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REVIEW

KINETIC MODELING ON DRUG RELEASE FROM CONTROLLED DRUG DELIVERY SYSTEMS

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Abstract: In this paper we review the mathematical models used to determine the kinetics of drug release from drug delivery systems. The quantitative analysis of the values obtained in dissolution/release rates is easier when mathematical formulae are used to describe the process. The mathematical modeling can ultimately help to optimize the design of a therapeutic device to yield information on the efficacy of various release models.

Keywords: dissolution, drug release kinetic models, model dependent method, model independent method

Over the past few decades, significant medical advances have been made in the area of drug delivery with the development of controlled release dosage forms. There are large variety of formulations devoted to oral controlled drug release, and also the varied physical properties that influence drug release from these formulations. 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 (1). The purpose of the controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible (2). In other words, they are able to exert a control on the drug release rate and duration (3). For this purpose, generally, controlled release system initially release part of the dose contained in order to attain rapidly the effective therapeutic concentration of the drug. Then, drug release kinetics follows a well defined behavior in order to supply the maintenance dose enabling the attainment of the desired drug concentration.

In the light of wide versatility of application of controlled release formulations, in the field of medical sciences, they are unavoidable tools for the exploitation of the modern concept of therapeutic treatment whose aim is to increase drug effectiveness and patient compliance, to reduce the administration frequency and side effects connected to dosing. As a matter of fact, controlled release formulations bring engineers and pharmacists to work together with the common aim of realizing more and more effective products. For this purpose, the use of mathematical modeling turns out to be very useful as this approach enables, in the best case, the prediction of release kinetics before the release systems are realized. More often, it allows the measurement of some important physical parameters, such as the drug diffusion coefficient and resorting to model fitting on experimental release data. Thus, mathematical modeling, whose development requires the comprehension of all the phenomena affecting drug release kinetics (4), has a very important value in the process optimization of such formulation. The model can be simply thought as a "mathematical metaphor of some aspects of reality" that, in this case, identifies with the ensemble of phenomena ruling release kinetics (5-9). For this generality, mathematical modeling is widely employed in different disciplines such as genetics, medicine, psychology, biology, economy and obviously engineering and technology.

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Fundamentals of kinetics of drug release

Noyes-Whitney Rule

The fundamental principle for evaluation of the kinetics of drug release was offered by Noyes and Whitney in 1897 as the equation (10):

$$dM/dt = KS (C_s - C_t) \quad (1)$$

where M, is the mass transferred with respect to time, t, by dissolution from the solid particle of instantaneous surface, S, under the effect of the prevailing concentration driving force ($C_s - C_t$), where C_t is the concentration at time t and C_s is the equilibrium solubility of the solute at the experimental temperature. The rate of dissolution dM/dt is the amount dissolved per unit area per unit time and for most solids can be expressed in units of $g \times cm^{-2} \times s^{-1}$.

When C_t is less than 15% of the saturated solubility C_s, C_t has a negligible influence on the dissolution rate of the solid. Under such circumstances, the dissolution of the solid is said to be occurring under 'sink' conditions. In general, the surface area, S is not constant except when the quantity of material present exceeds the saturation solubility, or initially, when only small quantities of drug have dissolved.

Nernst and Brunner Film Theory

Brunner and Nernst (11, 12) used Fick's law of diffusion to establish a relationship between the constant in the equation (1) and the diffusion coefficient of the solute, as the equation:

$$K = DS/h\gamma \quad (2)$$

where D is the diffusion coefficient, S is the area of dissolving surface or area of the diffusion layer, γ is the solution volume and h is the diffusion layer thickness. In formulating their theories, Nernst and Brunner assumed that the process at the surface proceeds much faster than the transport process and that a linear concentration gradient is confined to the layer of solution adhering to solid surface.

The ideal condition can never be achieved as the actual surface is changed permanently with the progress of dissolution processes during the usual determination of drug release. In the Noyes-Whitney equation, the dissolution process corresponds to a first order reaction.

Release kinetic modeling

There are number of kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of *in vitro* drug dissolution data to predict *in vivo* bio-performance can be considered as the rational development of controlled release formulations (7-9).

The methods of approach to investigate the kinetics of drug release from controlled release formulation can be classified into three categories:

- Statistical methods (exploratory data analysis method, repeated measures design, multivariate approach [MANOVA: multivariate analysis of variance] (13, 14).
- Model dependent methods (zero order, first order, Higuchi, Korsmeyer-Peppas model, Hixson Crowell, Baker-Lonsdale model, Weibull model, etc.) (15, 16).
- Model independent methods [difference factor (f_1), similarity factor (f_2) (17-19)].

Statistical methods

Exploratory Data Analysis methods

Although exploratory data analysis methods are not currently endorsed by the FDA, the method is useful in obtaining an improved understanding of the dissolution data of controlled release formulation and therefore, its use is recommended. This method can be used in the first step to compare dissolution profile data in both graphical and numerical manner. The dissolution profile data are illustrated graphically by plotting the mean dissolution profile data for each formulation with error bars extending to two standard errors at each dissolution time point. Then, the data of the dissolution profiles are summarized numerically and 95% confidence intervals for the differences in the mean dissolution profiles at each dissolution time point are evaluated (20).

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 10.0 for Windows was employed. The calculated statistics of this method were, Pillai's Trace, Wilks' Lambda, Hotelling's Trace, 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 (21).

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 repeat-

ed 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.

Model dependent methods

Model dependent methods 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. In order to determine the suitable drug release kinetic model describing the dissolution profile, the non-linear regression module of Statistica 5.0 was used. In non-linear regression analysis the Quasi-Newton and Simplex methods minimized the least squares (15, 16). The model dependent approaches included zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Baker-Lonsdale, Weibull, Hopfenberg, Gompertz and regression models (22, 23).

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t \quad (3)$$

Rearrangement of equation (3) yields:

$$Q_t = Q_0 + K_0 t \quad (4)$$

where Q_t is the amount of drug dissolved in time *t*, Q_0 is 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.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released *versus* time (24, 25).

Application: This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc. (26, 27).

First order model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\frac{dC}{dt} = -Kc \quad (5)$$

where *K* is first order rate constant expressed in units of time^{-1}.

Equation (5) can be expressed as:

$$\log C = \log C_0 - Kt / 2.303 \quad (6)$$

where C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time (28). The data obtained are plotted as log cumulative percentage of drug remaining *vs*. time which would yield a straight line with a slope of –K/2.303.

Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices (29, 30).

Higuchi model

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Huguchi in 1961 (31). Initially conceived for planar systems, it was then extended to different geometrics and porous systems (32). This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by the equation:

$$f_t = Q = A\sqrt{D(2C - C_s)\,C_s\,t} \quad (7)$$

where Q is the amount of drug released in time t per unit area A, *C* is the drug initial concentration, *Cs* is the drug solubility in the matrix media and *D* is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

This relation is valid during all the time, except when the total depletion of the drug in the therapeutic system is achieved. To study the dissolution from a planar heterogeneous matrix system, where 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):

$$f_t = Q = \sqrt{\frac{D\delta}{\tau}(2C - \delta C_s)\,C_s\,t} \quad (8)$$

where D is the diffusion coefficient of the drug molecule in the solvent, δ is the porosity of the matrix, τ is the tortuisity of the matrix and Q, A, C_s and t

have 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 (31) as (generally known as the simplified Higuchi model):

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

where, K_H is the Higuchi dissolution constant (23).

The data obtained were plotted as cumulative percentage drug release versus square root of time (30).

Application: This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs (31-33).

Hixson–Crowell model

Hixson and Crowell (1931) recognized that the particles' regular area is proportional to the cube root of its volume. They derived the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t \text{ ……} \quad (10)$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the 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 (34). To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cube root of drug percentage remaining in matrix *versus* time.

Application: This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time (35).

Korsmeyer-Peppas model

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation (12).

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer–Peppas model (36).

$$M_t / M_\infty = Kt^n \text{ …….} \quad (12)$$

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

In this model, the value of *n* characterizes the release mechanism of drug as described in Table 1. 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 (relaxational) transport, and $n > 0.89$ to super case II transport (37, 38). To find out the exponent of *n* the portion of the release curve, where $M_t / M_\infty < 0.6$ should only be used. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release *versus* log time.

Baker-Lonsdale model

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

$$f_1 = \frac{3}{2}\left[1 - (1 - \frac{M_t}{M_\infty})^{2/3}\right] \frac{M_t}{M_\infty} = k_t \quad (13)$$

where the release rate constant, *k*, corresponds to the slope (39).

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as [d (M_t / M_∞)] / dt with respect to the root of time inverse.

Application: This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres (40, 41).

Weibull model

This model has been described for different dissolution processes as the equation (42, 43):

$$M = M_0 \left[1 - e^{-\frac{(t-T)^b}{a}}\right] \quad (14)$$

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 meas-

Table 1. Interpretation of diffusional release mechanisms from polymeric films.

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
$0.45 < n = 0.89$	Non -Fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II transport	t^{n-1}

ured 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 15).

$$M = M_0 (1 - e^{-k(t - T)}) \quad (15)$$

If *b* has a higher value than 1, the shape of the curve gets sigmoidal with a turning point, whereas the shape of the curve with *b* lower than 1 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:

$$t_{(50\% \text{ resp. } 90\% \text{ dissolved})} = (- a \ln \frac{M_0 - M}{M_0})^{1/b} + T \quad (16)$$

Application: The Weibull model is more useful for comparing the release profiles of matrix type drug delivery (44, 45).

Hopfenberg model

Hopfenberg developed a mathematical model to correlate the drug release from surface eroding polymers so long as the surface area remains constant during the degradation process (46, 47). The cumulative fraction of drug released at time t was described as:

$$M_t / M_\infty = 1 - [1 - k_0 t / C_L a]^n \quad (17)$$

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

Application: This model is used to identify the mechanism of release from the optimized oilispheres using data derived from the composite profile, which essentially displayed site-specific biphasic release kinetics (48).

Gompertz model

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

$$X(t) = X_{max} \exp [-\alpha e^{\beta \log t}] \quad (18)$$

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. This model has a steep increase in the beginning and converges slowly to the asymptotic maximal dissolution (38, 49).

Application: The Gompertz model is more useful for comparing the release profiles of drugs having good solubility and intermediate release rate (49).

Regression model

Statistical optimization designs have been previously documented for the formulation of many pharmaceutical dosage forms (39). Several types of regression analysis are used to optimize the formulation from *in vitro* release study (40).

Linear or first order regression model (50-52).

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

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \quad (19)$$

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 (19) can be rewritten in a general form as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots \beta_k X_k \quad (20)$$

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. 21) are often analyzed by multiple linear regression technique by adding interaction terms to the first order linear model:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 \quad (21)$$

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

Quadratic model or second order regression model (53-55)

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X^2_1 + \beta_{22} X^2_2 + \beta_{12} X_1 X_2 \quad (22)$$

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.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 \quad (23)$$

The explanatory and response variables may be scalars of vectors. In the case, where both the explanatory and response variables are scalars, then

the resulting regression is called simple linear regression. When there are more than one explanatory variable, then the resulting regression is called multiple linear regression. It should be noted that the general formulae are the same for both cases. The least squares and robust regression analysis are mostly used to solve linear regression models.

Non linear regression models (56, 57)

A number of nonlinear regression techniques may be 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.

Model Independent Approach Using a Similarity Factor (17-19, 58)

A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles. The difference factor calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves. It is expressed as:

$$f_1 = \{[\sum_{t=1}^{n}(R_t - T_t)]/[\sum_{t=1}^{n}R_t]\} \times 100 \qquad (24)$$

where n is the number of time points, R is the dissolution value of the reference (prechange) batch at time t, and T_t is the dissolution value of the test (postchange) batch t at time t.

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves. This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available.

CONCLUSIONS

Reviews of the kinetic modeling on drug release show that these models have been established to describe the relationship between drug dissolution and geometry on drug release patterns 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 dependent methods present an acceptable 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 f_1 and f_2 which are sensitive to the number of dissolution time points 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 than 15%, f_2 equation should be used.

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