all the way to the plateau. As an example, σ^2/D^2 has been evaluated by eq. 47 using: $\beta = 0.8$ (or $\beta = 1$), $\sigma_D/D = 0.1$, $\sigma_\beta/\beta = 0.125$, $\sigma_K/K = 0.1$, and $K\sigma_{t_0} = 0.5$.

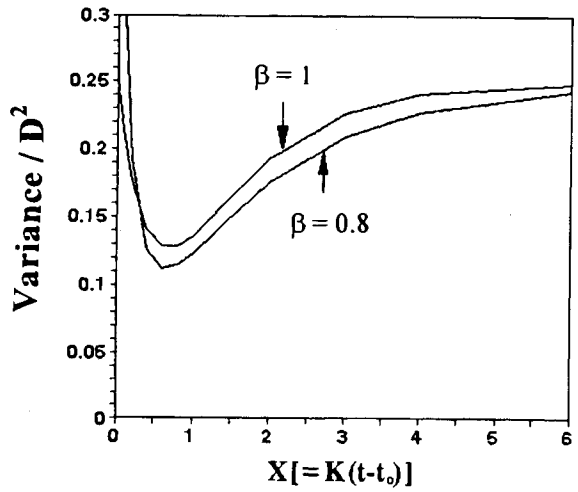

Fig. 7. With a non-sigmoidal dissolution profile ($\beta \leq 1$) and when the variability related to the dissolution lag-time is non-zero ($\sigma_{t_0} \neq 0$), the overall variance attains a maximum value as dissolution begins at $t = t_0$ ($X = 0$). Under these conditions, if the variabilities related to both dissolution lag-time and to dissolution extent are large enough while the variabilities related to the two other sources are small enough such that $\{K\sigma_{t_0}, \sigma_D/D\} >> \{\sigma_K/K, \sigma_\beta/\beta\}$, then, the overall variability reaches a minimum before it grows with t (or X). For example, σ^2/D^2 has been evaluated by eq. 47 using: $\beta = 0.8$ (or $\beta = 1$), $\sigma_D/D = 0.5$, $\sigma_\beta/\beta = 0.125$, $\sigma_K/K = 0.1$ and $K\sigma_{t_0} = 0.5$.

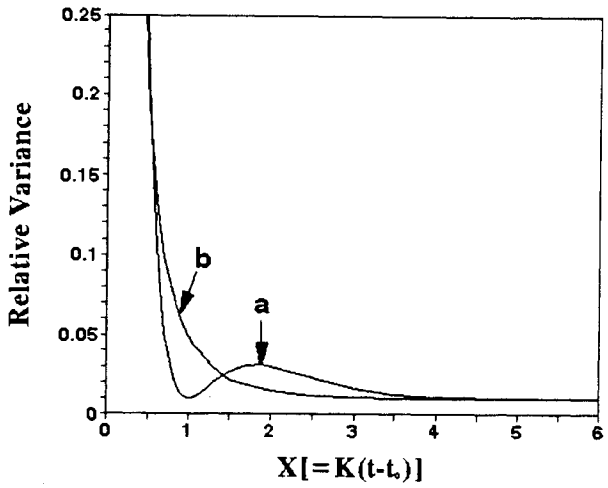

Fig. 8. Irrespective of the curve shape (β value) the *relative variance* (σ^2/F^2) diverges as dissolution begins and decreases as t increases at least up to $t = 1/K + t_0$ ($X = 1$). This means a decrease in the relative variance until (at least) 63% of the drug is related (eq. 1). Later, if the shape parameter variability is much larger than both the rate parameter and the dissolution lag-time variabilities such that $\sigma_\beta/\beta >> \{\sigma_K/K, K\sigma_{t_0}\}$, the relative variance may increase with t. Otherwise, it decreases with t up to the plateau of the dissolution curve. At the plateau, the relative variance attains a fixed value equal to the relative dissolution extent variance (σ_D^2/D^2). Two sets of parameter values have been used in eqs. 1 and 4 to demonstrate the two cases discussed above: a. $\beta = 1.2$, $\sigma_D/D = 0.1$, $\sigma_\beta/\beta = 0.666$, $\sigma_K/K = 0.001$, $K\sigma_{t_0} = 0.001$ b. $\beta = 1.2$, $\sigma_D/D = 0.1$, $\sigma_\beta/\beta = 0.0083$, $\sigma_K/K = 0.2$, $K\sigma_{t_0} = 0.2$.

relative variance may increase with t. Otherwise, it decreases all the way to the plateau of the dissolution curve (Fig. 8). At the plateau the relative variance attains a fixed value equal to the relative dissolution extent variance (σ_D^2/D^2).

APPENDIX A

Suppose that the drug transfer from the solid dosage unit to the sampling probe can be described by two consecutive first order processes. For instance, a first order dissolution process followed by a first order diffusion process. Let K_1 and K_2 be the appropriate first order rate constants.

The dose fraction F detected at the probe is given by:

$$F = D\left(1 - \frac{K_2}{K_2 - K_1} e^{-K_1 t} + \frac{K_1}{K_2 - K_1} e^{-K_2 t}\right) \quad (1A)$$

where D is the dose fraction detected at the probe as $t \to \infty$.

This equation presents a sigmoidal curve with an inflection point at

$$t = \ln(K_2/K_1)/(K_2 - K_1)$$

F may be approximated by the Weibull function. Use of eq. 1 in eq. 1A leads to:

$$K = \frac{1}{t}\left\{-\ln\left(\frac{K_2}{K_2 - K_1} e^{-K_1 t} - \frac{K_1}{K_2 - K_1} e^{-K_2 t}\right)\right\}^{1/\beta} \quad (2A)$$

where, for simplicity, $t_0 = 0$ was assumed.

By the use of a specific physical model, it is therefore demonstrated that the Weibull rate constant (K) may be a complex function of a few physical rate constants. Hence, in the general case, K may not be a function of the dissolution rate constant *alone*. Moreover, it is demonstrated that the Weibull K parameter may be time-dependent (K may not be a real constant). If this time dependency is weak enough, K may be considered a pseudo-constant. In that case, a particular curve defined by the general eq. 1A may be well fitted to the Weibull curve.

Example: $K_1 = 0.6$, $K_2 = 0.4$, $D = 1$ were used in eq. 1A. The Weibull function (with $D = 1$, $t_0 = 0$) was best fitted to the generated data using MINSQ, a minimum squares nonlinear fitting procedure (MicroMath Scientific Software, Salt Lake City, Utah). The result is an excellent fit to the data ($r^2 = 0.9997$), indicating that K and β are only weakly dependent on t. The best fitted values for K and β are 0.2193 and 1.5270, respectively.

It is clear that the best-fitted Weibull rate constant K value is far from either K_1 (the dissolution rate constant) or K_2 (the diffusion rate constant) included in the original physical model.

APPENDIX B

Differentiation of F(t) (eq. 1) with respect to the four Weibull parameters yields:

$$\frac{\partial F}{\partial K} = De^{-x^\beta} \beta X^{\beta-1}(t - t_0) \quad (1B)$$

$$\frac{\partial F}{\partial t_0} = -De^{-x^\beta} \beta X^{\beta-1} K \quad (2B)$$

$$\frac{\partial F}{\partial \beta} = -De^{-x^\beta} X^\beta \ln X \quad (3B)$$

$$\frac{\partial F}{\partial D} = 1 - e^{-x^\beta} \quad (4B)$$

Using eq. 3 in eqs. 1B–3B produces:

$$\frac{\partial F}{\partial K} = \frac{X}{K^2} F'(t) \quad (5B)$$

$$\frac{\partial F}{\partial t_0} = -F'(t) \quad (6B)$$

$$\frac{\partial F}{\partial \beta} = \frac{X \ln X}{\beta K} F'(t) \quad (7B)$$

By the use of eq. 1 in eq. 4B, we have:

$$\frac{\partial F}{\partial D} = \frac{F}{D} \quad (8B)$$

Introducing the above four derivations into eq. 2 provides eq. 4.

APPENDIX C

Differentiate eq. 4 with respect to t:

$$\frac{\partial(\sigma^2)}{\partial t} = 2F'(t)F''(t)\left[\frac{X^2}{K^4}\sigma_K^2 + \sigma_{t_0}^2 + \frac{X^2 \ln^2 X}{\beta^2 K^2}\sigma_\beta^2\right] + [F'(t)]^2\left[\frac{2X}{K^3} + (2XK\ln^2 X + 2KX\ln X)\frac{\sigma_\beta^2}{\beta^2 K^2}\right] + 2F'(t)F(t)\frac{\sigma_D^2}{D^2} \quad (1C)$$

Using eq. 17 in eq. 1C provides:

$$\frac{\partial(\sigma^2)}{\partial t} = \frac{2(F')^2K}{X}(\beta - 1 - \beta X^\beta)\left[\frac{X^2}{K^2}\frac{\sigma_K^2}{K^2} + \sigma_{t_0}^2 + \frac{X^2\ln^2 X}{K^2}\frac{\sigma_\beta^2}{\beta^2}\right] + \frac{2(F')^2X}{K}\left[\frac{\sigma_K^2}{K^2} + (\ln^2 X + \ln X)\frac{\sigma_\beta^2}{\beta^2}\right] + 2F'F\frac{\sigma_D^2}{D^2} \quad (2C)$$

By rearranging eq. 2C, we have:

$$\frac{\partial(\sigma^2)}{\partial t} = \frac{2(F')^2X}{K}(\beta - 1 - \beta X^\beta)\left[\frac{\sigma_K^2}{K^2} + \frac{K^2\sigma_{t_0}^2}{X^2} + \ln^2 X\frac{\sigma_\beta^2}{\beta^2}\right] + \frac{2(F')^2X}{K}\left[\frac{\sigma_K^2}{K^2} + (\ln^2 X + \ln X)\frac{\sigma_\beta^2}{\beta^2}\right] + 2F'F\frac{\sigma_D^2}{D^2} \quad (3C)$$

Combining terms in eq. 3C leads to eq. 19

APPENDIX D

Eq. 19 yields the following when $\beta = 1$:

$$\left[\frac{\partial(\sigma^2)}{\partial t}\right]_{\beta=1} = \frac{2(F')^2X}{K}\left[(1 - X)\frac{\sigma_K^2}{K^2} - \frac{K^2\sigma_{t_0}^2}{X} + \{(1 - X)\ln^2 X + \ln X\}\sigma_\beta^2\right] + 2F'F\frac{\sigma_D^2}{D^2} \quad (1D)$$

where F and F′ are evaluated for $\beta = 1$.

Eq. 1D is simplified to the following in the limit as $X \to 0$:

$$\lim_{x\to 0}\left[\frac{\partial(\sigma^2)}{\partial t}\right]_{\beta=1} = \lim_{x\to 0} 2F'\left(F\frac{\sigma_D^2}{D^2} - F'K\sigma_{t_0}^2\right) \quad (2D)$$

Eqs. 8 and 9 yield

$$\lim_{x\to 0}[F'(t)]_{\beta=1} = D\beta K \quad (3D)$$

$$\lim_{x\to 0}[F(t)]_{\beta=1} = 0 \quad (4D)$$

The use of eqs. 3D and 4D in eq. 2D leads to eq. 27.

APPENDIX E

The time derivative of the relative variance is:

$$\frac{\partial}{\partial t}\left(\frac{\sigma^2}{F^2}\right) = \frac{(\partial\sigma^2/\partial t)F^2 - 2FF'\sigma^2}{F^4} = \frac{1}{F^2}\left[\frac{\partial(\sigma^2)}{\partial t} - \frac{2F'\sigma^2}{F}\right] \quad (1E)$$

By the use of eqs. 19 and 4 in eq. 1E the following is derived:

$$\frac{\partial}{\partial t}\left(\frac{\sigma^2}{F^2}\right) = \frac{2(F')^2X}{KF^2}\left[\beta(1 - X^\beta)\frac{\sigma_K^2}{K^2} + (\beta - 1 - \beta X^\beta)\frac{K^2}{X^2}\sigma_{t_0}^2 + \{\beta(1 - X^\beta)\ln^2 X + \ln X\}\frac{\sigma_\beta^2}{\beta^2}\right] + \frac{2F'}{F}\frac{\sigma_D^2}{D^2} - \frac{2(F')^3}{F^3}\frac{X^2}{K^2}\left[\frac{\sigma_K^2}{K^2} + \frac{K^2\sigma_{t_0}^2}{X^2} + \ln^2 X\frac{\sigma_\beta^2}{\beta^2}\right] - \frac{2F'}{F}\frac{\sigma_D^2}{D^2} \quad (2E)$$

Combining terms in eq. 2E leads to eq. 34.

APPENDIX F

By expansion of $e^{-\alpha}$ to an infinite series we have

$$1 - e^{-\alpha} - \alpha = -\frac{\alpha^2}{2!} + \frac{\alpha^3}{3!} - \cdots + \frac{\alpha^n}{n!} - \cdots \quad (1F)$$

When $0 < \alpha < 1$ the above coverges.

According to the theory of infinite series (8), if the series:

$$a_1 - a_2 + a_3 - a_4 + \cdots a_n > 0$$

converges by the alternating series test, then

$$0 < |R_n| < a_{n+1}$$

where

$$R_n = S - S_n$$

R_n being the "remainder", S being the sum of the infinite series and S_n being the sum of the first n terms.

This theorem can be stated as follows: When a series converges by the alternating series test, the absolute value of the error, made in stopping at n terms, is less than the absolute value of first neglected term.

Therefore, the sign of the sum of an infinite series that converges by the alternating series test, where $|a_{n+1}| < a_n$, for every n, is equal to the sign of the first term of the series.

Hence, by eq. 1F:

$$1 - e^{-\alpha} - \alpha < 0 \quad \text{for} \quad 0 < \alpha < 1 \quad (2F)$$

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