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Technical Note

ABSPLOTS: A LOTUS 123 Spreadsheet for Calculating and Plotting Drug Absorption Rates

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The pharmacokinetic literature contains a useful series of equations for calculating drug absorption rates in multicompartmental systems. This communication briefly describes a LOTUS 123 spreadsheet template which rapidly calculates and electronically graphs these data on the IBM-PC and compatible systems.

The disposition models upon which the absorption rate calculations are based assume input into and elimination and sampling from the (central) plasma compartment. The model systems are arranged as follows: (i) one-compartment disposition model, linear elimination kinetics, single dose (Eq. 4 of Ref. 1); (ii) two-compartment disposition model, linear elimination kinetics, single dose (Eq. 5 of Ref. 1); (iii) three-compartment disposition model, linear elimination kinetics, single dose (Eq. 6 of Ref. 1); (iv) one-compartment disposition model, Michaelis–Menten elimination kinetics, single dose (Eq. 5 of Ref. 2); (v) one-compartment disposition model, linear elimination kinetics, multiple dosing; (vi) two-compartment disposition model, linear elimination kinetics, multiple dosing; and (vii) three-compartment disposition model, linear elimination kinetics, multiple dosing. Columns on the spreadsheet are formatted in a manner similar to Table 1 of Ref. 1. Regardless of the method employed, all integrals are calculated using either the trapezoidal or the log-trapezoidal rule, according to the criteria of Proost (3).

For two- and three-compartment disposition functions, the multiple-dose cases assume that the recent dose be administered at a time at which absorption from previous doses has ceased and drug remaining in the body is in a terminal disposition phase. The plasma level at the new zero time point is decayed monoexponentially (as per the disposition parameters), and calculated concentrations at each time point are automatically subtracted from observed concentrations. The resultant plasma concentrations, equivalent to those which would have been obtained following a single dose, are treated as in case ii or iii (*vide supra*) to calculate the absorption rates. For monoexponential disposition, the aforementioned conditions need not be assumed; however, the calculated rate of absorption will be the summated rates from previous as well as the most recent dose. In this case, the amount of drug absorbed per unit volume is calculated from Eq. 8 of Ref. 4.

To calculate absorption rate variables, the user enters the microscopic rate constants, dose, volume of the relevant compartment, plasma concentration–time data pairs, and data set's identification into the designated cells (all other cells have been protected to prevent their accidental alteration). For the Michaelis–Menten model, V_{max} [expressed as concentration/unit time (2)] and K_m [as concentration (2)] are used in lieu of the rate constants. If the volume term is unknown, the user enters a value of unity. Variables dependent on the volume term will therefore be off by that factor; the shape of the absorption rate-time curve, however, remains unaffected.

Once new data are entered, the spreadsheet variables are recalculated. The last four columns associated with each data set will display: (a) the cumulative fraction of the dose absorbed; (b) the absorption rate; (c) the natural logarithm of the absorption rate; and (d) the midpoint at each absorption rate interval, t_{mid}. Using LOTUS 123 graphic capabilities, plots of variables may be constructed, e.g., absorption rate versus t_{mid}.

Two additional regions are included on the spreadsheet. The first uses the dose, coefficients, and exponents characterizing drug disposition from one-, two-, or three-compartment disposition models (bolus i.v. dose) to calculate the needed volume of the central compartment and microscopic parameters. The second region calculates a new central-compartment elimination rate constant (two- or three-compartment disposition model) for the nonintravenous dose; this adjustment, based on differences in observed slopes following intravascular and nonintravascular doses, is sometimes necessary. In the case of the two-compartment model, the appropriate equation has been reported (5). We have derived an analogous equation for the three-compartment model (see the Appendix). As in the two-compartment model case, it is assumed that changes in the terminal exponential rate constant are due solely to fluctuations in the central compartment elimination rate constant (k_1 in the Appendix).

A final region of the spreadsheet gives directions for saving data in DIF (Data Interchange Format) files. DIF files

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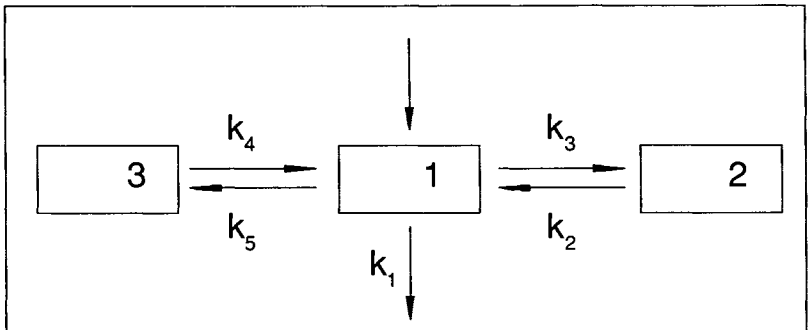
provide a means for electronically transporting data from the LOTUS 123 spreadsheet to other pharmacokinetic programs capable of reading these files. One could, for example, transfer the absorption rate and time data to files for subsequent curve fitting or graph preparation.

ABSPLOTS, which requires about 222K of memory, was written using Version 2 of LOTUS 123. Copies of the spreadsheet are available free of charge by sending a blank formatted diskette (double-sided, double-density, IBM-PC compatible) and a self-addressed stamped mailing package to the senior author.

APPENDIX: DERIVATION OF AN EXPRESSION FOR THE ELIMINATION RATE CONSTANT (k_1) IN A CONVENTIONAL THREE-COMPARTMENT OPEN MODEL, WHERE ELIMINATION OCCURS EXCLUSIVELY FROM THE CENTRAL COMPARTMENT

Following the assumptions and approach of Till *et al.*[5,6], Eq. (12) may be used to calculate k_1 (extravascular) based on distributional parameters (k_2, k_3, k_4, k_5) obtained following intravascular administration and the terminal dispostion rate constant (λ_3) obtained following extravascular administration. The derivation is provided in Scheme I.



	$\lambda_1+\lambda_2+\lambda_3=k_1+k_2+k_3+k_4+k_5$	Eq. 1
	$\lambda_1\lambda_2+\lambda_1\lambda_3+\lambda_2\lambda_3=k_1k_2+k_2k_5+k_1k_4+k_2k_4+k_3k_4$	Eq. 2
	$\lambda_1\lambda_2\lambda_3=k_1k_2k_4$	Eq. 3
Rearrangement of Eq. 1	$\lambda_1+\lambda_2=k_1+k_2+k_3+k_4+k_5-\lambda_3$	Eq. 4
Rearrangement of Eq. 2	$\lambda_3(\lambda_1+\lambda_2)+\lambda_1\lambda_2=k_1k_2+k_2k_5+k_1k_4+k_2k_4+k_3k_4$	Eq. 5
Rearrangement of Eq. 3	$\lambda_1\lambda_2=k_1k_2k_4/\lambda_3$	Eq. 6
substitute Eqs. 4+6 into Eq. 5	$\lambda_3(k_1+k_2+k_3+k_4+k_5-\lambda_3)+k_1k_2k_4/\lambda_3=k_1k_2+k_2k_5+k_1k_4+k_2k_4+k_3k_4$	Eq. 7
Multiply both sides by λ_3	$\lambda_3^2(k_1+k_2+k_3+k_4+k_5-\lambda_3)+k_1k_2k_4=\lambda_3(k_1k_2+k_2k_5+k_1k_4+k_2k_4+k_3k_4)$	Eq. 8
expand Eq. 8	$\lambda_3^2k_1+\lambda_3^2k_2+\lambda_3^2k_3+\lambda_3^2k_4+\lambda_3^2k_5-\lambda_3^3+k_1k_2k_4=\lambda_3k_1k_2+\lambda_3k_2k_5+\lambda_3k_1k_4+\lambda_3k_2k_4+\lambda_3k_3k_4$	Eq. 9
collect k_1	$\lambda_3^2k_1+k_1k_2k_4-\lambda_3k_1k_2-\lambda_3k_1k_4=\lambda_3^3+\lambda_3k_2k_5+\lambda_3k_2k_4+\lambda_3k_3k_4-\lambda_3^2k_2-\lambda_3^2k_3-\lambda_3^2k_4-\lambda_3^2k_5$	Eq. 10
factor out k_1	$k_1(\lambda_3^2+k_2k_4-\lambda_3k_2-\lambda_3k_4)=\lambda_3^3+\lambda_3k_2k_5+\lambda_3k_2k_4+\lambda_3k_3k_4-\lambda_3^2k_2-\lambda_3^2k_3-\lambda_3^2k_4-\lambda_3^2k_5$	Eq. 11
solve for k_1	$k_1=\dfrac{[\lambda_3^3+\lambda_3k_2k_5+\lambda_3k_2k_4+\lambda_3k_3k_4-\lambda_3^2k_2-\lambda_3^2k_3-\lambda_3^2k_4-\lambda_3^2k_5]}{[\lambda_3^2+k_2k_4-\lambda_3k_2-\lambda_3k_4]}$	Eq. 12

Scheme I

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