Kinetic modeling and comparison of invitro dissolution profiles

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ABSTRACT

This review describes that the quantitative analysis of the values obtained in dissolution release tests are easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. From the theoretical analysis of the occurring process, these mathematic models are derived. In most of the cases the theoretical concept does not exist and some empirical equations have proved to be more appropriate. The dissolved amount of drug is a function of the test time when drug release from solid dosage forms has been described by kinetic models. Some commonly used analytical definitions of the functions are zero order, first order, Hixson–Crowell, Weibull, Higuchi, Baker–Lonsdale, Korsmeyer–Peppas and Hopfenberg models. Other release parameters, such as dissolution time, assay time, dissolution efficacy, difference factor (f1) and similarity factor (f2) can be used to characterize drug release profiles.

Key words: Dissolution, drug release kinetic models, model dependent method, model independent method, statistical model.

INTRODUCTION

After oral administration, Drug absorption from solid dosage forms is based on the release of the drug substance from the prepared drug product by using an active and inactive ingredient and also based on the dissolution or solubilisation of the drug under physiological conditions, and the permeability across the GI (Gastro Intestinal) membrane. Due to this reason there is a need of an in vivo performance.[1, 2] In the drug bioavailability, dissolution is the rate limiting step. In the development of sustained release product, it is necessary that in-vitro release maintained in physiologic condition. The release patterns can be divided into those that release drug at a slow zero or first order rate and those that provide an initial rapid dose, followed by slow zero or first order release of sustained component. To achieve plasma concentration of the drug in humans in the development of sustained-release dosage forms is a main goal. The development process can be accelerated and products introduced more rapidly than if such predictions are unavailable by achieving this goal.[3, 4, 5] The dissolution method and designs are set by considering the solubility, permeability, dissolution, and pharmacokinetics of the drug substance. The method for the comparison of invitro dissolution profile can be categorised into three categories.

1. ANOVA (Analysis of Variance) based model
2. Model dependent based approach
3. Model independent based approach.

ANOVA based method is not rely on the curve fitting procedures and also the dissolution data which are used in their native form. The analysis of this model is to show the difference in profiles of level and shape. A model-independent method uses the dissolution data in their native form. The model-dependent methods, however, are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters.

NEED OF MATHEMATICAL MODELLING

Several methods are specify to elucidate dissolution data as a function of time, but its dependence on dosage form characteristics can best be abstracted by using generic equations which mathematically interprets the dissolution curves in

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the function of other constraints related to delivery device. Kinetics of drug release can be determined by the use of such mathematical models. The quantitative analysis of the values obtained in dissolution study is easier when mathematical principles are used to describe the process. The mathematical modeling significantly accelerates the optimization the design of an existing and new delivery device to yield information on the efficiency of various release models.

FACTORS INFLUENCING CHOICE OF MODEL

The choice of mathematical model is highly depend upon the class of drug (Class I, II, III, and IV), nature of excipients are used in the formulation, concentration of active ingredient and inactive ingredients used and also on the geometry of the delivery device.[3]

Several theories and kinetics models have been used for above mentioned factors to describe drug dissolution from conventional as well as modified release dosage forms. Based on these theories, there are different models to represent the drug dissolution profiles, described below, where *f is* a function of *t* (time) related to the amount of drug dissolved from the pharmaceutical dosage forms.

Noyes-Whitney rule: For estimation of the kinetics of drug release is a vital principle and it was offered by Noyes and Whitney in 1897 as the equation
dM/dt = KS (Cs - Ct)…………..Eq.1
Where,
dM/dt = the rate of dissolution
S = surface area of the solid,
Ct = concentration of the solid in the bulk dissolution medium,
Cs= concentration of the solid in the diffusion layer surrounding the solid,
K = diffusion coefficient,
L = diffusion layer thickness
The rate of dissolution dM/dt is the amount dissolved per unit area per unit time and for most solids can beexpressed in units of g × cm^{-2}× s^{-1}. On the dissolution rate of the solid, Ct has a negligible influence, when Ct is less than 15% of the saturated solubility Cs. Under such conditions, the dissolution of the solid is said to be occurring under 'sink' conditions.[4]

Nernst and Brunner Film Theory: By using Fick's law of diffusion Brunner and Nernst used to establish a relationship between the constant in the equation (1) and the diffusion coefficient of the solute, as the equation:
K = DS/ hγ……………Eq.2

Where,
D = diffusion coefficient,
S = the area of dissolving surface or area of the diffusion layer,
γ = the solution volume and
h = the diffusion layer thickness.

In formulating their theories, Nernst and Brunner assumed that the transport process proceeds much slower than at the surface and thata linear concentration gradient is confined to the layer of solution adhering to solid surface. As the actual surface is changed permanently with the progress of dissolution processes during the usual determination of drug release, the ideal condition can never be achieved. In the Noyes- Whitney equation, the dissolution process corresponds to a first order reaction.[6, 7]

RELEASE KINETIC MODEL
To describe the overall release of drug from the dosage forms the number of kinetic models are available. Because in a formulation qualitative and quantitative changes may alter drug release and in vivo performance. Product development by reducing the necessity of bio-studies is always desirable when developing tools are used. The methods of approach to investigate the kinetics of drug release from sustained release formulation can be classified into three categories.

STATISTICAL METHODS
1. Exploratory data analysis method,
2.Repeated measures design,
3. Multivariate approach [MANOVA: Multivariate Analysis Of Variance][8, 9]

MODEL DEPENDENT METHODS
1.Zero order,
2. First order,
3. Higuchi,
4. Korsmeyer-Peppasmodel,
5. Hixson Crowell,
6. Baker-Lonsdale model,
7. Weibull model
8. Hopfenberg model
9. Gompertz model[13, 15]

MODEL INDEPENDENT METHODS
1. Ratio factors
2. Fit factors
   ✓ Similarity factor
   ✓ Difference factor
   ✓ Resign index[13 ,16]

Another method of classification:-
A. Empirical and semi empirical models (Higuchi, Peppas and Sahlin, Power law),
B. Mechanistic and empirical.

STATISTICAL METHODS

Exploratory Data Analysis methods: By the FDA exploratory data analysis methods are not currently endorsed. For the improvement and understanding of the dissolution data of sustained release formulation, the method is useful and therefore, its use is recommended. In the first step to compare dissolution profile data in both graphical and numerical manner, this method can be used. By plotting the mean dissolution profile data for each formulation with error bars extending to two standard errors at each dissolution time point, the dissolution profile data are illustratedgraphically.95% confidence intervals for the differences in the mean dissolution profiles at each dissolution time point are evaluated and the data of the dissolution profiles are summarized numerically.

Multivariate approach (MANOVA): These methods were based upon repeated measures designs where time is the repeated factor and percent dissolved is the dependent variable. For statistical methods, SPSS (**Statistical Product and Service Solutions)** 10.0 for Windows was employed. The calculated statistics of this method were, Pillai's Trace, Wilks' Lambda, Hotelling's Trace, and Roy's Largest Root. Since the data were collected as repeated measurements over time on the same experimental unit, a repeated measures design was applied. When compared to Student's "*t-*" and paired "*t-*" tests, the major advantage of this design is increased precision. In repeated measures, ANOVA containing repeated measures factors with more than two levels, additional special assumptions enter the picture: These are compound symmetry assumption and the assumption of spherocity. Because these assumptions rarely hold, the MANOVA approach to repeated measures ANOVA has gained popularity in recent years. The compound symmetry assumption requires that the variances and covariances of the different repeated measures are homogeneous. This is a sufficient condition for the univariate "F" test for repeated measures to be valid. The spherocity assumption is a necessary and sufficient condition for the F test to be valid. When the compound symmetry or spherocity assumptions have been violated, the univariate ANOVA table will give erroneous results. Mauchly's test of spherocity results are used for the assumption of spherocity.[21]

MODEL DEPENDENT METHODS

On different mathematical functions model dependent methods are established, which describe the dissolution profile. After the appropriate function designation, the dissolution profiles are estimated depending on the derived model constraints. To determine the suitable drug release kinetic model, the nonlinear regression module of Statistica 5.0 was used. Quasi-Newton and Simplex methods minimized the least squares in non-linear regression analysis. The model dependent approaches included zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Baker-Lonsdale, Weibull, Hopfenberg, Gompertz, Non-conventional order 1, Non-conventional order 2, Reciprocal powered time and regression models.

1. Zero-order model
From dosage forms drug dissolution that do not disaggregate and release the drug slowly can be represented by the equation:
$Q_0 - Q_t = K_0 t$…………Eq. 3
Rearrangement of equation (3) yields:
$Q_t = Q_0 + K_0 t$…………Eq.4
Where,
$Q_t =$ the amount of drug dissolved in time *t,*
$Q_0 =$ the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time.

Plot: Data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time, to study the release kinetics.
Application: To describe the drug dissolution of several types of modified release pharmaceutical dosage forms, some transdermal systems and in the matrix tablets with low soluble drugs in coated forms, osmotic systems, etc. this model is generally used.[15]

2. First order model
To describe absorption and elimination of some drugs, this model has been used. The release of the drug which followed first order kinetics can be expressed by the equation:

$dC/dt = -KC$................Eq. 5
Where *K* is first order rate constant expressed in units of time^{-1}.
Equation (5) can be expressed as:

$\log C = \log C_0 - Kt / 2.303$…………Eq. 6
Where $C_0 =$ the initial concentration of drug, k = the first order rate constant, and t = time.

Plot: log cumulative percentage of drug remaining *vs.* time which would yield a straight line with a slope of -**K/2.303.**

Application: For dissolution of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices, this model has been used.[19]

3. Higuchi model

To describe drug release from a matrix system was proposed by Higuchi in 1961 was the first example of a mathematical model. Initially it was considered for planar systems, then it was extended to porous systems and different geometrics. This model is based on the hypotheses that (i) in the matrix, initial drug concentration is much higher than drug solubility; (ii) only in one dimension (edge effect must be negligible), drug diffusion takes place;(iii) system thickness is grater then the drug particles; (iv) dissolution and matrix swelling are negligible; (v) drug diffusivity is constant; and (vi)in the release environment, perfect sink conditions are always attained. Accordingly, model expression is given by the equation:

$$f_t = Q = A \sqrt{D(2C - C_s) C_s t} \qquad \text{Eq.7}$$

Where Q = the amount of drug released in time t per unit area A,

C = the drug initial concentration, Cs = the drug solubility in the matrix media and

D = the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

Except when the total depletion of the drug, this relation is valid during all the time in the therapeutic system is achieved. The drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by equation (8), to study the dissolution from a planar heterogeneous matrix system:

$$f_t = Q = \sqrt{\frac{D\delta}{\tau} (2C - \delta C_s) C_s t} \qquad \text{Eq. 8}$$

Where D = the diffusion coefficient of the drug molecule in the solvent, δ = the porosity of the matrix, τ = the tortuisity of the matrix and Q, A, Cs and thave the meaning assigned above. Tortuisity is defined as the dimensions of radius and branching of the pores and canals in the matrix. In a general way it is possible to simplify the Higuchi model as the simplified Higuchi model. [10]

$$f_t = Q = K_H \times t^{1/2} \dots\dots\dots\text{Eq. (9)}$$

Where, K_H = the Higuchi dissolution constant.

Plot: Cumulative percentage drug release versus square root of time.

Application: To describe dissolution of drug from several types of modified release pharmaceutical dosage forms, transdermal systems and matrix tablets with water soluble drugs this relationship can be used.

4. Korsmeyer – Peppas model

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer Peppas model and the equation derived is as:

$$M_t / M_\infty = Kt^n \dots\dots\dots (10)$$

Where M_t / M_∞ = a fraction of drug released at time t, k = the release rate constant and n = the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II(relaxation) transport, and $n > 0.89$ to super case II transport. To find out the exponent of *n* the portion of the release curve, where $M_t / M_\infty < 0.6$should only be used. [12]

Plot: log cumulative percentage drug release versus log time, to study the release kinetics, data obtained from in vitro drug release studies were plotted.

5. Hixson Crowell

Hixson and Crowell (1931) suggest that the particles regular area is proportional to the cuberoot of its volume. They derived the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t \dots\dots\dots \text{Eq. (11)}$$

Where, $W_0$is = initial amount of drug in the pharmaceutical dosage form,

W_t = remaining amount of drug in the pharmaceutical dosage form at time t and κ(kappa) is a constant incorporating the surface-volume relation. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets.

Plot: Cube root of drug percentage remaining in matrix versus time, to study the release kinetics, data obtained from in vitro drug release studies were plotted.

Application: This model is mainly applicable to that if the tablet dimensions diminish proportionally, where the dissolution occurs in planes that are parallel to the drug surface, In such a manner that the initial geometrical form keeps constant all the time.[11]

6. Baker-Lonsdale model

From the Higuchi model, this model was developed by Baker and Lonsdale (1974) and described the drug release from spherical matrices according to the equation:

$$f_1 = \frac{3}{2} \left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{2/3} \right] \frac{M_t}{M_\infty} = k_t \qquad \text{.Eq. 12}$$

Where, the release rate constant, *k*, corresponds to the slope.

Plot: Data obtained from in vitro drug release studies were plotted as [d (M$_t$ / M$_\infty$)] / dt with respect to the root of time inverse, to study the release kinetics.

Application: Linearization of release data from several formulations of microcapsules or microspheres, this model has been generally used.[13]

7. Weibull model

This model has been used for different dissolution processes as the equation;

$$M = M_0 \left[1 - e^{-\frac{(t-T)^b}{a}} \right]$$

.......Eq. 13

In this equation, M is the amount of drug dissolved as a function of time t. M_0 is total amount of drug being released. T accounts for the lag time measured as a result of the dissolution process. Parameter *a* denotes a scale parameter that describes the time dependence, while *b* describes the shape of the dissolution curve progression. For $b = 1$, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant $k = 1/a$ (equation

$$M = M_0(1 - e^{-k(t-T)}) \ldots\ldots\ldots Eq. (14)$$

The shape of the curve gets sigmoidal with a turning point If *b* has a higher value than 1, whereas if *b* has lower than 1 value then the shape of the curve would show a steeper increase than the one with $b = 1$.

The time, when 50% (w/w) and 90% (w/w) of drug being in each formulation was released, was calculated using the inverse function of the Weibull equation:

$$t_{(50\% \text{ resp. } 90\% \text{ dissolved})} = (-a \ln \frac{M_0 - M}{M_0})^{1/b} + T$$

Eq. (15)

Application: For comparison of the release profiles of matrix type drug delivery this Weibull model is used.[14]

8. Hopfenberg model

To correlate the drug release from surface eroding polymers so long as the surface area remains constant during the degradation process Hopfenberg has developed a mathematical model. The cumulative fraction of drug released at time t was described as:

$$/ M_\infty = 1 - [1 - k_0 t / C_L a]^n \ldots\ldots\ldots\ldots Eq. 16$$

Where k_0 = the zero order rate constant describing the polymer degradation (surface erosion) process, C_L = the initial drug loading throughout the system, a = the system's half thickness (i.e. the radius for a sphere or cylinder), and n = an exponent that varies with geometry n = 1, 2 and 3 for slab (flat), cylindrical and spherical geometry, respectively.

Application: To identify the mechanism of release from the optimized oil is pheresusing data derived from the composite profile, which essentially displayed site-specific biphasic release kinetics this model is used.[15]

9. Gompertz model

By a simpler exponential model, the in vitro dissolution profile is often described known as Gompertz model, expressed by the equation:

$$X(t) = X_{max} \exp[-\alpha e^{\beta \log t}] \ldots\ldots\ldots Eq. (17)$$

Where X (t) = percent dissolved at time t divided by 100; X_{max} = maximum dissolution; α determines the undissolved proportion at time t = 1 and described as location or scale parameter; β = dissolution rate per unit of time described as shape parameter. In the beginning this model has a steep increase and converges slowly to the asymptotic maximal dissolution.

Application: For comparison of the release profiles of drugs having good solubility and intermediate release rate, this model is widely used.[16, 17]

REGRESSION MODEL

For the formulation of many pharmaceutical dosage forms, statistical optimization designs have been previously documented. [25] To optimize the formulation from in vitro release study several types of regression analysis are used. [26]

1. Linear or first order regression model. [27-29]

For determining the parameters of a linear system, linear regression is used. The empirical model relating the response variable to the independent variables are described by the following equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \ldots\ldots\ldots\ldots Eq.(18)$$

Where Y represents the response, X_1 and X_2 represent the two independent variables. The parameter β_0 signifies the intercept of the plane. β_1 and β_2, called partial regression coefficients, where β_1 measures the expected change in 'Y', the response, per unit change in X_1 when X_2 kept constant and vice versa for β_2. The equation (18) can be rewritten in a general form as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\beta_k X_k \ldots\ldots\ldots Eq. (19)$$

The model is a multiple linear regression model with 'k' regression variables. The model describes a hyperplane in the k-dimensional space.

Further complex model (equation. 19) are often analysed by multiple linear regression technique by adding interaction terms to the first order linear model:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 \ldots\ldots\ldots\ldots Eq.(20)$$

Where X_1 and X_2 are the interaction effects of two variables acting simultaneously.

2. Quadratic model or second order regression model [30-32]

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2 \ldots\ldots\ldots\ldots Eq. 21$$

If we put, $X_{21} = X_3$, $X_{22} = X_4$, $X_1 X_2 = X_5$ and $\beta_{11} = \beta_3, \beta_{22} = \beta_4$, $\beta_{12} = \beta_5$, then the above equation is reduced to a linear model. Any model is linear if

the (β) coefficients are linear, regardless of the shape of the response surface that it generates.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 \ldots\ldots\ldots Eq.(22)$$

The explanatory and response variables may be scalars of vectors. The resulting regression is called simple linear regression when both explanatory and response variables are scalars. The resulting regression is called multiple linear regression when there are more than one explanatory variable. It should be noted that the general formulae are the same for both cases. The robust regression and least squares analysis are mostly used to solve linear regression models.

NON-LINEAR REGRESSION MODELS [33-34]

There are number of nonlinear regression techniques are used to obtain a more accurate regression. Due to the large number of dissolution media available for solid dosage forms, a statistical method to choose the appropriate medium is critical for testing solid dosage forms. It should be noted that an often-used alternative is a transformation of the variables such that the relationship of the transformed variables is again linear. The method was designed using software to detect factors contributing to differences in the dissolution process of the drug delivered in dosage form.

1. Non- Convention Model 1

By the use of simple model known as nonconventional model 1, the in vitro dissolution profile can be described and expressed by the equation:

$$1 - (1-F)^{1-n} = (1-n) k_{1-n} t \ldots\ldots. Eq. 23$$

Where F is as fraction of drug released up to time t, k is parameter of model. On basis of non-linear regression, this model was calculated.

Application

For the determination of kinetics drug release from the nanoparticles, the non-conventional model 1 is useful.

2. Non- Convention Model 2

By the use another simple model known as nonconventional model 2, the in-vitro dissolution profile is described, expressed by the equation:

$$\frac{1}{(1-F)^{n-1}} - 1 = (n-1) K_{n-1} \ldots\ldots\ldots.Eq. 24$$

Where F denotes fraction of drug released upto time t, k is parameter of model. This model was calculated on basis of non-linear regression.[17, 18, 19]

Application

For the determination of kinetics drug release from the nanoparticles, the non-conventional model 2 is useful.

MODEL INDEPENDENT METHODS[35, 36]

1. Ratio factors

Ratio tests are performed as ratios of percent drug dissolved, area under the dissolution curve, and mean dissolution times of the reference formulation with those of a test formulation at the same sampling time. The most common ratio test is performed by comparison of two mean dissolution times (MDTs), which are calculated by

$$MDT = \frac{\sum_i^n \overline{t_i} \Delta M_i}{\sum_i^n \Delta M_i}$$

Where *i* is the sample number, *n* is the number of dissolution sample times, $t_{1} = t_{i-1} + t_1/2$ is the time at mid point between t_i-1 and t_i, and ΔM_i is the additional amount of drug dissolved between t_i-1 and t_i.

The variance of dissolution times (VTs) is estimated by

$$VT = \frac{\sum_i^n \left(\overline{t_i} - MDT\right)^2 \Delta M_i}{\sum_i^n \Delta M_i}$$

And the relative dispersion of dissolution time is given by

$$RD = VT / MDT^2$$

2. Fit factors

Fit factors include a difference factor *f*1 and a similarity factor *f*2. The difference factor *f*1 calculate the % difference between the two curves at each time point and is a measurement of the relative error between two curves which is given by,

$$F1 = [\{\sum_{t=1}^n (Rt - Tt)/ (\sum_{t=1}^n Rt)] \times 100$$

Where Rt and Tt are the percent drug dissolved of the reference and test products, respectively, at each sample point i.

The similarity factor *f*2 is a logarithmic reciprocal square root transformation of the sum of square error and is a measurement of similarity in the % dissolution between the two curves which is given by

$$F2 = 50 \times log [\{ 1 + (1 + (1/n) \sum_{t=1}^n (Rt - Tt)^2)^{-0.5} \times 100]$$

CONCLUSION

Reviews of the kinetic modeling on drug release exemplify that these models have been predictable to describe the relationship between drug dissolution and geometry on drug release arrays mathematically. It is evident from the pharmaceutical literature that no single approach is widely accepted to determine if dissolution profiles

are similar. The application and evaluation of model dependent methods and statistical methods are more complicated, whereas the model independent methods present satisfactory model approach to the true relationship between the dependent and independent variables of the dissolution data. The disadvantages of the model independent methods are the values of f1 and f2 which are sensitive to the number of dissolution timepoints and the basis of the criteria for deciding the difference or similarity between dissolution profiles is unclear. The limitation is that only when the within-batch variation is less than15%, f2 equation should be used. Overall, these models, though some are more complicated, helps the formulation and research scientists to forecast possible rate and mechanism of drug release.

Table 1: Some models with linear equations for graphical presentation [1]

Sr. no	Model name	Linear equation	Plot	
			X - axis	**Y- axis**
1	Zero order	$Q_t = Q_0 + K_0 t$	Time	Cumulative amount of drug release
2	First order	$\log C = \log C_0 - Kt/ 2.303$	Time	Log cumulative percentage of drug
3	Higuchi model	$f_t = Q = K_H \times t^{1/2}$	Square root of time	Cumulative percentage of drug release
4	Hixson Crowell	$W_0^{1/3} - W_t^{1/3} = \kappa t$	Time	Cube root of drug percentage remaining
5	Korsmeyer Peppas	$M_t / M_\infty = K t^n$	Time	Log cumulative percentage drug release
6	Baker Lonsdale	$f_1 = \dfrac{3}{2}\left[1 - (1 - \dfrac{M_t}{M_\infty})^{2/3}\right]\dfrac{M_t}{M_\infty} = k_t$	Root of time inverse	$[d(M_t/ M_\infty)] / dt$
7	Weibull	$M = M_0\left[1 - e^{-\frac{(t - T)^b}{a}}\right]$	Log $[-\ln(1-M)]$	Log $(t- T_i)$

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