PK Solutions 2.0

Noncompartmental Pharmacokinetics Data Analysis

Reprint of the noncompartmental pharmacokinetics equations cataloged in the PK Solutions 2.0 User Guide. This reprint is also available as a hyper-text document for running within an internet browser. The HTML folder can be downloaded from Summit Research Services' web site. A demo file, description, and ordering information for PK Solutions 2.0 can also be obtained from the web site. For additional information or inquiries please contact Summit Research Services at the address below.

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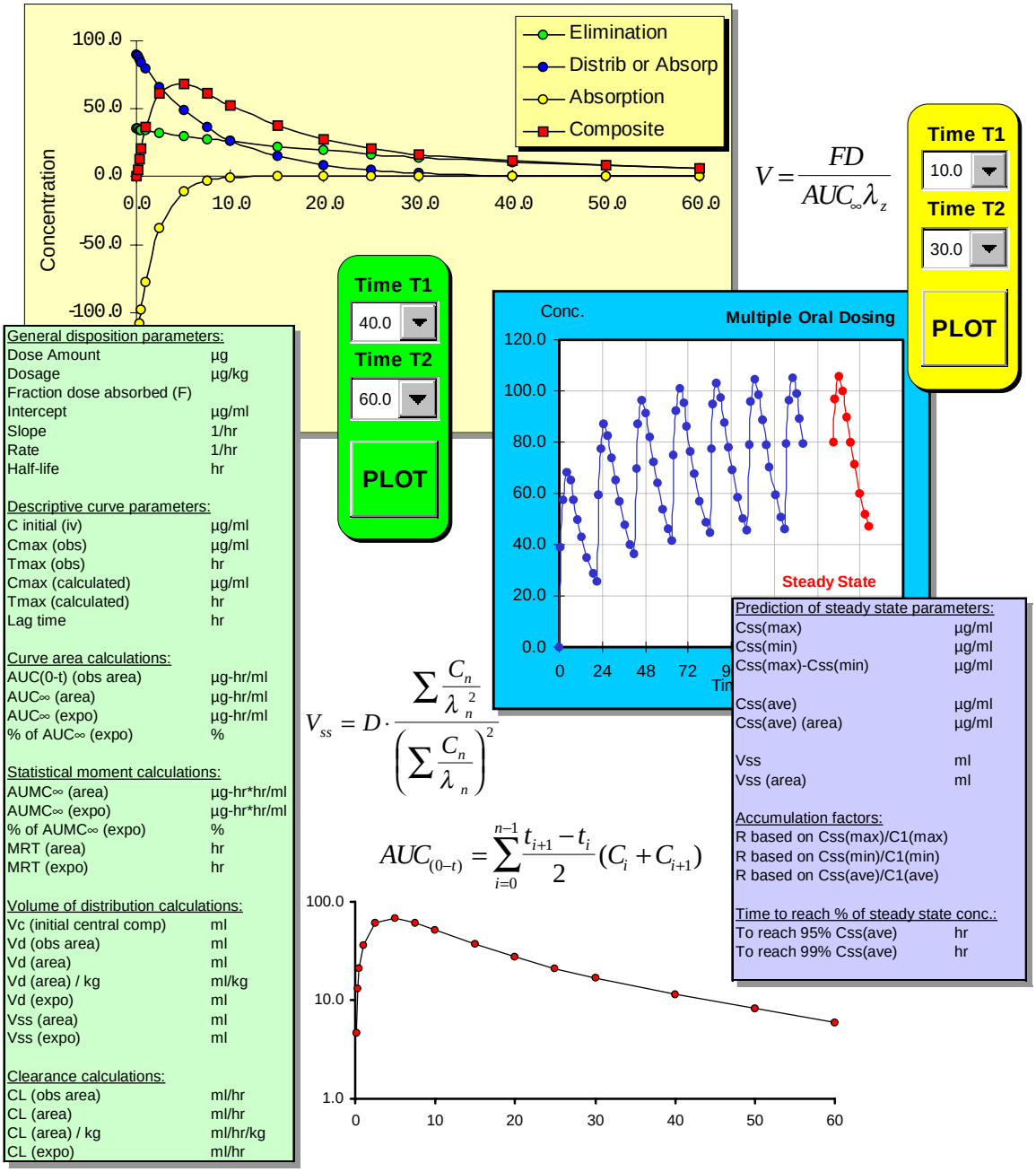
Forward

PK Solutions 2.0 - Noncompartmental Pharmacokinetics Data Analysis

SRS 050597, 010299,100100

PK Solutions 2.0

Collage illustrating several program features. See additional information on web site at www.SummitPK.com



Introduction

About PK Solutions 2.0

Pharmacokinetics is the study of the time course of absorption, distribution, metabolism, and excretion of a drug or other substance in the body. *PK Solutions* is designed to provide a fast and easy means of computing and graphing the basic and most commonly reported pharmacokinetic parameters associated with blood (plasma, serum) concentration-time data following oral and intravenous dosing. Approximately 60 pharmacokinetic parameters are computed for each data set, including tables and graphs projecting multiple dose regimes based on single dose results. A modest understanding of the principles of pharmacokinetics is presumed, but no programming or construction of equations is required. The program is automated, operating mainly by click-and-point methods. In addition to concentration-time data, *PK Solutions* can independently or simultaneously compute and graph results using disposition constants imported, for example, from a curve-fitting program or other source. Once the calculation mode is selected, a few mouse selections are all that is needed to analyze either type of data and produce graphs and parameter tables ready for printing and saving. Dynamic updating of tables and graphs provides a means of trying out "what if" cases and makes *PK Solutions* an ideal tool for learning the principles of pharmacokinetic analysis.

Methodology

PK Solutions relies on the use of noncompartmental methods of analysis for the estimation of pharmacokinetic parameters. Two noncompartmental techniques are employed and their results compared where appropriate in the parameter tables. One technique is based on the estimation of the area associated with the curve described by the concentration-time profile. In this case, the classical trapezoidal rule is used to compute the area under the curve (AUC).

The second and more extensively used noncompartmental technique is based on the method of residuals (also called curve stripping or feathering) which resolves a curve into a series of exponential terms corresponding to the absorption (oral data), distribution, and elimination phases occurring during the time course of the drug in the blood. These exponential terms are used to calculate the various single and multiple dose pharmacokinetic parameters following well established textbook calculations. The curve stripping approach assumes that the disposition phases of the drug follow apparent first-order rate processes, which is evidenced by linearity in the terminal portion of a semi-log plot. This is, in fact, the case for the over-whelming majority of drugs, making *PK Solutions* a widely useful tool.

Calculation of PK parameters based on curve area and curve-stripping methods are called noncompartmental because they are free of any assumption about the underlying compartmental model that the drug obeys. Nonetheless, noncompartmental methods can yield results that confer specific model characteristics on a drug's behavior. The model-independent approach, which serves as the basis for *PK Solutions*, can be contrasted with mathematical curve-fitting programs that are specifically designed to elaborate compartmental models and their descriptive equations. *PK Solutions'* focus is on producing graphs and tables representing model-independent pharmacokinetic *solutions* rather than on compartmental equations. While compartmental programs service special needs, the types of calculations produced by *PK Solutions* are those most commonly reported in the tables of drug metabolism and pharmacokinetics literature.

Typical Users

PK Solutions is intended to be used by researchers, by those who need and publish basic pharmacokinetic parameters, by students and educators who can make use of the program's interactivity to study the principles of PK analysis, and by pharmacists and physicians to view the effects of dosing regimens on

blood levels. It is designed to augment rather than replace or compete with compartmental analysis, experimental curve-fitting, or clinical dose prediction software. Any one who works with blood level data in pharmaceutical or agrochemical product development or other research and teaching areas will benefit from the quick solutions and range of results provided by *PK Solutions*.

Excel-Based Program

PK Solutions was developed as a Microsoft Excel workbook in order to make use of Excel's extensive feature set, its cross-platform compatibility between Windows-PCs and Macintosh computers, and its ready integration with other Microsoft Office software, internet and intranets applications, external databases and other software. Unlike proprietary programs that require long learning curves and are limited in scope to the effort programmers expend on design and functions, *PK Solutions* PK Solutions gives you easy access to pharmacokinetic analysis and the power of Excel to enhance, customize, and integrate your results with the rest of your working world.

Noncompartmental Pharmacokinetics Equations

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Noncompartmental Pharmacokinetics Equations from PK Solutions 2.0

Single Dose Pharmacokinetics

General Disposition Parameters and Constants	Single Dose Pharmacokinetics
Dose Amount	D
Fraction of dose absorbed. Used to correct dose amount for some oral dose calculations.	F
Exponential expression for 1st order kinetics.	$C = \sum C_n e^{-\lambda_n t}$ for *n* exponential terms
Y-Intercept. Coefficient of each exponential term. Note: the sign of the absorption coefficient is negative.	C_n
Slope	$s = \frac{-\lambda_n}{2.303}$
Rate constant	$\lambda_n = -2.303s$
Elimination rate constant	λ_z
Half-life	$t_{½} = \frac{0.693}{\lambda_n}$

Descriptive Curve Parameters — Single Dose Pharmacokinetics

$C_{initial}$
Initial concentration extrapolated to time zero for iv dose.

$$C_0 = \sum C_n$$

Cmax (obs)
Applies to oral doses only.

$$C_{max} = maximum\ observed\ conc$$

Tmax (obs)
Applies to oral doses only.

$$T_{max} = time\ point\ at\ C_{max}$$

Cmax (calculated)
For biexponential oral data only.

$$C_{max} = \frac{FD}{V} e^{-\lambda_z t_{max}}$$

where V is Vd (area).

Tmax (calculated)
For biexponential oral data only.

$$t_{max} = \frac{2.303}{\lambda_a - \lambda_z} \log \frac{\lambda_a}{\lambda_z}$$

where λ_a and λ_z are the apparent absorption and elimination rate constants, respectively.

Lag time
For biexponential oral data only.

$$t_{lag} = \frac{\log C_a - \log C_z}{\left(\frac{\lambda_a}{2.303} - \frac{\lambda_z}{2.303} \right)}$$

where λ_a and λ_z are the apparent absorption and elimination rate constants, respectively.

Curve Area Calculations — Single Dose Pharmacokinetics

AUC(0-t) (obs area)
Trapezoid calculation of AUC using observed data points only (not extrapolated to infinity). Useful when final concentration values tend to exaggerate calculated AUC_{∞}

$$AUC_{(0-t)} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i + C_{i+1})$$

where *n* is the number of data points.

AUC∞ (area)
Total AUC computed by combining AUC(0-t) with an extrapolated value.

$$AUC_{\infty} = AUC_{(0-t)} + \frac{C_n}{\lambda_z}$$

where C_n is the last concentration.

AUC∞ (expo)
Total AUC computed using exponential terms.

$$AUC_{\infty} = \sum \frac{C_n}{\lambda_n}$$

% of AUC∞ (expo)
Percent each exponential term contributes to the total AUC.

$$\%\, AUC_{\infty} = 100\frac{(C_n/\lambda_n)}{AUC_{\infty}}$$

Statistical Moment Calculations — Single Dose Pharmacokinetics

AUMC∞ (area)
Calculation of total area under the first-moment curve (plot of $C \bullet t$ vs t) by combining trapezoid calculation of $AUMC_{(0\text{-}t)}$ and extrapolated area.

$$AUMC_{(0-t)} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i t_i + C_{i+1} t_{i+1})$$

$$+ \frac{C_{last} \cdot t_{last}}{\lambda_z} + \frac{C_{last}}{\lambda_z^2}$$

AUMC∞ (expo)
Total AUMC computed using exponential terms.

$$AUMC_{\infty} = \sum \frac{C_n}{\lambda_n^2}$$

% of AUMC∞ (expo)
Percent each exponential term contributes to the total AUMC.

$$\%\ AUMC_{\infty} = 100\frac{(C_n/\lambda_n^2)}{AUMC_{\infty}}$$

MRT (area)
Mean Residence Time calculated using trapezoid area calculations extrapolated to infinity.

$$MRT = \frac{AUMC_{\infty}}{AUC_{\infty}}$$

where both area terms use trapezoidal calculations.

MRT (expo)
Mean Residence Time calculated using exponential terms.

$$MRT = \sum \frac{1}{\lambda_n}$$

Volume of Distribution Calculations — Single Dose Pharmacokinetics

Vc (initial central compartment)
Apparent volume of the central compartment for iv doses only.

$$V_c = \frac{D}{\sum C_n}$$

Vd (obs area)
Apparent volume of distribution based on $AUC_{(0\text{-}t)}$ trapezoid calculation and elimination rate. Use when AUC_{∞} (area) is exaggerated due to high last concentration.

$$V = \frac{FD}{AUC_{(0-t)}\lambda_z}$$

Vd (area)
Apparent volume of distribution based on trapezoid AUC_{∞} (area) and elimination rate. Applies mainly to iv, but also to oral if complete absorption ($F = 1$) is assumed.

$$V = \frac{FD}{AUC_{\infty}\lambda_z}$$

Vd (area) / kg
Apparent volume of distribution normalized by animal weight. Uses same formula as Vd (area).

$$V_{normalized} = \frac{V}{Body\,Weight\,(kg)}$$

Vd (expo)
Apparent volume of distribution calculated from exponential terms.

$$V = \frac{FD}{\lambda_z \sum \frac{C_n}{\lambda_n}}$$

where λ_z is the elimination rate

Vss (area)
Apparent volume of distribution at steady state estimated graphically from trapezoidal total area measurements. Applies to iv dose.

$$V_{ss} = \frac{D \cdot [AUMC_\infty]}{[AUC_\infty]^2}$$

Vss (expo)
Apparent volume of distribution at steady state estimated from exponential terms. Applies only after iv and assumes elimination from central compartment.

$$V_{ss} = D \cdot \frac{\sum \frac{C_n}{\lambda_n^2}}{\left(\sum \frac{C_n}{\lambda_n}\right)^2}$$

Systemic Clearance Calculations — Single Dose Pharmacokinetics

CL(sys) (obs area)
Systemic clearance based on $AUC_{(0\text{-}t)}$ trapezoid calculation. Use when total AUC_∞ (area) is exaggerated due to high last concentration.

$$CL = \frac{FD}{AUC_{(0-t)}}$$

CL (area)
Systemic clearance based on trapezoid AUC_∞ (area). Applies mainly to iv data. Limited to oral data only if complete absorption (F=1) is assumed.

$$CL = \frac{FD}{AUC_\infty}$$

CL (area) / kg
Systemic clearance normalized by animal weight. Uses same formula as CL (area).

$$CL_{normalized} = \frac{CL}{Body\,Weight\,(kg)}$$

CL (expo)
Systemic clearance calculated using exponential terms.

$$CL = \frac{FD}{\sum \frac{C_n}{\lambda_n}}$$

Half-life based on Vd and CL
Alternate calculation of half-life using V (area) and CL (area). For iv data only.

$$t_{½} = \frac{0.693 \cdot V}{CL}$$

Two-compartment Open Model Microconstants — Single Dose Pharmacokinetics

k12
Microconstant calculated using exponentials. Applies to 2 compartment iv dose data only.).

$$k_{12} = \lambda_1 + \lambda_z - k_{21} - k_{10}$$

k21
Microconstant calculated using exponentials. Applies to 2 compartment iv dose data only.

$$k_{21} = \frac{C_1\lambda_z + C_z\lambda_1}{C_1 + C_z}$$

k10
Microconstant calculated using exponentials. Applies to 2 compartment iv dose data only.

$$k_{10} = \frac{\lambda_1\lambda_z}{k_{21}}$$

Multiple Intravenous Dose Pharmacokinetics

General — Multiple IV Dose Pharmacokinetics

Dose Interval (tau)
Time span between dosing intervals. Distinguish from time after dose (t).

τ Constant dose interval
.

First Dose Concentration Calculations — Multiple IV Dose Pharmacokinetics

C1(max)
Maximum concentration after first dose interval (τ). Equal to $C_{initial}$

$$C_{1(\max)} = \sum C_n$$

C1(min)
Minimum concentration at end of first dose interval (τ).

$$C_{1(\min)} = \sum C_n e^{-\lambda_n \tau}$$

C1(ave)
Average concentration during first dose interval (τ).

$$C_{1(ave)} = \sum \frac{C_n (1 - e^{-\lambda_n \tau})}{\lambda_n \tau}$$

Prediction of Steady State Parameters — Multiple IV Dose Pharmacokinetics

Css(max)
Maximum concentration during any dosing interval at steady state. Included on graph.

$$C_{ss(\max)} = \sum \frac{C_n}{1 - e^{-\lambda_n \tau}}$$

Css(min)
Minimum concentration during any dosing interval at steady state. Included on graph.

$$C_{ss(\min)} = \sum \frac{C_n e^{-\lambda_n \tau}}{1 - e^{-\lambda_n \tau}}$$

Css(max) - Css(min)
Difference between peak and trough concentration during steady state.

$$\Delta_{\bar{C}_{ss}} = C_{ss(\max)} - C_{ss(\min)}$$

Css(ave)
Average concentration at steady state. Included on graph.

$$\overline{C}_{ss} = \sum \frac{C_n}{\lambda_n \tau}$$

Css(ave) (area)
Average concentration at steady state calculated from trapezoidal AUC data for a single dose.

$$\overline{C}_{ss} = \frac{AUC_{\infty}}{\tau}$$

Accumulation Factors — Multiple IV Dose Pharmacokinetics

R based on Css(max)/C1(max)
Accumulation ratio based on maximum concentrations after first dose and at steady state.

$$R = \frac{C_{ss(\max)}}{C_{1(\max)}}$$

R based on Css(min)/C1(min)
Accumulation ratio based on minimum concentrations after first dose and at steady state.

$$R = \frac{C_{ss(\min)}}{C_{1(\min)}}$$

R based on Css(ave)/C1(ave)
Accumulation ratio based on average concentrations after first dose and at steady state.

$$R = \frac{\overline{C}_{ss}}{C_{1(ave)}}$$

Time to Reach Percent of Steady State — Multiple IV Dose Pharmacokinetics

To reach 95% Css(ave)
Time required to reach 95% of average steady state concentration. Assumes one-compartment characteristics apply.

$$t_{0.95\overline{C}_{ss}} = -3.32 \cdot t_{1/2} \cdot \log(1 - f_{ss})$$

where f_{ss} is the fraction of the steady state concentration.

To reach 99% Css(ave)
Time required to reach 95% of average steady state concentration. Assumes one-compartment characteristics apply.

$$t_{0.99\overline{C}_{ss}} = -3.32 \cdot t_{1/2} \cdot \log(1 - f_{ss})$$

where f_{ss} is the fraction of the steady state concentration.

Calculated loading dose
Loading dose required to produce an immediate steady state minimum concentration, Css(min).

$$D_{load} = \frac{D}{1 - e^{-\lambda_n \tau}}$$

Total time through Nth dose
Total time elapsed between first dose (t=0) and specified dose (N).

$$t_N = N\tau$$

C(ave) during Nth dose
Average concentration during any dose interval (N). Becomes Css(ave) when steady state reached.

$$\overline{C}_N = \sum \frac{C_n(1 - e^{-N\lambda_n \tau})}{\lambda_n \tau}$$

Fraction of Css(ave) after N doses
Fraction of the ultimate average steady state concentration reached after N doses.

$$f_{ss} = \frac{\sum C_n(1 - e^{-N\lambda_n \tau})/\lambda_n}{\sum C_n/\lambda_n}$$

where f_{ss} is the fraction of the steady state concentration.

Css at t after ss dose
Steady state concentration at any time (*t*) during a dosing interval at steady state.

$$C_{ss} = \sum \frac{C_n e^{-\lambda_n t}}{1 - e^{-\lambda_n \tau}}$$

Conc. at any time and dose
Computes the concentration at any time during a dosing interval. Enter both time (t) and dose interval (N).

$$C_N = \sum \frac{C_n(1 - e^{-N\lambda_n \tau})}{1 - e^{-\lambda_n \tau}} \cdot e^{-\lambda_n t}$$

Multiple Oral Dose Pharmacokinetics

General and Graphing Function — Multiple Oral Dose Pharmacokinetics

Dose Interval (tau)
Constant time span between dosing intervals. Distinguish from time after dose (*t*).

τ Assume equal dose intervals

Graphing Function
The graphing function is based on a mathematical generalization of the graphical superimposition principle. It involves the addition of a decay function (C_N) to the initial concentration (C_1) at repeated time points for a progressive series of doses (N). Assumes constant dose intervals given during the postdistribution phase.

$$C_{(N,t)} = C_{1(t)} + C_{N(t)}$$

where

$$C_{1(t)} = \sum C_n e^{-\lambda_n t}$$

and

$$C_{N(t)} = \frac{C_z e^{-\lambda_z \tau}(1 - e^{-(N-1)\lambda_z \tau}) e^{-\lambda_z t}}{1 - e^{-\lambda_z \tau}}$$

First Dose Concentration Values — Multiple Oral Dose Pharmacokinetics

C1(max)
Observed maximum concentration taken from data set.

$C_{\max}$

C1(min)
Minimum concentration at end of first dose interval (τ).

$$C_{1(\min)} = \sum C_n e^{-\lambda_n \tau}$$

C1(ave)
Average concentration during first dose interval (τ).

$$C_{1(ave)} = \sum \frac{C_n (1 - e^{-\lambda_n \tau})}{\lambda_n \tau}$$

Prediction of Steady State Parameters — Multiple Oral Dose Pharmacokinetics

Css(max)
Computed from a simplification of the graphing function to a steady state form as shown. The Css(max) is evaluated as the maximum concentration during the steady state dosing interval.

$$C_{ss(t)} = C_{1(t)} + \frac{C_z \cdot e^{-\lambda_z \tau} \cdot e^{-\lambda_z t}}{1 - e^{-\lambda_z \tau}}$$

where

$$C_{1(t)} = \sum C_n e^{-\lambda_n t}$$

Css(min)
Computed using same steady state equation as Css(max) and evaluating the minimum concentration during a steady state dose interval.

Same as above.

Css(max) - Css(min)
Difference between peak and trough concentration during steady state.

$$\Delta_{\overline{C}_{ss}} = C_{ss(\max)} - C_{ss(\min)}$$

Css(ave)
Average concentration at steady state.

$$\overline{C}_{ss} = \sum \frac{C_n}{\lambda_n \tau}$$

Css(ave) (area)
Average concentration at steady state calculated from trapezoidal AUC data for a single dose.

$$\overline{C}_{ss} = \frac{AUC_{\infty}}{\tau}$$

Accumulation Factors — Multiple Oral Dose Pharmacokinetics

R based on Css(min)/C1(min)
Accumulation factor based on elimination rate constant.

$$R = \sum \frac{1}{1 - e^{-\lambda_z \tau}}$$

R based on Css(ave)/C1(ave)
Accumulation ratio based on average concentrations after first dose and at steady state.

$$R = \frac{\overline{C}_{ss}}{C_{1(ave)}}$$

Additional Oral Dose Calculations — Multiple Oral Dose Pharmacokinetics

Tmax (1st dose, observed)
Observed time of largest concentration value from data set.

$$t_{\max}$$

Tmax (1st dose, calculated)
Calculation of time at which maximum concentration occurs after a single dose. Applies to 1-compartment characteristics, but calculated also to illustrate magnitude for 2-compartments.

$$t_{\max_{calculated}} = \frac{2.303}{\lambda_a - \lambda_z} \log \frac{\lambda_a}{\lambda_z}$$

where λ_a is the absorption rate and λ_z is the elimination rate.

Tmax(ss)
Calculation of time at which maximum concentration occurs after dosing during steady state. Applies to 1-compartment characteristics, but calculated also to illustrate magnitude for 2-compartments.

$$t_{\max_{ss}} = \frac{2.303}{\lambda_a - \lambda_z} \log \frac{\lambda_a (1 - e^{-\lambda_z \tau})}{\lambda_z (1 - e^{-\lambda_a \tau})}$$

where λ_a is the absorption rate and λ_z is the elimination rate.

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