ESTIMATION OF ABSORPTION RATE CONSTANT (k_a) FOLLOWING ORAL ADMINISTRATION BY WAGNER-NELSON, LOO-RIEGELMAN, AND STATISTICAL MOMENTS IN THE PRESENCE OF A SECONDARY PEAK

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SUMMARY

The objective of this study was to evaluate the performance of Wagner-Nelson, Loo-Reigelman, and statistical moments methods in determining the absorption rate constant(s) in the presence of a secondary peak. These methods were also evaluated when there were two absorption rates without a secondary peak. Different sets of plasma concentration versus time data for a hypothetical drug following one or two compartment models were generated by simulation. The true k_a was compared with the k_a estimated by Wagner-Nelson, Loo-Riegelman and statistical moments methods. The results of this

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study indicate that Wagner-Nelson, Loo-Riegelman and statistical moments methods may not be used for the estimation of absorption rate constants in the presence of a secondary peak or when absorption takes place with two absorption rates.

KEY WORDS

absorption rate constant, single or multiple-compartment model, simulated concentrations, secondary peak

INTRODUCTION

The assessment of drug absorption plays an important role in drug development. The estimation of the absorption rate constant (k_a) is important because along with the elimination rate constant (k), one can predict peak and trough plasma concentrations following multiple dosing. The estimation of absorption rate constants (k_a) is also important in establishing *in vitro* and *in vivo* correlations. The absorption kinetics of drugs is a complex process and may be affected by rate of disintegration, solubility, and excipients of oral dosage forms. Due to these complexities, sometimes one observes different rates of absorption of an oral dosage form from the gastrointestinal tract. These different rates of absorption may produce a plasma concentration-time profile with multiple peaks.

The following methods are widely used for the estimation of k_a: (i) the Wagner-Nelson method, (ii) the Loo-Reigelman method, (iii) the deconvolution method, and (iv) the statistical moments method /1/. Wagner-Nelson and Loo-Reigelman methods are based on compartmental analysis. Wagner-Nelson and Loo-Reigelman methods are generally used for drugs which follow one- and two-compartment first order oral absorption, respectively. Limitations and the problems associated in estimating k_a by Wagner-Nelson and Loo-Reigelman methods have been discussed in detail by Chan and Gibaldi /2/. The statistical moments method is a non-compartmental method and appears to be simple and comparatively accurate compared to the Wagner-Nelson and Loo-Reigelman methods /2/.

Wagner-Nelson, Loo-Reigelman and statistical moments methods have been used to estimate k_a in the absence of a secondary peak

assuming that k_a is uniform throughout the absorption phase. A review of the literature indicates that there are many drugs which exhibit multiple peaks /3-7/. There are also reports about drugs with two rapid rates of absorption but without a secondary peak /8,9/. The performance of Wagner-Nelson, Loo-Reigelman and statistical moments methods in estimating k_a has not been established in the presence of a secondary peak or when absorption takes place with two or more absorption rates without a secondary peak. The objective of this study was to assess the performance of Wagner-Nelson, Loo-Reigelman, and statistical moments methods in the estimation of k_a under the following conditions:

i. when absorption takes place with a single absorption rate (k_a),
ii. when absorption takes place with two different absorption rates (k_{a1}, k_{a2}) with or without a secondary peak.

It should be noted that in this study, the appearance of a secondary peak is not due to enterohepatic recycling, rather than to the absorption of the drug from different segments of the gastrointestinal tract. Assuming linear kinetics, different sets of plasma concentration versus time data were generated by simulation as described in the Methods section.

METHODS

Plasma concentration-time profiles of a hypothetical drug (one- and two-compartment model) with first order absorption and elimination were simulated on a spread sheet (Microsoft Excel 4.0) following intravenous and oral administration using the following pharmacokinetic parameters:

One- and two-compartment i.v. administration:

Dose = 100 mg, volume of distribution of the central compartment (V) = 10 l, elimination rate constant (k or β) = 0.231 h^{-1}, intercompartmental rate constant (k_{21}) = 0.6 h^{-1}, rate constant of distribution phase (α) = 2.0 h^{-1}.

The following equations were used to generate plasma concentration-time data following i.v. administration:

One-compartment:

$$C = C_0 e^{-kt} \quad (1)$$

Two-compartment:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

where C_0, A, and B are intercepts on the y-axis.

$$C_0 = \frac{Dose}{V} \quad (3)$$

$$A = \frac{Dose\ (\alpha\text{-}k21)}{V\ (\alpha\text{-}\beta)} \quad (4)$$

$$B - \frac{Dose\ (k21\text{-}\beta)}{V\ (\alpha\text{-}\beta)} \quad (5)$$

One- and two-compartment oral administration:

Dose = 100 mg, k or β = 0.231 h^{-1}, absolute bioavailability (F) = 0.5, k_{21} and α were same as for i.v. administration. k_a was varied as follows:

For single rate: k_a = 0.50 h^{-1}

For secondary peak: k_a = 0.50 h^{-1} and 4.5 h^{-1}. Rate was changed at 4 hours and 5 hours for the one- and two-compartment models, respectively, so that a secondary peak could be obtained.

For two rates without secondary peak: k_a = 0.50 h^{-1} and at 2 hours rate was changed to 1.2 h^{-1}.

The following equations were used to generate plasma concentration-time data following oral administration:

One-compartment:

$$C = \frac{Dose*ka*F}{V(k_a\text{-}k)}\ (e^{-kt} - e^{-kat}) \quad (6)$$

Two-compartment:

$$C = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-kat} \quad (7)$$

where

$$A = \frac{Dose*ka*F(k21\text{-}\alpha)}{V(k_a\text{-}\alpha)\ (\beta\text{-}\alpha)} \quad (8)$$

$$B = \frac{Dose*ka*F(k21-\beta)}{V(k_a-\beta)(\alpha-\beta)} \quad (9)$$

$$C = \frac{Dose*ka*F(k21-k_a)}{V(\alpha-k_a)(\beta-k_a)} \quad (10)$$

For the one-compartment model drug, following i.v. and oral administration, sampling schedules were at time 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 4.25, 4.5, 4.75, 5, 6, 8, 12, 18 and 24 hours. For the two-compartment model drug, for both i.v. and oral administration, sampling schedules were at time 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 5.25, 5.5, 5.75, 6, 8, 12, 18 and 24 hours. A lag time of 4 hours and 5 hours for the secondary peak and 2 hours for the two rates of absorption was used for the one- and two-compartment models, respectively. Frequent sampling between 4 and 5 hours for the one-compartment and 5 to 6 hours for the two-compartment model was necessary in order to obtain a secondary peak.

k_a was estimated by Wagner-Nelson, Loo-Reigelman, and statistical moments methods and compared with the true k_a. When the statistical moments method was used, mean absorption time (MAT) was calculated from the difference between mean residence time (MRT) following oral and i.v. administration.

$$MAT = MRT_{oral} - MRT_{iv} \quad (11)$$

where MRT = AUMC/AUC (AUMC = area under the moment curve; AUC = area under the curve).

k_a was then calculated from the reciprocal of MAT (k_a = 1/MAT). A pharmacokinetic and pharmacodynamic program (Kinetica, version 1.1, SIMED SA, France) was used for the estimation of k_a for the Wagner-Nelson, Loo-Riegelman and statistical moments methods.

The simulated plasma concentration-time data with a secondary peak as well as for two absorption rates without a secondary peak were fitted to one- or two-compartment models. The TOPFIT 2.0 /10/ program was used to model plasma concentration-time data assuming first-order absorption.

RESULTS

Table 1 summarizes the values of k_a estimated from Wagner-Nelson, Loo-Riegelman, and statistical moments methods for a hypothetical drug which follows a one- or two-compartment model. All three methods provided good estimates of k_a when absorption of drug took place with a single rate. On the other hand, in the presence of a secondary peak or when the drug was absorbed with two rates without a secondary peak, it was noted that the estimated absorption rates by all three methods were not in agreement with the true absorption rates.

Figure 1 represents the simulated two-compartment data fitted to a two-compartment conventional pharmacokinetic model (assuming that there is no secondary peak), and Figure 2 shows a two-compartment, two-segment pharmacokinetic model. Compartmental fitting of the simulated data with a secondary peak presented interesting observations. From Figure 2 it can be seen that the two-segment absorption model fitted the plasma concentration-time data extremely well, whereas the predicted plasma concentrations were in error when a two-compartment conventional pharmacokinetic model was used to describe the data. Table 2 is a summary of the estimated pharmacokinetic parameters for one- and two-compartment models estimated by the conventional and a two-segment absorption model. For both one- and two-compartment models with a secondary peak, the predicted pharmacokinetic parameters (except V/F) from the two-segment absorption model were comparable with the true values. On the other hand, in the presence of two absorption rates but without a secondary peak (Table 3), the two-segment absorption model provided a good estimate of pharmacokinetic parameters for the one-compartment model but the predicted pharmacokinetic parameters for the two-compartment model were in error.

Figures 3-5 plot the log of percentage drug unabsorbed versus time generated by the Loo-Riegelman method. Figure 3 shows a plot of log of percentage drug unabsorbed versus time when absorption was assumed to take place with a single rate. The plot was linear till 8 hours, indicating that absorption is taking place with one constant rate. An examination of Figures 4 and 5 indicates a shoulder at 5 hours and 2 hours, respectively, indicating that the rate of absorption was changed at this time, and indeed this was the case. Using the linear portion of the plot (from 0.25 to 2 hours, Figs. 4-5), the predicted k_{a1}

TABLE 1

Estimation of k_a (h^{-1}) using Wagner-Nelson, Loo-Riegelman, and statistical moments methods for a hypothetical drug with or without secondary peak

	True k_a	Wagner-Nelson	Loo-Riegelman	Statistical moments
One compartment				
Single rate	0.50	0.47	NA	0.52
Secondary peak				
First rate	0.50	0.21		0.36
Second rate	4.50	ND		NA
Two rates				
First rate	0.50	0.34		0.50
Second rate	1.20	ND		NA
Two compartment				
Single rate	0.50	NA	0.51	0.51
Secondary peak				
First rate	0.50		0.20	0.35
Second rate	4.50		ND	NA
Two rates				
First rate	0.50		0.37	0.55
Second rate	1.20		ND	NA

NA = not applicable; ND = not determined.

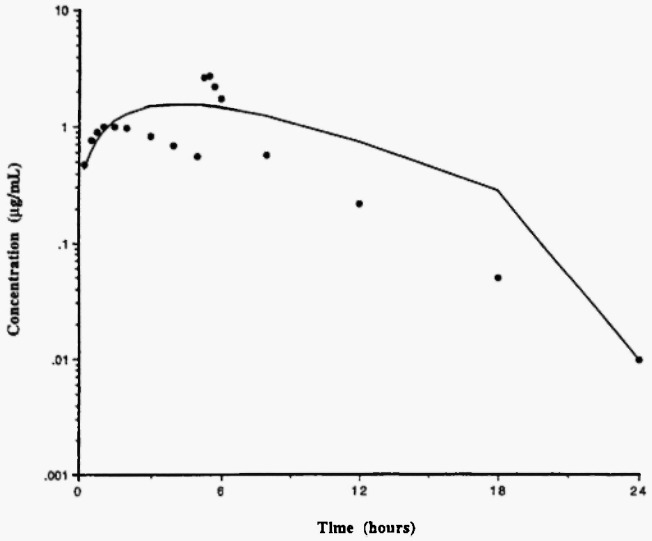

Fig. 1: Plasma concentration-time profile of a two-compartment hypothetical drug fitted to a conventional pharmacokinetic model. The solid line is the predicted plasma concentration and the solid circles are the observed concentrations.

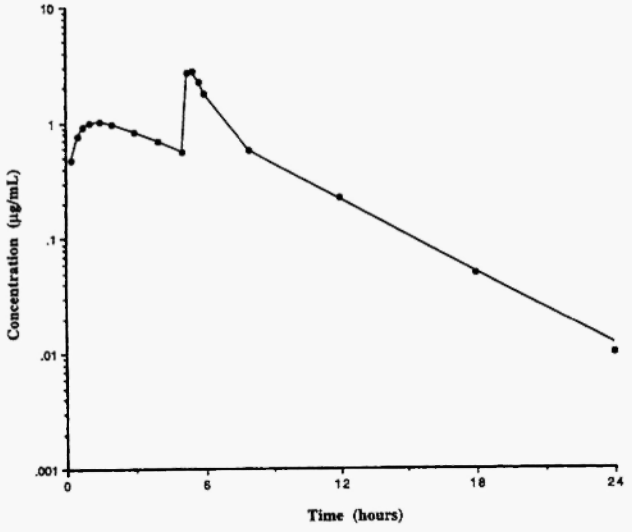

Fig. 2: Plasma concentration-time profile of a two-compartment hypothetical drug fitted to a multi-segment pharmacokinetic model. The solid line is the predicted plasma concentration and the solid circles are the observed concentrations.

TABLE 2

Pharmacokinetic parameters of a hypothetical drug using conventional pharmacokinetics and a two-segment absorption model in the presence of a secondary peak

	k_{a1} (h^{-1})	k_{a2} (h^{-1})	V/F (l)	AUC model (µg*h/ml)	$t_{½}$ (h)	Lag time (h)	SSR	AIC
True values	0.50	4.50	20.0	32.1	3.0	4.0	-	-
1 compartment								
Conventional	0.25	-	11.7	33.7	2.7	-	3.6	29.6
2-segment model	0.48	5.1	14.0	27.3	2.7	4.14	0.004	-74.3
2 compartment								
True values	0.50	4.50	20.0	11.1	3.0	5.0	-	-
Conventional	0.22	-	0.53	18.7	3.1	-	6.6	44.1
2-segment model	0.35	4.20	0.13	10.4	2.8	5.0	0.0002	-124

k_{a1}, k_{a2} are absorption rate constants; V/F = volume of distribution, AUC = area under the curve; $t_{½}$ = half-life; SSR = sum of the residual squares; AIC = Akaike information criteria.

TABLE 3

Pharmacokinetic parameters of a hypothetical drug using conventional pharmacokinetics and a two-segment absorption model when absorption takes place with two rates without a secondary peak

	k_{a1} (h^{-1})	k_{a2} (h^{-1})	V/F (l)	AUC model (µg*h/ml)	$t_{½}$ (h)	Lag time (h)	SSR	AIC
True values	0.50	1.20	20.0	25.9	3.0	2.0	–	–
1 compartment								
Conventional	0.29	–	12.6	27.5	2.4	–	0.59	-1.4
2-segment model	0.52	1.7	16.0	25.0	2.7	2.6	0.001	-79.6
2 compartment								
True values	0.50	1.20	20.0	8.5	3.0	2.0	–	–
Conventional	0.43	–	6.7	8.2	1.6	–	0.25	-9.3
2-segment model	0.20	0.80	0.17	8.6	0.12	1.9	0.0004	-90.2

k_{a1}, k_{a2} are absorption rate constants; V/F = volume of distribution; AUC = area under the curve; SSR = sum of the residual squares; AIC = Akaike information criteria.

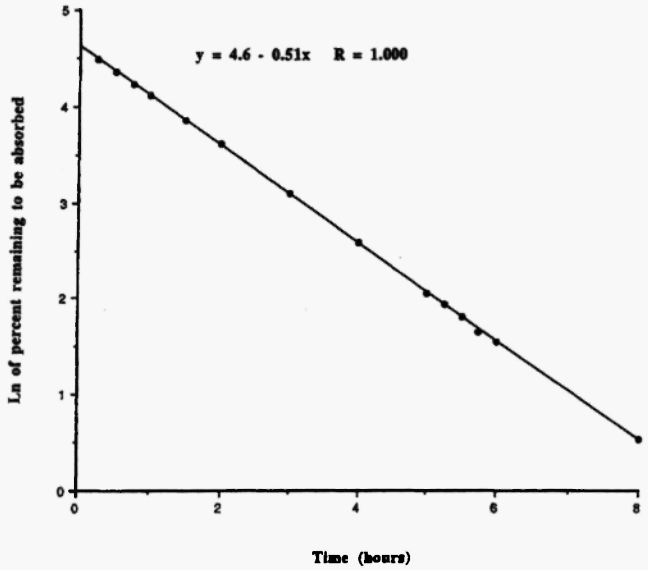

Fig. 3: Plot of log of percentage drug remaining to be absorbed versus time using the Loo-Reigelman method with a constant rate.

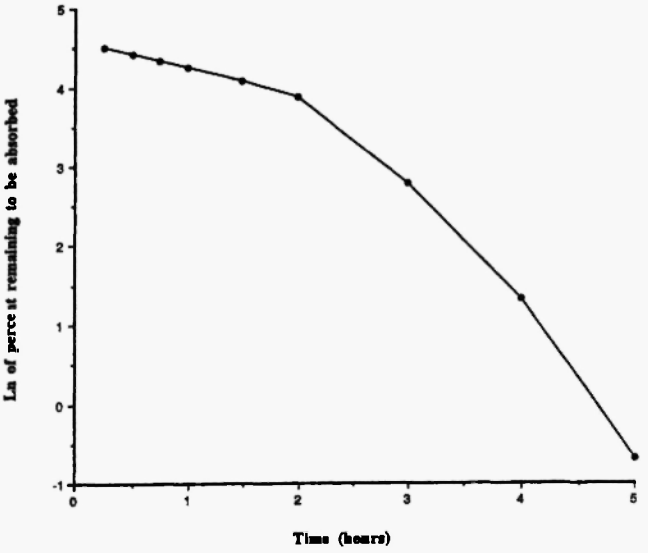

Fig. 4: Plot of log of percentage drug remaining to be absorbed versus time using the Loo-Reigelman method in the presence of a secondary peak.

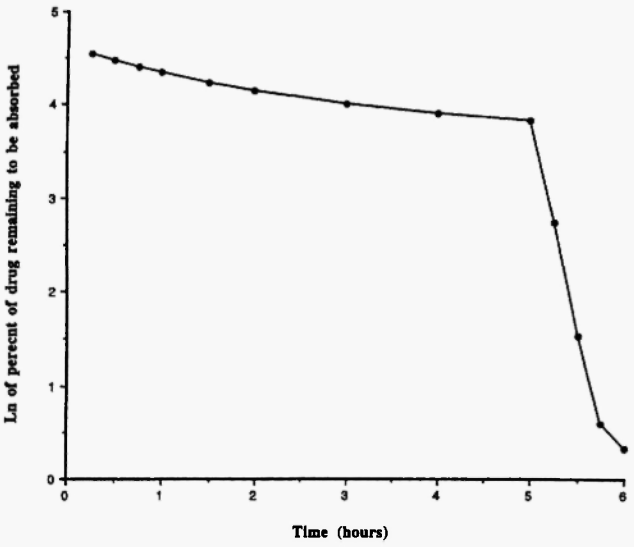

Fig. 5: Plot of log of percentage drug remaining to be absorbed versus time using the Loo-Reigelman method with two different rates without a secondary peak.

was 0.20 h^{-1} (for the secondary peak) and 0.37 h^{-1} (two rates), respectively. It should be noted that k_{a2} could not be estimated from the plots. A similar observation was noted when absorption rate(s) were estimated by the Wagner-Nelson method.

From these observations, it can be concluded that it may not be possible to accurately estimate absorption rate(s) by Wagner-Nelson, Loo-Riegelman and statistical moments methods in the presence of a secondary peak or when absorption takes place with two different rates without a secondary peak, although it is possible to detect more than one absorption rate and the time of change in absorption rate by Wagner-Nelson and Loo-Riegelman methods. This observation, however, cannot be obtained from the statistical moments method.

DISCUSSION

Multiple peaks have been observed with penicillamine /3/, ranitidine /4/, cimetidine /5/, diltiazem /6/, diclofenac sodium /7/,

sulfisoxazole and allopurinol /8/. Multiple peaks following oral administration may be due to either enterohepatic recirculation or due to the variability in gastric emptying rate, which may result in two absorption peaks. In this study it has been assumed that the occurrence of a secondary peak is not due to enterohepatic recirculation but due to the absorption of drug from different segments of the gastrointestinal tract.

Multi-segment absorption models are useful for comparing the absorption profiles of different sustained release formulations. Such models are also useful for the prediction of plasma concentrations after multiple oral administration and to design a suitable dosage regimen for drugs which exhibit multiple peaks.

The objective of this study was to evaluate the performance of Wagner-Nelson, Loo-Riegelman, and statistical moment methods in determining absorption rate constant(s) in the presence of a secondary peak or when absorption is taking place with two different rates without a secondary peak. It has been reported in the literature that atenolol /9/ and selegiline /11/ are absorbed with two rapid rates. Therefore, for a given drug it may be important to estimate both absorption rates with accuracy in order to design a suitable dosage form, especially with sustained release products.

The present study indicates that Wagner-Nelson, Loo-Riegelman, and statistical moment methods cannot determine multiple rates of absorption accurately. It should be emphasized that the predicted absorption rate by Wagner-Nelson, Loo-Riegelman, and statistical moment methods was in good agreement with the true rate when absorption took place with one single rate. Tables 4 and 5 summarize the percentage of drug remaining to be absorbed. It can be seen from these tables that the presence of two rates (with or without a secondary peak) affects the percentage of drug remaining to be absorbed in such a way that a plot of time versus log of percentage of drug remaining to be absorbed gives an inaccurate estimation of the absorption rate. It should also be noted that both Wagner-Nelson and Loo-Riegelman methods did indicate that more than one absorption rate was involved. The time at which the absorption rate was changed was also accurately depicted by these methods.

One interesting observation was the compartmental fitting of plasma concentration-time data using multi-segment pharmacokinetic

TABLE 4

Summary of percentage of drug remaining to be absorbed (Wagner-Nelson method)

Time (h)	Constant absorption rate	With secondary peak	2 absorption rate
	Percent remaining to be absorbed	Percent remaining to be absorbed	Percent remaining to be absorbed
0.25	88.95	92.79	90.83
0.50	78.96	86.28	82.57
0.75	70.34	80.68	75.47
1.00	62.58	75.64	69.10
1.50	49.69	67.30	58.57
2.00	39.73	60.90	50.52
3.00	25.73	51.97	26.41
4.00	17.11	46.54	9.08
5.00	11.60	14.64	3.99
6.00	8.25	4.12	2.59
8.00	4.66	3.18	2.02
12.00	1.82	1.88	1.19
18.00	0.30	0.38	0.32
24.00	0.008	0	0.002

models. From Figures 1 and 2, it can be seen that the fit obtained by a multiple segment model was much superior to the conventional pharmacokinetic model. The conventional pharmacokinetic model provided an inaccurate estimate of the absorption rate (Table 2), whereas a multi-segment pharmacokinetic model provided reasonably good estimates of k_{a1} and k_{a2}.

A multi-segment pharmacokinetic model was also used to describe the data with two rates but without a secondary peak. The multi-segment absorption model predicted the first absorption rate (k_{a1}) and pharmacokinetic parameters accurately (except volume of distribution [V/F]) for the one-compartment model (Table 3). The two-compartment multi-segment absorption model provided poor estimates of pharmacokinetic parameters as well as the absorption rates when there were two rates without a secondary peak.

TABLE 5

Summary of percentage of drug remaining to be absorbed (Loo-Riegelman method)

Time (h)	Constant absorption rate Percent remaining to be absorbed	With secondary peak Percent remaining to be absorbed	2 absorption rate Percent remaining to be absorbed
0.25	88.38	93.26	91.01
0.50	77.99	87.23	82.99
0.75	68.89	81.94	75.95
1.00	60.69	77.18	69.61
1.50	47.50	69.52	59.42
2.00	36.96	63.40	47.81
3.00	22.29	54.87	16.12
4.00	13.19	49.57	3.76
5.00	7.80	46.42	0.50
6.00	4.69	1.38	0.00
8.00	1.7	0.00	0.14
12.00	0.079	3.38	0.49
18.00	0.073	4.48	1.02
24.00	0	4.99	1.04

Both conventional and multi-segment pharmacokinetic models failed to predict volume of distribution (V/F) accurately especially for a two-compartment model drug. The reason for poor estimates of V/F using a multi-segment absorption model is not known. In short, this study indicates that Wagner-Nelson, Loo-Riegelman and statistical moment methods may not be used to estimate the rate of absorption in the presence of a secondary peak or when absorption is taking place with two different rates without a secondary peak. Furthermore, fitting the data to a multi-segment first order absorption model may provide an excellent fit but the estimated pharmacokinetic parameters may be in error. At this time there is no specific type of analysis that can model a multi-absorption rate constant. More research is needed in this direction.

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