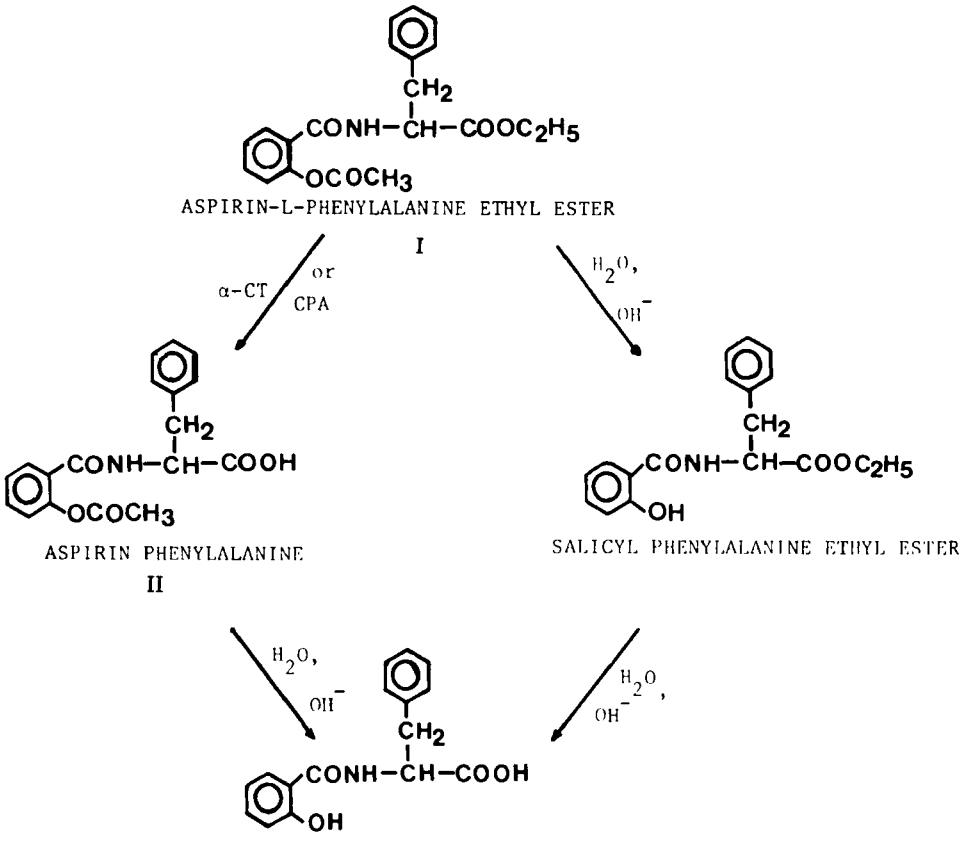

Scheme III

at concentrations ranging from 4.4×10^{-4} to 1.2×10^{-3} *M* were obtained in the presence of 1×10^{-5} *M* enzyme. The details of these experiments will be published in a later paper.

Since I is hydrolyzed to II by α-chymotrypsin and II does not cleave to aspirin in the presence of carboxypeptidase A, I is not a prodrug for aspirin.

Based on the previous work (8–10) and the additional data obtained in this laboratory, Scheme III is proposed for the hydrolysis of aspirin phenylalanine ethyl ester.

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Comment on a Second-Degree Polynomial Mathematical Model for Tablet Friability and *In Vitro* Dissolution

Keyphrases □ Dissolution—*in vitro*, polynomial mathematical model, effect of moisture and crushing strength □ Friability—effect of moisture and crushing strength, mathematical model

To the Editor:

In a recent report, Chowhan *et al.* (1) have used a function of a two-variable model to describe the effect of moisture and crushing strength on tablet friability and *in vitro* dissolution. Elliptical shape and ridge contour curves were unfortunately not reproduced on a computer[1] using all published data. Further examination of the mathematical equation (Eq. 1) using SAS contour plot procedure[2] on the same computer showed indeed that Figs. 5 and 6 contour plots in the article did not agree with the analytical expression.

[1] IBM 3033.
[2] SAS Institute Inc., Cary, NC 27511.

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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.

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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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