Drug Development and Industrial Pharmacy, 26(7), 737–743 (2000)

RESEARCH PAPER

A New In Vitro/In Vivo Kinetic Correlation Method for Nitrofurantoin Matrix Tablet Formulations

G. Ertan,[1,*] H. Y. Karasulu,[1] E. Karasulu,[2] M. A. Ege,[3] T. Köse,[4] and T. Güneri[1]

[1]*Departments of Pharmaceutical Technology and* [2]*Pharmacokinetic and* [3]*Computer Center, Faculty of Pharmacy,* [4]*Department of Computer Engineering, Faculty of Engineering, University of Ege, 35100, Bornova, Izmir, Turkey*

ABSTRACT

*The kinetic distributions of in vitro percentage release and in vivo percentage urinary excretion rates of nitrofurantoin from matrix tablets were plotted using a kinetic program. In vitro release rates were determined using the USP paddle and half-change methods. Urinary excretion curves of the drug were characterized by means of the statistical moments. The individual linear correlations between each in vitro and in vivo kinetic distribution were established, and regression equations were calculated. The application results of the best correlations obtained were evaluated according to in vivo results. A reversed kinetic procedure was applied for transformation of the correlated kinetic values to the drug percentage release rates. The modified Langenbucher kinetic showed excellent linear correlation (*r = .9985*). The method that is proposed in this study, the kinetic correlation program, is simple, independent of time, and suggests that it is possible to use kinetic distributions in the in vitro/in vivo correlation. This study also suggests using kinetic correlation to investigate the suitability of the in vitro dissolution methods with the in vivo drug dissolution.*

Key Words: *In vitro/in vivo kinetic correlation; Matrix tablet; Nitrofurantoin.*

* To whom correspondence should be addressed. Fax: 902323885258. E-mail: ertang@eczacilik.ege.edu.tr

INTRODUCTION

In vitro/in vivo correlations are important for a slow-release form of a drug because such correlation allows development of product specifications with bioavailability implications that provide maximum assurance and predictability (1). In addition, investigating the absorption behavior of sustained-release products in humans has encountered several complicated practical problems (e.g., volunteer selection, dosing intervals, blood sampling times, drug analytical method, side effect risk, and physiological effects). From the economic, technical, and ethical perspectives of bioavailability studies, however, it is necessary to establish an in vitro test method that can predict the progress of drug release and the absorption of products in vivo (2). A number of methods (2–8) have been presented to study the correlation between in vitro parameters such as mean dissolution time, dissolution and log of dissolution rates, quantity dissolved at one precise time, and so on and in vivo performance of dosage form such as mean residence time, mean plasma concentration, percentage absorbed at one precise time, time to peak plasma concentration, normalized peak serum level, and the like, but single-point correlation does not represent the overall in vivo kinetic profile. Other in vitro/in vivo correlation methods involve the linear (9–16) and nonlinear (17) regression analysis and deconvolution (18,19) methods called level A correlation, comparing in vitro and in vivo profiles completely. From these methods, the recently developed nonlinear regression method requires developments in the same way. However, deconvolution is not usually preferred by the practitioner due to difficulties (20) in the learning and application of the method.

In 1931, Hixson-Crowel first presented a kinetic model known as the cube-root law for linearization of in vitro dissolution results. Then, Higuchi (square root of time), zero order, Langenbucher, Hopfenberg, RRSBW (Rosin-Rammer-Sperling-Bennet-Weibull), first-order, and $(Bt)^a$ equations were developed. Generally, kinetic distributions dealing with the in vitro dissolution results were given in the research articles, but they have not yet been used in the in vitro/in vivo correlations. In this study, kinetic models were used to establish in vitro/in vivo correlations using the linear regression method for nitrofurantoin matrix tablets.

Equations of Kinetic Models

Kinetic models used for linearization of dissolution profiles are defined as follows:

Hixson-Crowel

$$m = (100^{1/3} - k_c t)^3 \tag{1}$$

Higuchi

$$m = 100 - k_d \sqrt{t} \tag{2}$$

Zero order

$$m = 100 - k_o t \tag{3}$$

Langenbucher

$$3\sqrt{\frac{m_t}{m_0}} = 1 - \frac{t}{T} \tag{4}$$

Modified Langenbucher

$$3\sqrt{1 - \frac{m_t}{m_0}} = Lnt \tag{5}$$

Hopfenberg

$$m_t/m_\infty = 1 - [1 - k_0/C_0 a_0]^n \tag{6}$$

RRSBW

$$m_d = 1 - \exp[-(t - T_i)^{b/a}] \tag{7}$$

First order

$$m = e^i \, e^{-k_f t} \tag{8}$$

$(Bt)^a$

$$3\sqrt{\frac{m_t}{m_0}} = 1 - (bt)^a \tag{9}$$

where m is the percentage of drug undissolved at time t (min); m_0 is the initial weight of drug in the solid; m_t is the weight of drug in the solid; m_d is the material in solution at time; k_c is the cube root dissolution rate constant ($mg/min^{1/3}$); k_d is the Higuchi rate constant ($mg/min^{1/2}$); k_f is the first-order dissolution rate constant (min^{-1}); k_0 is the zero-order dissolution rate constant (min); k is the erosion rate constant; t is the time; T is the total dissolution time; C_0 is the uniform initial concentration of drug in the matrix; a_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab; n is 1 for a slab, 2 for a cylinder, or 3 for a sphere; a is the scale parameter, which defines the timescale of the process; T_i is the location parameter, which represents the time lag before the actual onset of the dissolution process and, in most cases, will be equal to zero; b is the shape parameter; and i is the intercept of the drug log-linear plot of the type.

EXPERIMENTAL

Materials

The materials used were nitrofurantoin (Eaton, Lucerne, Switzerland); stearic acid (Merck, Darmstadt, Germany); and polyvinylpyrrolidone (BASF, Brussels, Belgium). The other chemicals used were analytical grade.

Methods

In Vitro and In Vivo Experiments

The in vitro and in vivo data for nitrofurantoin matrix tablets treated in this study were abstracted from reports developed in our laboratory by Karasulu et al. (21,22). Matrix tablets containing 100 mg nitrofurantoin, 100 mg polyvinylpyrrolidone, and 10 mg stearic acid were prepared by conventional dry granulation, and the granules were compressed using a single-punch tablet machine with a 9-mm punch. The amounts of nitrofurantoin in the dissolution medium were determined using both USP 22 (23) paddle and the half-change methods (Fig. 1). The kinetics of drug release were evaluated by a computer program (24), and the release rate constants k, correlation coefficients r, and determination coefficients r^2 were calculated. Two dose treatments using two different dosage forms (tablet and pure drug in a hard gelatin capsule) were studied. Two panels of three human volunteers each were used in crossover studies. In the first study, when the first three subjects received tablets, the second three subjects received pure drug; in the second study, when the first three subjects received pure drug, the second three subjects received tablets. Urine samples were collected from the volunteers at 0, 2, 4, 6, 8, 10, and 12 hr; 5 μl of sample was assayed for the drug by thin-layer chromatography (TLC) scanner and plotted using an average of six determinations (Fig. 1). Urinary excretion curves were characterized by means of the statistical moments proposed by Yamaoka et al. (25,26).

Correlation Between In Vitro and In Vivo Kinetics

The linear correlation was established between in vitro percentage release and in vivo percentage excretion rates (Fig. 1). Then, the in vivo results were also evaluated kinetically by the same computer program, and each in vitro and in vivo kinetic result was correlated. The best result of the correlated kinetics according to the dissolution methods was evaluated. After the calculation of the kinetic values of the percentage in vitro release and percentage in vivo urinary excretion rates using the kinetic program, the regression equations were found between these kinetic values using a linear regression analysis program, and the figure of the best correlation was drawn (Fig. 2).

Application of the Method

The in vitro kinetic values dealing with the best correlations were applied to the related regression equations,

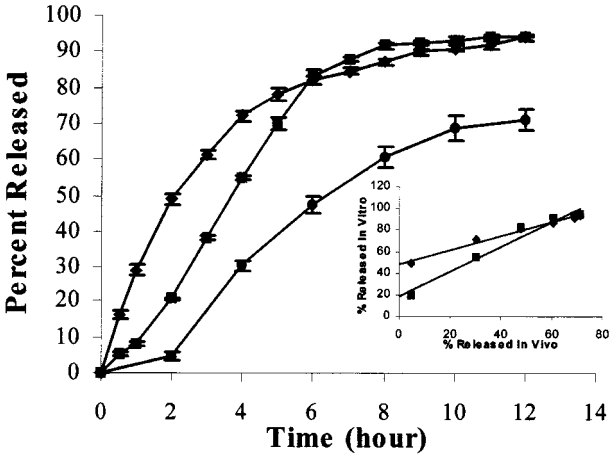


Figure 1. In vitro dissolutions and in vivo excretion rates of nitrofurantoin matrix tablets and in vitro/in vivo linear correlation profiles, mean ± SE. ◆, phosphate buffer, $n = 3$; ■, half-change, $n = 3$; ●, in vivo, $n = 6$.

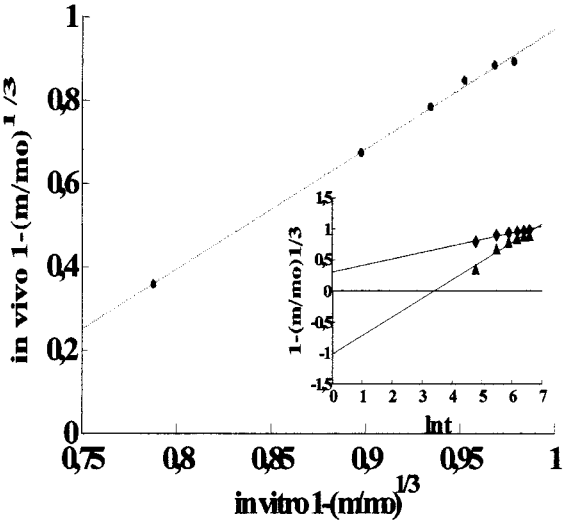
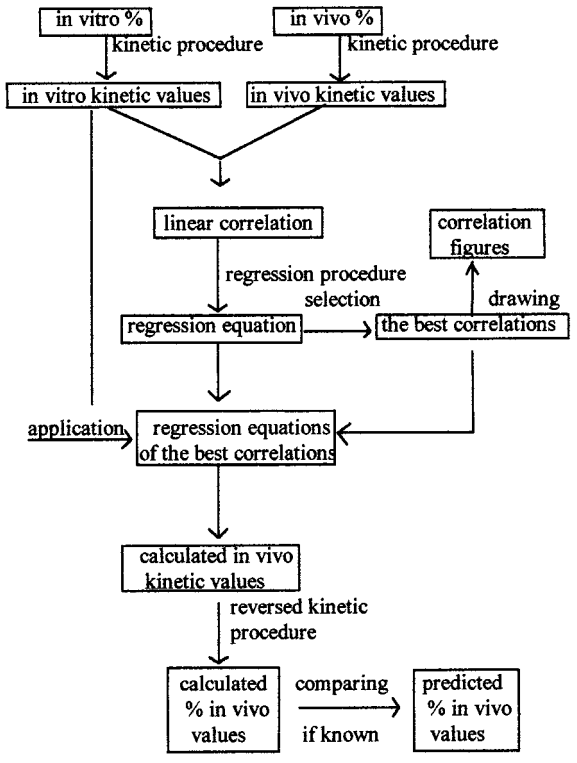


Figure 2. The modified Langenbucher distributions of nitrofurantoin matrix tablets in phosphate buffer, in vivo excretion rates, and their in vitro/in vivo kinetic correlation plot. ◆, phosphate buffer; ▲, in vivo; ●, in vitro/in vivo correlation.

and calculated in vivo kinetic results were transformed to the calculated drug percentage in vivo rates. Then, if the predicted percentage in vivo rates were known, calculated percentage in vivo rates could be compared to the predicted in vivo rates. The correlation procedure is illustrated in Scheme 1.

Transformation of the Correlated Kinetic Values to the Percentage Drug Release Rates (Reversed Kinetic Procedure)

For the transformation of the correlated in vivo kinetic values to the in vivo drug percentage rates, the kinetic formulas were applied in the reversed way. For example, in the first-order kinetic, the 4.6 as an in vitro percentage release rate is taken from 100 ($100 - 4.6 = 95.4$), and the log of 95.4 is 1.979; the reversed kinetic procedure is $100 - 10^{1.979} = 4.6\%$. For the modified Langenbucher kinetic, the kinetic procedure is $4.6 \rightarrow 1 - (m/m_0)^{1/3} \rightarrow 0.359$; the reversed kinetic procedure is $0.359^3 \rightarrow m = 1 - 0.359^3 \times 100 \rightarrow 100 - m = 4.6\%$.



Scheme 1. Correlation procedure and its application beginning from percentage in vitro and in vivo values of nitrofurantoin.

RESULTS AND DISCUSSION

The in vitro and in vivo dissolution results and linear correlations between these profiles are presented in Fig. 1. While approximately 94% of the drug was released from matrix tablets, only 71% of the drug was excreted in the urine. The dose excreted in the urine as unchanged nitrofurantoin was given as about 35–80% in the literature (27,28). In the linear correlation, correlation coefficients were .9874 and .9813 for phosphate buffer and half-change methods, respectively (Fig. 1). The Higuchi kinetic model is not include in the kinetic correlation system because the in vitro and in vivo drug percentage release rates are used directly in this kinetic distribution. RRSBW was found to be the best model for the in vitro dissolution profiles, and determination coefficients were .993 and .981 for dissolution using phosphate buffer and half-change methods, respectively. For the in vivo profile, first order was the best model ($r^2 = .973$). The kinetic correlations were performed by placing in vitro kinetic results on the abscissa and in vivo kinetic results on the ordinate. Excellent correlations were found by the modified Langenbucher model to both phosphate ($r = .9985$) (Fig. 2) and half-change ($r = .9945$) methods. The correlation coefficients for the first-order model were .9895 and .9899, respectively. Correlation coefficients of the linear correlations increased from .9874 to .9985 in the phosphate buffer and from .9813 to .9945 in the half-change method using the kinetic correlation method. In Table 1, the correlation procedures could be seen beginning from the spectroscopic absorbances of the in vitro dissolution media for both the phosphate and half-change methods for the modified Langenbucher method. Since the best kinetic model is the RRSBW for in vitro dissolution and the first-order method is best for the in vivo profile, the best kinetic correlations were obtained for the modified Langenbucher equation. We suggest that a good correlation probably will also be obtained between in vitro RRSBW and in vivo first-order models. Our studies are continuing on correlation between different kinetic models.

It has been stated that, if a good correlation exists between an in vitro dissolution parameter and some bioavailability parameter, then monitoring the dissolution profile should permit the prediction of bioavailability (7). In the present study, monitoring the spectrophotometric absorbances of the in vitro dissolution media permitted the calculation of urinary excretion rates of nitrofurantoin by a hand calculator from the sustained-release matrix tablet form (Table 1). Since the method is independent of time, a dissolution sample can also be taken at any time.

Table 1

Calculation of the Correlated In Vivo Drug Percentage Release Rates Using the Modified Langenbucher Kinetic Model Beginning with the Spectroscopic Absorbances of the Dissolution Media for the Phosphate (Up) and Half-Change (Down) Methods

						In Vivo			
	In Vitro					Calculated		Predicted	
Time (hr)	Absorbance	Determination Equation	Drug %	Langenbucher	Regression Equation	Langenbucher	Drug %	Drug %	Langenbucher
2	0.424	$12.8\,Abs - 0.017 \times 9000$[a]	48.9	0.787	$2.874x - 1.904$[b]	0.360	4.6	4.6	0.3583
4	0.629	$12.8\,Abs - 0.017 \times 9000$[a]	72.3	0.897	$2.874x - 1.904$[b]	0.675	30.8	30.5	0.6731
6	0.710	$12.8\,Abs - 0.017 \times 9000$[a]	81.6	0.934	$2.874x - 1.904$[b]	0.781	47.7	48.0	0.7829
8	0.752	$12.8\,Abs - 0.017 \times 9000$[a]	86.4	0.952	$2.874x - 1.904$[b]	0.833	57.8	60.7	0.8467
10	0.790	$12.8\,Abs - 0.017 \times 9000$[a]	90. 8	0.968	$2.874x - 1.904$[b]	0.875	67.9	68.9	0.8832
12	0.815	$12.8\,Abs - 0.017 \times 9000$[a]	93.7	0.978	$2.874x - 1.904$[b]	0.908	74.9	71.0	0.8921
2	0.181	$12.8\,Abs - 0.017 \times 9000$[a]	20.6	0.590	$1.312x - 0.415$[c]	0.359	4.6	4.6	0.3583
4	0.480	$12.8\,Abs - 0.017 \times 9000$[a]	55.1	0.819	$1.312x - 0.415$[c]	0.660	28.8	30.5	0.6731
6	0.722	$12.8\,Abs - 0.017 \times 9000$[a]	83.0	0.939	$1.312x - 0.415$[c]	0.817	54.7	48.0	0.7829
8	0.798	$12.8\,Abs - 0.017 \times 9000$[a]	91.7	0.971	$1.312x - 0.415$[c]	0.859	63.5	60.7	0.8467
10	0.812	$12.8\,Abs - 0.017 \times 9000$[a]	93.3	0.977	$1.312x - 0.415$[c]	0.867	65.1	68.9	0.8832
12	0.816	$12.8\,Abs - 0.017 \times 9000$[a]	94.3	0.980	$1.312x - 0.415$[c]	0.871	66.2	71.0	0.8921

[a] $r^2 = .998$

[b] $r = .9985 (p < .001)$, $\frac{\Sigma\ \mathrm{Re}\ s^2}{n-2} = 1.18E-03$

[c] $r = .9945\ (p < .001)$, $\frac{\Sigma\ \mathrm{Re}\ s^2}{n-2} = 5.59\ E-0.3$

In general, the kinetic distribution concerning in vitro dissolution profiles were given in the research articles, but introducing an appropriate kinetic model for both in vitro and in vivo drug dissolution is more important. According to the literature (15,29), only zero-order and first-order rate constants have been used in the correlations. For the first time, in this study, all kinetic distributions were used in the in vitro/in vivo correlations. When developing the method, the problem was obtaining the application results of the kinetic correlation as a kinetic value, not as a percentage value. Therefore, a transformation of kinetic values to the drug percentage was made (reversed kinetic procedure). Similarly, in the literature, there was a time transformation (30) of the in vitro data to the theophylline correlation using the Weibull parameters, and a proportional reversed hazards model (17) has also been used in the nonlinear in vitro/in vivo correlation.

In vitro dissolution methods such as the USP 22 paddle and basket, half-change, NF 13 rotating bottle, through-flow cell, and other methods have been used for modeling in vivo dissolution conditions, but it is difficult to arrive at a meaningful decision on the appropriate method for in vivo drug dissolution. In the solubility studies made with these dissolution methods, the method that shows better correlation with the in vivo dissolution of a drug is, at the same time, a more suitable dissolution method for in vivo drug release. For example, the USP 22 paddle method was found to be a more suitable method than the half-change method for the in vivo nitrofurantoin dissolution because this method showed better correlation; therefore, it should be preferred for the nitrofurantoin dissolution studies. A similar result was obtained in our last study (22), which contained a time-relevant linear correlation of nitrofurantoin having more low correlation coefficients than kinetic correlation. So, kinetic correlation can also be used to increase the low coefficients obtained from linear correlations applied in some studies (9,10). For example, the coefficients of linear correlation have been given as .9539, .8491, and 0.9726 in the study by Aiache et al. (9) dealing with bioavailability of theophylline for three types of controlled-release formulations. However, if the correlation had been made using kinetic correlation, the correlation coefficients would be .9995, .9949, and .992 for RRSBW, RRSBW, and first-order kinetics, respectively. These significant improvements prove the applicability and usefulness of the kinetic correlation.

In the sustained-release dosage forms, numerous investigations have been conducted recently and have long in vitro dissolution time. Moreover, in some studies (11,31), 20 and 30 hr in vitro dissolution studies have also been performed. Since automatic equipment are used in these studies, there is loss of time and money. Long-term dissolution studies may be completed in 1–2 hr if the dissolution rate is accelerated with a temperature increase, rapid rotation rate of paddle or basket, through the use of surface-active agents, by changing the pH of the dissolution medium, by changing the dissolution medium, and so on. Then, the new dissolution profile may be correlated with both in vitro and in vivo release profiles using kinetic correlations. Such accelerated dissolution studies (dual correlation) would be particularly useful and available for the drug producer who has to perform long-term dissolutions for every batch of dosage form produced.

In our recent study (32), we presented a dual kinetic distribution for one- and two-hole cylindrical devices that showed two different in vitro kinetic distribution profiles. Several previous attempts have been made to develop in vitro/in vivo correlations for theophylline products, and acceptable correlations could only be achieved over periods of 4 to 5 hr (11,30,33,34). For this reason, one of the investigators derived the mathematical correlation via a ''biphasic regression'' (34). Similarly, a correlation could be carried on for fractioned dissolution profiles using our kinetic correlation procedure and dual kinetic distribution. This method could be applied to studies that have not developed any (35,36) correlations and to incomplete correlations (11,30,33,34).

There are two important opinions concerning the linear model used for in vitro/in vivo correlations. One of them (17), the linear model, represents a very simple type of in vitro/in vivo relationship; therefore, one might not expect to find such a relationship very often in practice. The other (1,17) is that the present state of science and technology does not always permit meaningful correlation between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and/or urinary excretion of drug or metabolites, which may be due in part to the restricted nature of the linear model commonly employed. The restricted nature of the linear model may be eliminated using kinetic correlation as there is a suitable kinetic model for every in vitro or in vivo dissolution profile. Furthermore, dissolution kinetics have also been developed for this purpose.

In conclusion, application of the findings of the method presented here to the kinetic models that have been developed for approximately 70 years cannot only be used for in vitro/in vivo correlations, but also for de-

veloping accelerated dissolution studies (dual correlation), more suitable in vitro dissolution methods for in vivo drug dissolution, a correlation between different in vitro/in vivo kinetic models, a correlation to fractioned dissolution profiles, a correlation for studies that do not have any correlation due to nonlinearity and distinctness of in vitro/in vivo dissolution times, and finally to increase the low coefficients of linear correlations.

ACKNOWLEDGMENT

We thank the computer center of the Faculty of Pharmacy and Department of Computer Engineering of the Faculty of Engineering, University of Ege, Izmir, Turkey, for their technical assistance in writing the kinetic correlation program.

REFERENCES

1. J. P. Skelly, G. L. Amidon, W. H. Barr, L. Z. Benet, J. E. Carter, J. R. Robinson, V. P. Shah, and A. Yacobi, Pharm. Res., 7, 975 (1990).
2. S. Y. Lin, Y. H. Kao, and H. N. Chang, J. Pharm. Sci., 79, 326 (1990).
3. V. P. Shah, V. K. Prasad, C. Freeman, J. P. Skelly, and B. E. Cabana, J. Pharm. Sci., 72, 309 (1983).
4. A. El-Yazigi and R. J. Sawchuk, J. Pharm. Sci., 74, 161 (1985).
5. P. N. Huguenin, H. W. Zulliger, and R. Niederer, Arzneim.-Forsch., 38, 305 (1988).
6. S. K. Das and B. K. Gupta, Drug Dev. Ind. Pharm., 14, 537 (1988).
7. L. H. Block and U. V. Banakar, Drug Dev. Ind. Pharm., 14, 2143 (1988).
8. K. Wingstrand, B. Abrahamson, and B. Edgar, Int. J. Pharm., 60, 151 (1990).
9. J. M. Aiache, N. Pierre, E. Beyssac, V. K. Prasad, and J. P. Skelly, J. Pharm. Sci., 78, 261 (1989).
10. Z. Hussein and M. Friedman, Pharm. Res., 7, 1167 (1990).
11. L. I. Harrison, A. K. Mitra, C. R. Kehe, N. M. Klinger, K. A. Wick, S. E. McCarville, K. M. Cooper, S. F. Chang, P. J. Roddy, S. M. Berge, J. C. Kisicki, and R. J. Dockhorn, J. Pharm. Sci., 82, 644 (1993).
12. J. M. Cardot and E. Beyssac, Eur. J. Drug Metab. Pharmacokinet., 8, 113 (1993).
13. C. Caramella, F. Ferrari, M. C. Bonferroni, M. E. Sangalli, M. De Bernardi Di Valserra, F. Feletti, and M. R. Galmozzi, Drug Dispos., 14, 143 (1993).
14. H. Humbert, M. D. Cabiac, and H. Bosshardt, J. Pharm. Sci., 83, 131 (1994).
15. J. E. Polli, J. R. Crison, and G. L. Amidon, J. Pharm. Sci., 85, 753 (1996).
16. T. Prueksaritonont, L. M. Gorham, and K. C. Yeh, J. Pharm. Sci., 86, 1345 (1997).
17. A. Dunne, T. O'Hara, and J. Devane, J. Pharm. Sci., 86, 1245 (1997).
18. W. R. Gillespie and P. Veng-Pedersen, J. Pharmacokin. Biopharm., 13, 289 (1985).
19. K. K. H. Chan, F. Langenbucher, and M. Gibaldi, J. Pharm. Sci., 76, 446 (1987).
20. Short course on convolution, deconvolution and linear systems, announcement, Satellite of the Fifth European Congress on Biopharmaceutics and Pharmacokinetics, Brussels, April 19, 1993.
21. H. Y. Karasulu, G. Ertan, and T. Güneri, Eur. J. Drug. Metab. Pharmacokinet., 18, 108 (1993).
22. H. Y. Karasulu, G. Ertan, T. Köse, and T. Güneri, Eur. J. Drug. Metab. Pharmacokinet., 21, 27 (1996).
23. U.S. Pharmacopeial Convention, *The United States Pharmacopeia 22*, Author, Rockville, MD, 1990, p. 1788.
24. I. T. Agabeyoglu, Un Programme Dans la Langue Basique de Microcomputer Pour la Determination des données de Dissolution, 17th Semain Medical Balkanique, Istanbul, 1984, p. 327.
25. M. Concheiro, M. L. Labres, R. Vilo-Jato, R. Martinez, and J. Blanco, Drug Dev. Ind. Pharm., 13, 2301 (1987).
26. J. L. Vilo-Jato, A. Concheiro, and B. Seijo, Drug Dev. Ind. Pharm., 13, 1315 (1987).
27. Martindale, *Extra Pharmacopoeia*, 29th ed., Pharmaceutical Press, London, 1989, pp. 272–274.
28. D. E. Cadwallader, and H. W. Jun, Anal. Profiles Drug Subst., 5, 345 (1976).
29. M. Dey, R. Enever, M. Marino, J. Michelucci, D. Smith, R. Warner, and R. Weierstall, Int. J. Pharm., 49, 121 (1989).
30. R. Dietrich, R. Rrausse, G. Benedikt, and V. W. Steinijans, Arzneim.-Forsch., 38, 1229 (1988).
31. T. Dahl, T. Ling, J. Yee, and A. Bormeth, J. Pharm. Sci., 79, 389 (1990).
32. G. Ertan, E. Karasulu, D. Demirtas, M. Arici, and T. Güneri, J. Pharm. Pharmacol., 49, 229 (1997).
33. B. H. Chung and C. K. Shim, J. Pharm. Sci., 76, 784 (1987).
34. D. Brockmeier, H. J. Dangler, and D. Voegele, Eur. J. Clin. Pharmacol., 28, 291 (1985).
35. K. C. Cundy, I. L. Sue, G. C. Visor, J. Marshburn, C. Nakamura, W. A. Lee, and J. P. Shaw, J. Pharm. Sci., 86, 1334 (1997).
36. K. J. Simons, E. M. Frith, and F. E. R. Simons, J. Pharm. Sci., 71, 505 (1982).