KINETIC MODELING AND DISSOLUTION PROFILES COMPARISON: AN OVERVIEW

HUSSAIN LOKHANDWALA, ASHWINI DESHPANDE *
AND SHIRISH DESHPANDE.

School of Pharmacy and Technology Management, SVKM'S NMIMS, shirpur (Dhule), Maharashtra, India - 425405.

ABSTRACT

This review shares different mathematical models used to determine the kinetics of drug release from delivery systems. It consists of an overview of applied method for comparison like model dependent, model independent and statistical model. The mathematical modeling can finally help to optimize the design of a therapeutic device to yield a system with programmed release rate characteristics which is now a prerequisite for controlled release drug delivery system. For the ease of application of these models linear forms to plot the graphs were also discussed. This review also consists of various software programs available to describe the release kinetics from therapeutic device.

KEY WORDS: Dissolution, drug release kinetic models, model dependent method, model independent method, statistical model, pairwise comparison.

ASHWINI DESHPANDE
School of Pharmacy and Technology Management, SVKM'S NMIMS, shirpur (Dhule), Maharashtra, India - 425405.

*Corresponding author

INTRODUCTION

Drug absorption from solid dosage forms after oral administration is based on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the perilous nature of the first two of these steps, in vitro dissolution may be applicable to the approximation of in vivo performance. Dissolution is one of the great problems in pharmaceutical science, being the rate limiting step in the drug bioavailability. In addition, in the development of controlled release system, especially for oral application, it is necessary that in-vitro release be 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 [1]. The main goal in the development of novel controlled-release dosage forms is to deliver predictable plasma concentration of the drug in humans. By achieving such a goal, the development process can be accelerated and products introduced more rapidly than if such predictions are unavailable. Application of a wide-range bioavailability model facilitates screening of potential drug candidates for controlled release, optimizing formulation design, and interpreting bioavailability data [2-4].

Need of mathematical modeling

Numerous methods are available to elucidate dissolution data as a function of time, but its dependence on dosage form characteristics can best be deducted by using generic equations which mathematically translates the dissolution curves in the function of other parameters 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 formulae are used to describe the process. The mathematical modeling significantly facilitates the optimization

the design of an existing and new delivery device to yield information on the effectiveness of various release models.

FACTORS INFLUENCING CHOICE OF MODEL

The choice of appropriate mathematical model highly depends on the class of drug, excipient used, concentration of drug and excipients in delivery device and geometry of delivery device [2].

Several theories / kinetics models considered 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 system.

Noyes-Whitney Rule

The well-known Noyes-Whitney equation illustrates the dissolution rate:

$$\frac{dw}{dt} = \frac{DA(C_s-C)}{L} \dots\dots \dots\dots \text{ Eq.1}$$

Where,

$\frac{dw}{dt}$ = The rate of dissolution,

A = surface area of the solid,

C = concentration of the solid in the bulk dissolution medium,

C_s = concentration of the solid in the diffusion layer surrounding the solid,

D = diffusion coefficient,

L = diffusion layer thickness.

The rate of dissolution may be modified primarily by altering the particle size and surface area of the solid. The rate of dissolution may further be altered by choosing a suitable polymorph of a compound as crystalline forms dissolve slower than amorphous forms [3].

Nernst and Brunner Film Theory

Brunner and Nernst integrated Fick's law of diffusion to establish a relationship between the

constant in the equation and the diffusion coefficient of the solute, as the equation:

K = DS/ hγ………   Eq. 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 (1904) 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.[5,6]

Release kinetics model

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] [7,8].
> Model dependent methods (zero order, first order, Higuchi, Korsmeyer-Peppas model, HixsonCrowell, Baker-Lonsdale model, Weibull model, etc [13,15].
> Model independent methods [13,16].
>> • Ratio tests
>> • Pairwise procedure (similarity factor; difference factor; resign index).

Another method of classification:-

> Empirical and semi empirical models(Higuchi,Peppas and Sahlin, Power law),
> Mechanistic and empirical.

STATISTICAL METHODS

ANOVA-based methods

In this model, the percent drug dissolved is dependent variable and time is the repeated factor. Sources of variation are time, drug product, and interaction between time and drug product. Firstly, a multivariate approach (MANOVA) is to be applied. It tests the possibility of significant differences among the percents dissolved at each time level without considering the drug products, and among the drug products regarding the percent dissolved depending on time, i.e. whether the dissolution profiles of the drug products are parallel. *P*-values in MANOVA is obtained by the Wilks lambda statistic [20]. In the second step, a single group univariate repeated measures analysis (univariate ANOVA) is to be applied. This time, the percents dissolved is tested separately at each time point to see if there are differences among the drug products. Pair wise comparisons of test product against reference product can be performed by multiple comparisons using Dunnett's *t*-test (two-sided) and repeated contrasts can be applied separately to each drug product for the comparison of percents dissolved at the sequential times.

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 can easily be evaluated depending on the derived model parameters. In non-linear regression analysis the Quasi-Newton and Simplex methods minimizes the least squares. The model dependent approaches includes 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 .

Zero-order model

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

$Q_0 - Q_T = K_0 T$……   Eq. 3

Rearrangement of equation 3 yields:

$Q_t = Q_0 + K_0 t$……..   Eq. 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 of the times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time.

Plot: Cumulative amount of drug released *versus* time.

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 solubility drugs in coated forms, osmotic systems, etc [14].

First order model
This model has 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 followes first order kinetics can be expressed by the equation:

$$\frac{dc}{dt} = -kc \dots\dots \quad \text{Eq. 5}$$

Where K is first order rate constant expressed in units of time^{-1}.
Equation 5 can be expressed in log form as:
log C = log C$_0$ - Kt / 2.303 …….. (6)
Where C_0 is the initial concentration of drug, K is the first order rate constant, and t is the time.
Plot: 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. [18]

Higuchi model
This model is used to study the release of water soluble and poorly soluble drugs incorporated in semi-solid and/or solid matrices. Mathematical expressions are obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. To study the dissolution from a planar system having a homogeneous matrix, the relation obtained is as following:

$$f = Q = \sqrt{D(2C - Cs)Cst} \dots\dots \quad \text{Eq. 7}$$

Where Q is the amount of drug released in time t per unit area, C is the drug initial concentration or the drug solubility in the matrix media and D is the diffusivity of the drug molecules (diffusion constant) in the matrix substance. This relation was first proposed by Higuchi [9] to describe the dissolution of drugs in suspension from ointments bases, but is clearly in accordance with other types of dissolution from other pharmaceutical dosage forms. To these dosage forms a concentration profile, which may exist after application of the pharmaceutical system, can be represented. 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:
Where D is the diffusion coefficient of the drug molecule in the solvent, δ is the porosity of the matrix, τ is the tortuosity of the matrix and Q, A, Cs and t have the meaning assigned above.
In a general way it is possible to simplify the Higuchi model as (generally known as the simplified Higuchi model):
f t = Q = K$_H$ × t$^{1/2}$ ……. Eq. 8
Where, K_H is the Higuchi dissolution constant.

Plot: The data obtained is to be plotted as cumulative percentage drug release versus square root of time.

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

Hixson-Crowell model
Hixson and Crowell [10] recognized that the particles regular area is proportional to the cube root of its volume. They derived the equation:
w$_o^{1/3}$ − w$_t^{1/3}$ = κ t …….. Eq. 9
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].

Plot: Data is to be 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.

Korsmeyer-Peppas model
Korsmeyer et al.[11], derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data is to be fitted in Korsmeyer-Peppas model.

$M_t / M_\infty = kt^n$ ………. Eq. 10

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. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, n < 0.89 to non-Fickian transport, n = 0.89 to Case II (relaxational) 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.

Plot: Data is to be plotted as log cumulative percentage drug release *versus* log time.

Baker-Lonsdale model
This model was developed by Baker and Lonsdale [12] from the Higuchi model and described the drug release from spherical matrices according to the equation:

$$f1 = \frac{3}{2}\left[1 - \frac{\left(1 - \frac{Mt}{M\infty}\right)2}{3}\right]\frac{Mt}{M\infty} = kt \quad \text{............. Eq. 11}$$

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

Plot: Data obtained is to be plotted as [d (*Mt / M∞*)] / dt versus root of time inverse.

Application
This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres.

Weibull model
This model has been described for different dissolution processes as the equation:

$M = M_0[1 - e^{-\frac{(t-T)^b}{a}}]$ ………. Eq. 12

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*.

$M = M_0[1-e^{-k(t-T)}]$ .... Eq. 13

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 equation may be converted to the straight line equation by log transformation as indicated:

$$b \log(t - T_i) - \log a = \log[-\ln(1 - M)]$$

.... Eq. 14

Application
The Weibull model is more useful for comparing the release profiles of matrix
type drug delivery [13].

Hopfenberg model
Hopfenberg[14] 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. The cumulative fraction of drug released at the time t was described as:

$M_t / M_\infty = 1 - [1 - k_0 t / C_L a]^n$ .... Eq. 15

where k_0 is the zero order rate constant describing the polymer degradation (surface erosion) process, C_L is the initial drug loading throughout the system, a is the systemic 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 oil spheres using data derived from the composite profile, which essentially displayed site-specific biphasic release kinetics.

Gompertz model
It is a type of mathematical model for a time series, where release rate is slowest at the start and end of a time period. The *in-vitro* dissolution profile is often described by a simpler exponential model known as Gompertz model, expressed by the equation:

$X(t) = X_{max} \exp[-\alpha e^{\beta \log t}]$ .... Eq. 16

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[15, 16].

Application
The Gompertz model is more useful for comparing the release profiles of drugs having good solubility and intermediate release rate.
Table 1 summarizes some of these models with the key to its graphical presentation.

Nonlinear regression models
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 often used alternative is a transformation of the variables such that the relationship of the transformed variables is again linear. Following are nonlinear kinetics model.

Non- Convention Model 1
The *in-vitro* dissolution profile can be described by the use of simple model known as nonconventional model 1, expressed by the equation:

$1 - (1-F)^{1-n} = (1-n) k_{1-n} t$ .... Eq. 17

Where F denotes fraction of drug released up to time t, k is parameter of model. This model was calculated on basis of non-linear regression.

Application
The non-conventional model1 is useful for the determining kinetics drug release from the nanoparticles.

Non- Convention Model 2

The *in-vitro* dissolution profile is also described by the use of simple model known as nonconventional model 2, expressed by the equation:

$$\frac{1}{(1-F)^{n-1}} - 1 = (n-1) \, K_{n-1}$$ .... Eq. 18

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

Application

The non-conventional model1 is useful for the determining kinetics drug release from the nanoparticles.

MODEL INDEPENDENT APPROACHES

A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) 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_2 = 50 + log {[1+ (1/n) $\sum_{t=1}$ * n (R_t-T_t) ^{2}]$^{-0.5}$ *100}……. Eq. 19

where n is the number of time points, R is the dissolution value of the reference (prechange)

MODEL SELECTION CRITERIA [23]

The ''best model'' for drug dissolution / release phenomena can be selected based on different criteria. One common method uses the coefficient of determination, R^2, to assess the "fit" of a model equation. But, this value tends to get greater with the addition of more model parameters, irrespective of the significance of

batch at time t, and Tt is the dissolution value of the test batch 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 [20, 21, 22].

Significance and applications of similarity factor

The wide application of similarity factor signifies it as an efficient tool for comparison of dissolution profiles. Similarity factor finds its main application as

- Response or dependent variable usually for optimization purposes, e.g. to compare manufacturing processes for establishing experimental conditions maximizing similarity between formulations.
- Part of a decision criterion to establish similarity of two formulations. The regulatory suggestion "decide similarity if (the sample) f2 exceeds 50" is applied in a literal sense.

the variable added to the model. This is best suited where the same number of parameters are in consideration in the subset of model equations. When comparing models with different numbers of parameters, the adjusted coefficient of determination ($R^2_{adjusted}$) is more adjusted meaningful:

$$R^2_{adjusted} = 1 - \frac{(n-1)}{(n-p)} (1 - R^2)$$ ………. Eq. 20

where *n* is the number of dissolution data points (*M/t*) and *p* is the number of parameters in the model. Whereas R^2 always increases or at least stays constant when adding new model parameters, $R^2_{adjusted}$ can actually decrease, thus giving an indication if the new parameter

really improves the model or might lead to over fitting. In other words, the ''best'' model would be the one with the highest adjusted coefficient of determination. The other criteria are the correlation coefficient (*R*), the sum of squares of residues (SSR), the mean square error

(MSE), the Akaike Information Criterion (AIC) and the *F*-ratio probability are also used to test the applicability of the release models. The Akaike Information Criterion is a measure of goodness of fit based on maximum possibility. When comparing several models for a given set of data, the model associated with the smallest value of AIC is regarded as giving the best fit out of that set of models. The AIC will give appropriate values when used to compare models with same weighing scheme.

$$AIC = n \times \ln(WSSR) + 2 \times p$$ ………………….. Eq. 21

where *n* is the number of dissolution data points (*M/t*) and *p* is the number of parameters in the model, WSSR is the weighed sum of square of residues. The AIC criterion has become a standard tool in model fitting, and its computation is available in many statistical programmes.(21) Different type of software program available for determination of drug release from the controlled release formulation like: Zorel, MicroMath Scientist, GraphPad Prism, SigmaPlot, SYSTAT, DDSolver etc. But in case of unavailability of such kind of models, and to represent the linear equation in a more simplify manner can be expressed as followed:

Table No. 1
Some models with linear equation for graphical presentation

S.No	Model No.	Linear Equation	Plot	
			On X Axis	On Y Axis
1.	Zero order	$Q_t = Q_0 + K_0 t$	Time	Cumulative amount of drug released
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 drug release
4.	Hixon crowell	$w_0^{1/3} - w_t^{1/3} = \kappa\, t$	Time	cube root of drug percentage remaining
5.	Korsmeyer-Peppas model	$M_t / M_\infty = kt^n$	Log Time	log cumulative percentage drug release
6.	Baker-Lonsdale model	$f_1 = \frac{3}{2}[1-(1-\frac{Mt}{M\infty})^{2/3}]\frac{Mt}{M\infty} = k_t$	The root of time inverse	$[d\,(Mt / M\infty)] / dt$
7.	Weibull model	$M = M_0[1-e^{-\frac{(t-T)^b}{a}}]$	$\log[-\ln(1 - M)]$	$\log(t - T_i)$

CONCLUSION

Reviews of the kinetic modeling on drug release illustrate that these models have been recognized 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 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 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%, 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.

REFERENCES

1. Hintz, R.J.; Johnson, K.C. The effect of particle size distribution on dissolution rate and oral absorption. Int J Pharm., 51, 9-17 (1989).
2. Ozturk, S.S.; Palsson, B.O.; Donohoe, B.; Dressman; Kinetics of release form enteric-coated tablets. J. Pharm Res., 5,550-565 (1988).
3. Noyes, A.A.; Whitney, W.R.; The rate of solution of solid substances in their own solutions. J. Am. Chem. Soc., 19, 930–934 (1897).
4. FDA, Guidance for Industry: Imediate Release Solid Oral Dosage Forms – Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalance Documentation. Center for Drug Evaluation and Research, Rockville, MD November,1995.
5. Nernst, W. Z. Oscillometric investigation of sparingly soluble sulfates. Physik. Chem., 47, 52 (1904).
6. Brunner, E. Z. Reaktionsgeschwindigkeit in heterogenen Systemen. Physik. Chem, 47-56 (1904).
7. Mauger, J.W.; Chilko, D.; Howard, S. On the analysis of the dissolution data. Drug Dev. Ind. Pharm., 12, 969–992 (1986).
8. Polli, J.E.; Rekhi, G.S.; Augsburger, L.L.; Shah, V.P. Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tartrate tablets. J. Pharm. Sci., 86, 690–700 (1997).
9. Higuchi, T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drug dispersed in solid matrices. J. Pharm. Sci., 52, 1145–1149 (1963).
10. Hixson, A.W.; Crowell, J.H. Dependence of reaction velocity upon surface and agitation I — theoretical consideration. Ind. Eng. Chem., 23, 923–931 (1931).
11. Korsmeyer, R.W.; Gurny, R.; Doelker, E.; Buri, P.; Peppas, N.A. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm., 15:25–35 (1983).
12. Baker, R.W.; Lonsdale, H.S. Controlled release of biologically active agents. New York: Plenum. (1974).
13. Thawatchai P., Tamotsu K., Garnpimol C.R.: Chitosan citrate as film former: compatibility with water-soluble anionic dyes and drug dissolution from coated tablet Int. J. Pharm. 198, 97-111 (2000).
14. Hopfenberg, H.B., In: Paul, D.R., Harris, F.W. (Eds.), Controlled Release Polymeric Formulations. ACS Symposium Series 33. American Chemical Society, Washington, DC, pp. 26–31 (1976.).
15. Costa, P.; Modeling and comparison of dissolution profiles, Eur. J. Pharm., 13, 123 – 133 (2001)
16. Moore, J.W.; Flanner, H.H.; Mathematical comparison of dissolution profiles. Pharm. Technol. June, 64–74 (1996,).
17. Crank, J. The mathematics of diffusion. Clarendon Press, Oxford (2004).
18. Narsimhan, B.; Mallapragada S.K.; and Peppas, N.A. Release Kinetics, Data Interpretation, Encyclopedia of Controlled Drug Delivery, E. Mathiowitz (ed.), John Wiley & Sons, 921-935 (1999).
19. Hadjiioannou,T.P.; Christian,G.D.; Koupparis, M. A. Quantitative Calculations in PharmaceuticalPractice and Research.

New York, NY: VCH Publishers Inc; 345–348 (1993).

20. Shah, V. P.; Tsong, Y.; Sathe, P.; Liu, J.-P. In vitro dissolution profile comparison — statistics and analysis of the similarity factor,f2. Pharm. Res, 15, 889–896 (. 1988).

21. Shah, V.P.; Lesko, L.J.; Fan, J.; Fleischer, N.; Handerson, J.; Malinowski, H.; Makary, M.; Ouderkirk, L.; Roy, S.; Sathe, P.; Singh, G.J.P.; Tillman, L.; Tsong, Y. and Williams, R.L. FDA guidance for industry: dissolution testing of immediate release solid oral dosage forms. Dissolution Technol. 4, 15–22 (1997).

22. Yuksel, N.; Kanik, A.E.; Baykara, T.; Comparison of in vitro dissolution profiles by ANOVA-based, model-dependent and independent methods. Int J Pharm.; 209:57–67 (2000).

23. Anderson, N.H.; Bauer, M.; Boussac, N.; Khan-Malek, R.; Munden, P.; Sardaro, M. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. J PharmBiomed Anal.; 17:811–822 (1998).