The mathematical model (2):

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1^2 + b_1X_1X_2 + b_5X_2^2 + \text{Error} \quad \text{(Eq. 1)}$$

can be rearranged and rewritten as shown below:

$$Y = b_3X_1^2 + b_4X_1X_2 + b_5X_2^2 + b_1X_1 + b_2X_2 + b_0 + \text{Error} \quad \text{(Eq. 1)}$$

$$Z = AX^2 + BXY + CY^2 + DX + EY + F \quad \text{(Eq. 2)}$$

According to a well-known theorem (3), the surface (Eq. 2) is an elliptic parabaloid which has ellipses for horizontal cross sections if $B^2 - 4AC$ is negative, a hyperbolic parabaloid if $B^2 - 4AC$ is positive, and a parabolic cylinder if $B^2 - 4AC$ is zero. The type of a parabaloid can, therefore, be obtained by computing the discriminant $B^2 - 4AC$ in the equation. Using those suggested coefficients b_0, b_1, b_2 . . . b_5 to substitute for Eq. 1 for the case of tablet friability response, the discriminant $B^2 - 4AC$ is positive, the level curves (contour curves) are hyperbolas, and the surface is a hyperbolic parabaloid; for the dissolution response, the discriminant $B^2 - 4AC$ is negative and A and C are negative, the level curves are ellipses, and the surface is an elliptic parabaloid that opens downward. No evidence was given showing that the mathematical model had been tested. No explanation or reference was provided to show how the contour curves were derived and drawn. No examination was given to discuss whether the part of error in the equation (Eq. 1) was due to lack-of-fit.

By definition (3), a level curve (or contour curve) of a function $f(x,y)$ is the curve $f(x,y) = C$ in the XY-plane. It consists of the points (x,y) where the function has the value C. In a real situation, it appears to be difficult for tablet friability and dissolution response to satisfy the necessary conditions for the curve $f(x,y) = C$, respectively. In other words, no tablets can be obtained with zero crushing strength; however, if $x = 0, y = 0$, the tablet friability response curve should remain $f(x,y) = C$. As a consequence, the quadratic response model does not adequately represent the true response surface.

In addition, the authors stated that "The friability contour plot consists of a series of ellipsoidal curves" (p. 1375) in the *Results* and *Discussions* section. There was no proof or test for ellipsoids, $Z^2 = AX^2 + BY^2 + C$. An ellipsoid is defined (4) as a surface, all plane sections of which are ellipses or circles. Mathematically speaking, $Z^2 = AX^2 + BY^2 + C$, if A and B are negative, the cross sections are all ellipses, and the surface is an ellipsoid. The Eq. 1 mathematical form does not automatically equate with the equation $Z^2 = AX^2 + BY^2 + C$.

It is a suitable approach to sketch a graph geometrically for the range of tablet specifications to obtain a desired quality product. A particularly chosen mathematical model should be carefully examined and thoroughly tested to determine the suitability and validity of the model for explaining scientific observations.

(1) Z. T. Chowhan, I. C. Yang, A. A. Amaro, and Li-Hua Chi, *J. Pharm. Sci.*, **71**, 1371 (1982).

(2) The RSREG Procedure, SAS Technical Report P115 (1982), SAS Institute, Inc., Cary, NC 27511.

(3) A. Shenk, "Calculus and Analytical Geometry," 2nd ed., 1979.

(4) "Webster's New Collegiate Dictionary," Merriam, Springfield, Mass.

Liang-Lii Huang
Wm. H. Rorer, Inc.
Fort Washington, PA 19034

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A Rebuttal on a Second-Degree Polynomial Mathematical Model Used to Evaluate the Effect of Moisture and Crushing Strength on Tablet Friability and *In Vitro* Dissolution

Keyphrases □ Dissolution—*in vitro*, effect of moisture and crushing strength, friability □ Crushing strength—effect on tablet friability and *in vitro* dissolution □ Friability—effect of moisture and crushing strength

To the Editor:

Huang's communication (1) refers critically to the report of Chowhan *et al.* (2); the basis of his criticism stems from his attempt to reproduce the response surface contour plots in Figs. 5 and 6 using the regression coefficients given in Table I (1) by means of a program package[1], RSREG, on a computer[2]. To confirm our results, the experimental data were evaluated by the same program package[1] and computer[2] and a completely separate data analysis package, RSM[3]. The results from both analyses were consistent with the results reported earlier (2) in Figs. 5 and 6. Closer scrutiny of the published regression coefficients in Table I (2) revealed a printing error; coefficient b_3 for tablet friability should read (positive) +0.06228 rather than (negative) −0.06228. This makes the discriminant $B^2 - 4AC$ negative, which corresponds to an elliptical level curve with an elliptical parabaloid surface that opens upwards. These results are completely consistent with the model chosen over the ranges evaluated. The tablet crushing strength and the granulation moisture were evaluated only within the practical limitations of tableting. It was stated clearly that within the practical ranges of tablet crushing strength and granulation moisture content, the data could be analyzed using a general quadratic response surface model. Within the practical limitations of tableting, the usefulness of this method in establishing *rational* specifications for the in-process variables, such as granulation moisture (x) and initial tablet crushing strength (y), to ensure proper control of the tablet friability and *in vitro* dissolution was also discussed. Since the experimental data were evaluated within the practical limitations of tableting, and this point was emphasized in the discussion, there is no justification for Huang to be critical of conditions such as $f(x,y) = C$ with $x = 0, y = 0$, which are unrealistic and of no consequence for optimizing *in vitro* dissolution and tablet friability.

Table I (2) gives the values of multiple correlation coefficients. The model was tested using lack-of-fit, F ratio, and t test. It was stated in the report that contour curves

[1] SAS Institute, Inc. Cary, NC 27511.
[2] IBM 3033.
[3] Compuserve, Santa Clara, CA 95054.

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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.

(1) L. Huang, *J. Pharm. Sci.*, **72**, 1096 (1983).

(2) Z. T. Chowhan, I. C. Yang, A. A. Amaro, and L.-H. Chi, *J. Pharm. Sci.* **71**, 1371 (1982).

(3) "Webster's New Collegiate Dictionary," Merriam, Springfield, Mass.

Z. T. Chowhan ˣ
I.-C. Yang
A. A. Amaro
Li-hua Chi
Institute of Pharmaceutical Sciences
Syntex Research
Palo Alto, CA 94304

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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.

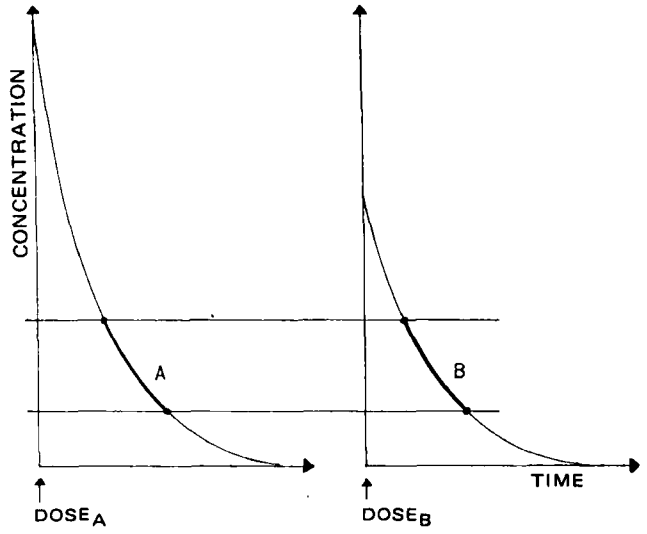

Figure 1—*Illustration of the congruence property of a pharmacokinetic system satisfying the differential equation, Eq. 1: Curve segment A = curve segment B.*

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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