were derived and drawn using the SAS contour plot procedure, RSREG. No further clarification was deemed necessary.

Since the model tested in the paper is $Z = AX^2 + BXY + CY^2 + DX + EY + F$, the possible contour surfaces are hyperbolic paraboloid, elliptic paraboloid, and an elliptic cylinder, depending on the sign of the coefficients of the equation. The dictionary definition (3) of the suffix "-oid" is, "having the form or appearance of." In the two-dimensional representation of the contour surface, the dictionary definition is implicit and the term ellipsoidal translates into elliptical as it is stated in the article. It does not imply that the resulting contour level curves for tablet friability are ellipsoidal in the mathematical sense, but rather is the elliptical projection onto a plane of the response surface at a fixed value of Z.

In conclusion, we iterate that a general multiple linear regression analysis, if used within the practical limitations of tableting, is helpful in understanding the role of the granulation moisture and tablet crushing strength on tablet friability and *in vitro* dissolution. Rational in-process specifications for the granulation moisture content and tablet crushing strength may be established by superimposing the contour plots of tablet friability and drug dissolution.

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Model-Independent Method of Predicting Peak, Trough, and Mean Steady-State Levels in Multiple Intravenous Bolus Dosing in Nonlinear Pharmacokinetics

Keyphrases □ Pharmacokinetics—nonlinear, model-independent method, use of simulated data

To the Editor:

Nonempirical methods for dosage predictions and adjustments of drugs showing nonlinear pharmacokinetics are apparently all based on nonlinear pharmacokinetic models. However, the disproportional behavior of such drugs necessitates particularly reliable calculations, which are generally not provided by structured pharmacokinetic models, due to their inherent nonuniqueness and often unrealistic kinetic assumptions. The model-independent method proposed here should overcome some of the disadvantages of such methods.

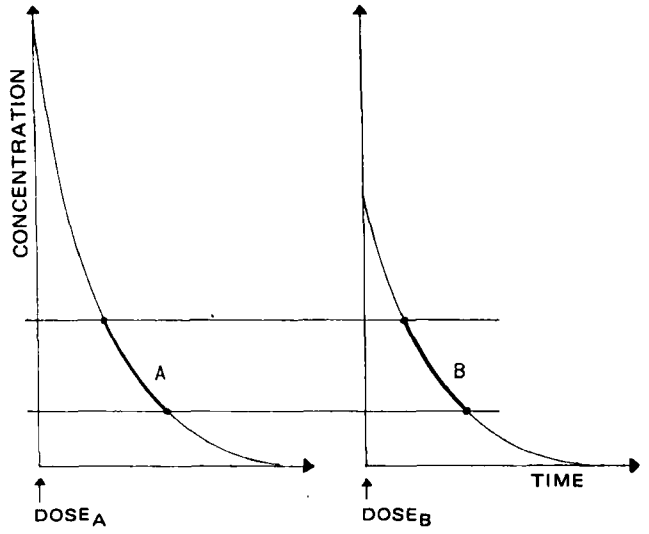

Figure 1—*Illustration of the congruence property of a pharmacokinetic system satisfying the differential equation, Eq. 1: Curve segment A = curve segment B.*

In nonlinear pharmacokinetics it is often observed that the slopes of the drug concentration *versus* time profiles at arbitrary drug levels are independent of the intravenous bolus dose given, which results in the congruence property illustrated in Fig. 1. Such kinetic behavior will be found for any nonlinear (or linear) pharmacokinetic system when the rate of change of the drug level depends only on the drug level, *i.e.*:

$$\frac{dC}{dt} = f(C) \qquad \text{(Eq. 1)}$$

where $f(\ )$ can be any function only dependent on the concentration C. For example, a parallel first-order and Michaelis–Menten elimination:

$$\frac{dC}{dt} = -kC - \frac{V_m C}{K_m + C} \qquad \text{(Eq. 2)}$$

will result in this behavior; so will any other system incorporating nonlinear binding, excretion, metabolism, *etc.*, as long as the kinetics can be described in the general form of Eq. 1. Due to the model-independent nature of the method proposed, there is of course no need to postulate a specific kinetic relationship. The congruence property (Fig. 1) makes drug level predictions particularly simple: Once drug level data from an intravenous bolus injection have been well approximated by an arbitrary function then this function can serve as a base function for drug level predictions. For example, to predict the drug level profile at steady state starting at point P (Fig. 2), the corresponding point P′ on the base curve is found. The base curve segment starting at P′ and stretching over a time interval of length T (where T is the dosing period) then defines the steady-state profile (Fig. 2).

The peak and trough levels at steady state can be derived from the base function as follows: The difference between the peak and trough levels at steady state is equal to the concentration increment, ΔC_D, resulting from the dose injected at the completion of the dosing period:

$$C_{ss}^{max} - C_{ss}^{min} = \Delta C_D \qquad \text{(Eq. 3)}$$

Equation 3 can be transformed into the equivalent base

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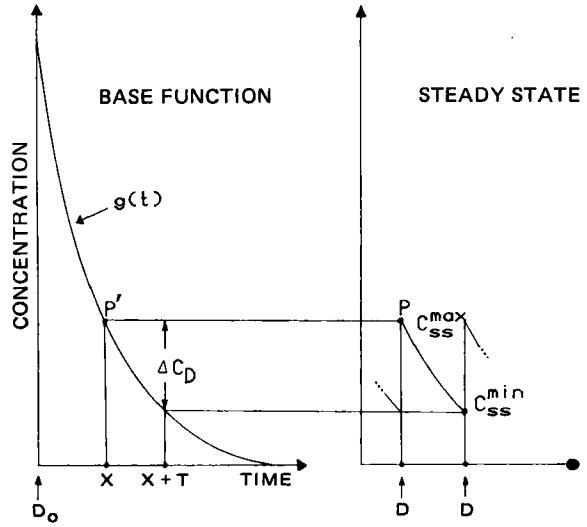

Figure 2—*Base function approach to obtain peak, trough, and mean steady-state levels in multiple intravenous bolus dosing in nonlinear pharmacokinetics.*

function relationship (Fig. 2):

$$g(x) - g(x + T) = \Delta C_D \qquad \text{(Eq. 4)}$$

The basic principle behind the methodology expressed by Eq. 4 is simply to find a certain level $g(x)$ (point P′, Fig. 2) on the base function, which over a period (x to $x + T$) equal to the dosing period T results in a reduction $g(x) - g(x + T)$, which is equal to the concentration increment Δc_D resulting from the maintenance dose. The particular curve segment on the base curve with the property expressed by Eq. 4 is determined numerically by finding the particular value of the unknown quantity x which satisfies Eq. 4. The method assumes that the pharmacokinetics show a dose linear boundary condition, so that c_D is proportional to the dose:

$$\Delta C_D = D/V \qquad \text{(Eq. 5)}$$

This appears to be a reasonable assumption, since the nonlinearity of the drug is more likely due to secretion and metabolic processes than to its initial distribution. The proportionality term, V, in Eq. 4 can be estimated from the base function and its intravenous bolus dose D_0:

$$V = D_0/g(0) \qquad \text{(Eq. 6)}$$

Substituting Eqs. 5 and 6 into Eq. 4 yields the following final expression:

$$g(x + T) + \frac{D}{D_0} g(0) - g(x) = 0 \qquad \text{(Eq. 7)}$$

If the function g fitted to the single-dose data is monotonically decreasing and D_0 has been chosen slightly larger than a normal loading dose so that $g(0) > C_{ss}^{max}$, then Eq. 7 can be solved for x to subsequently give the steady-state peak and trough levels (Fig. 2):

$$C_{ss}^{max} = g(x) \qquad \text{(Eq. 8)}$$

$$C_{ss}^{min} = g(x + T) \qquad \text{(Eq. 9)}$$

Thus, the procedure to determine the steady-state peak and trough levels resulting from intravenous bolus doses D, injected at regular dosing intervals T, can be summarized as follows: Plasma level data from an intravenous bolus dose $D_0 (D_0 > D$, *e.g.*, a loading dose) is obtained and an arbitrary, monotonically decreasing function is fitted to the data to give the base function g. The dose D_0 should be chosen sufficiently large to ensure that the initial base function value $g(0)$ is larger than the expected steady-state peak level. Equation 7 is then solved numerically for x. Most computer program libraries for scientific computations will have programs suitable for this task (1, 2). The peak and trough levels are subsequently calculated from the base function according to Eqs. 8 and 9.

The mean steady-state level, $\bar{C}_{ss}$, can also be calculated from the base function once x has been found:

$$\bar{C}_{ss} = \int_x^{x+T} g(t)dt/T \qquad \text{(Eq. 10)}$$

The sum of exponential functions which are fitted so successfully to intravenous bolus data in linear pharmacokinetics apparently do not fit nonlinear pharmacokinetic data properly. Preliminary investigations were, therefore, carried out to identify a suitable type of function that could be used. It was found that the following empirical function:

$$g(t) = \frac{p_1 e^{-p_2 t}}{1 + e^{p_3 - p_4 t}} \qquad p_i > 0 \qquad \text{(Eq. 11)}$$

produced excellent fit to all typical Michaelis–Menten type data investigated. Extension of the numerator and denominator (Eq. 11) to include more exponential terms may perhaps be fairly universally applicable to most nonlinear pharmacokinetic data.

The following example using simulated data illustrates the methodology. Fifteen concentration–time data with 10% normally distributed errors added were generated from the arbitrarily chosen nonlinear model, Eq. 2. The kinetic parameters $V_m = 12$, $K_m = 27$, $k = 0.08$, $C(0) = D/V = 70$, $t = 0.2,, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.5, 3.0, 3.5, 4$, and 8 were chosen to produce a pronounced nonlinearity indicated by a typical Michaelis–Menten type semilogarithmic concavity. Using the nonlinear regression program FUNFIT (3), the empirical equation Eq. 11 produced an excellent least-squares fit to the simulated data with $p_1 = 494$, $p_2 = 0.532$, $p_3 = 1.88$, and $p_4 = 0.414$.

Equation 7 was subsequently used to make steady-state predictions for a maintenance dose half the size of the above loading dose when given every 4 hours. This was done by inserting Eq. 11 into Eq. 7 with $D/D_0 = 0.5$ and $T = 4$ to give:

$$\frac{p_1 e^{-p_2(x+4)}}{1 + e^{p_3 - p_4(x+4)}} + 0.5 \frac{p_1}{1 + e^{p_3}} - \frac{p_1 e^{-p_2 x}}{1 + e^{p_3 - p_4 x}} = 0 \qquad \text{(Eq. 12)}$$

This equation was solved numerically for x with the above least-squares p-values using a fairly standard, commonly used root-finding algorithm (1). The peak, trough, and mean steady-state levels $C_{ss}^{max} = 47.7$, $C_{ss}^{min} = 15.0$, and $\bar{C}_{ss} = 29.8$ were calculated from the obtained x value ($x = 1.64$) according to:

$$C_{ss}^{max} = \frac{p_1 e^{-p_2 x}}{1 + e^{p_3 - p_4 x}} \qquad \text{(Eq. 13)}$$

$$C_{ss}^{min} = \frac{p_1 e^{-p_2(x+4)}}{1 + e^{p_3 - p_4(x+4)}} \qquad \text{(Eq. 14)}$$

$$\bar{C}_{ss} = \frac{1}{4}\int_x^{x+4} \frac{p_1 e^{-p_2 t}}{1 + e^{p_3 - p_4 t}}\, dt \qquad \text{(Eq. 15)}$$

The integral in Eq. 15 was evaluated numerically by a commonly used integration algorithm (4).

Special caution must be taken in applying a loading dose of a nonlinear drug. It may not be desirable to use a loading dose for a drug showing a narrow therapeutic index. However, in certain clinical situations it may be necessary to quickly establish high therapeutic levels by a loading dose. For example, the treatment of an epileptic emergency may call for an intravenous loading dose of phenytoin (5). The loading dose required for the method only needs to be slightly larger than a normal loading dose.[1] It should, therefore, not add much additional risk to the administration of such a loading dose. The method may also be used in dosing adjustments requiring lower steady-state drug levels, in which case the drug level data needed to make the predictions may be obtained from the later part of the dosing period.

[1] However, if the function $g(\ )$ is well chosen, it can be used to extrapolate to required levels and a loading dose may not be required.

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BOOKS

Progress in Medicinal Chemistry, Vol. 19. Edited by G. P. ELLIS and G. B. WEST. Elsevier Biomedical Press BV, Amsterdam, The Netherlands. 1982. 345 pp. 14 × 21 cm. Price $93.50 (Dfl. 220).

Contained in this volume are six reviews of independent topics covering a variety of subjects. Chapter I, "Immunopharmacology of Gold," by A. J. Lewis and D. T. Walz denotes the pathology of rheumatoid arthritis, the historical use of gold for therapeutic purposes, pharmacokinetics of gold compounds, and gold–protein interaction with tissue sulfhydryl groups, hydrolytic enzyme, prostaglandin synthetase complement, and collagen. The response systems as well as their current clinical uses in rheumatoid arthritis, pemphigus, asthma, and cancer are described.

Chapter II, "Calcium and Histamine Secretion from Mast Cells," by F. L. Pearce deals with the role of calcium in histamine release, membrane ionophones, phospholipid vesicles and permeability, and calcium pools inside and outside the cell. The activation of vasoamine release by the mast cell *via* the translocation of calcium was related to membrane phosphatidylinositol metabolism, phospholipid methylation, and cAMP levels. Known inhibitors of these processes were evaluated.

Chapter III, "Biological and Pharmacological Properties of Phospholipids," by A. Bruni and P. Palatini is a discussion of the phospholipid bilayer model including flexibility, stability, asymmetry, head groups, and fusion of the components. Phospholipid–protein interrelations, including lipid-binding proteins, mode of association, specificity of the interreaction, mutual influence of components in the membrane, and structural models are presented. The pharmacological aspects of liposomes or bilayer envelopes including pharmacokinetics; interaction with cells; delivery of drugs, genetic material, or immune components; and lipid chemical mediators were presented by the authors.

Chapter IV, "Cyclophosphamide Analogues," by G. Zon includes a cursory historical review of cyclophosphamide as an antineoplastic agent including novel chemical substitutions, related conformational effects, prodrug models, structure–activity relationships of active metabolites, and miscellaneous analogues.

Chapter V, "Chartruesin, a Glycosidic Antitumor Antibiotic from *Streptomyces*," by J. A. Beisler covers the natural, microbial, and biochemical sources and structure determination of chartruesin. Partial and total synthetic routes of aglycones are reviewed. The antitumor activity, mode of action, and toxicity of chartruesin are briefly eluded to in the discussion.

Chapter VI, "Recent Progress in the Medicinal Chemistry of 2,4-Diaminopyrimidines," by B. Roth and C. C. Cheng covers the classical aspects of antimetabolites of folic acid and descriptions of dihydrofolate reductase enzymes from bacteria and vertebrate sources. Pharmacological action was discussed in three areas: (*a*) antibacterial action of diaminopyrimidines of the 2,4-diamino-5-(substituted benzyl) pyrimidines, 6-substituted 2,4-diamino-5-benzyl pyrimidines, isosteres of the benzylpyrimidines, dihydro-*sym*-triazines, and bicyclic analogues of diamino-pyrimidines; (*b*) antimalarial dihydrofolate reductase inhibitors—pyrimethamine and cycloguanil, monocyclic 2,4-diamino-pyrimidines and isosteres, dihydro-*sym*-triazines, and quinazolines; (*c*) anticancer—dihydrofolate reductase inhibitions by methotrexate, modifications of the glutamic acid, benzene ring, bridge atoms between the rings, and pteridine portions. Miscellaneous and nonclassical dihydrofolate reductase inhibitors are included in the chapter.

Whereas all six of these topics are relevant to medicinal chemistry, this reviewer found the text somewhat disappointing from two aspects: (*a*) much of the material was redundant with basic conceptual ideas presented on numerous occasions in the literature; (*b*) the topics selected were not those that would be at the forefront of current research today. However, the chapters are well referenced with a number of figures, tables, and diagrams, and the text is organized and clearly written for understanding by the reader. The major use of the text as a reference book would be for graduate students and individuals not versed in these areas of research. The current status of each of the six topics is accurately assessed by the authors, and the text is an excellent overview of both chemical and biological ideas regarding the topics, which is important in medicinal chemistry because of the diversity of the field.

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