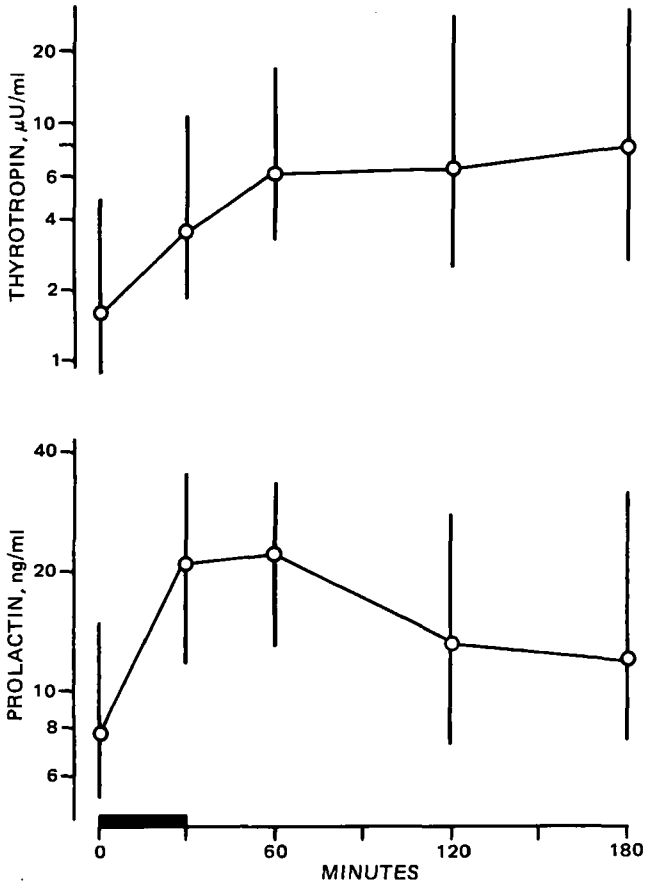

Figure 1—*Plasma thyrotropin and prolactin profiles after buccal application of 20 mg of protirelin. Circles are geometric means of 10 subjects (thyrotropin) and nine subjects (prolactin), respectively. Vertical bars indicate observed range. Horizontal bar indicates time of application.*

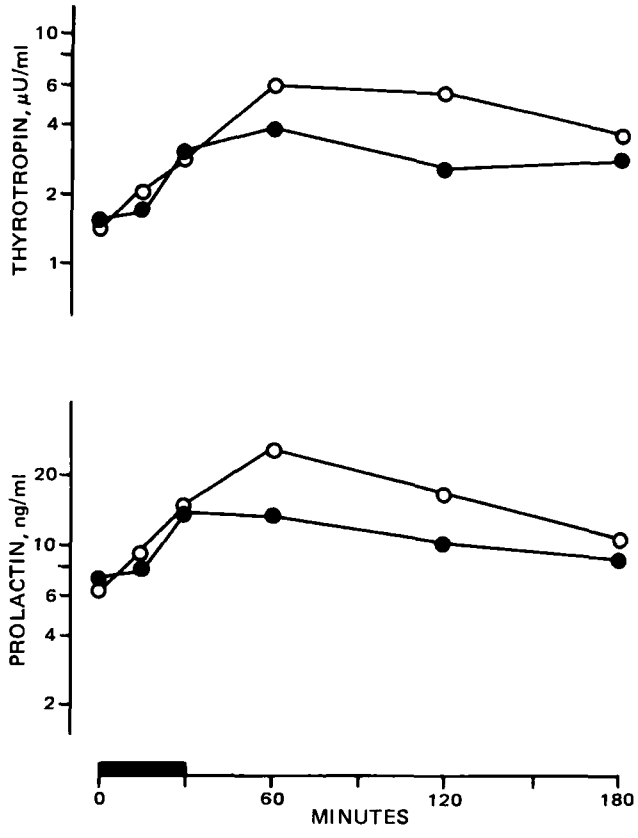

Figure 2—*Plasma thyrotropin and prolactin profiles after buccal application of protirelin under constant withdrawal of excess saliva. Filled and open circles indicate two subjects. Horizontal bar indicates time of application.*

These results also reveal that buccal protirelin administration is a clear alternative to both the peroral and the intravenous tests. As compared with the intravenous test, the obvious advantage of buccal protirelin is the fact that none of the aforementioned side effects were observed. This appears to be due to the lower incremental increase of plasma protirelin and, therefore, to the more moderate stimulation kinetics after buccal administration. In addition, buccal protirelin with a maximum stimulation 30 to 60 min after application, provokes a faster response than the peroral test, which usually requires a period of 2–3 hr to reach its peak (3, 7). We therefore suggest this test be evaluated for diagnostic use. Suitable dosage forms are presently under investigation.

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Practical Solution to the Michaelis–Menten Equation

Keyphrases □ Michaelis–Menten equation—mathematical solution

To the Editor:

The mathematical solution of the Michaelis–Menten equation apparently only exists in implicit form. The explicit form required in practical usage is obtained by numerical means either using numerical integration or by solving the implicit form using a root-solving algorithm. To avoid this numerical complexity methods have been proposed which are based on a numerical solution in-

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volving the use of a table of function values (1, 2). Such methods may be useful when operating a nonprogrammable calculator. However, if several calculations are required, such as in plotting curves, the methods become quite tedious and slow because of the repetitive readings of the table values. Furthermore, the published tables are also of limited usefulness because they do not extend far enough to include all values that may occur in clinical practice (1, 2). The following explicit method does not have this limitation. It enables the Michaelis–Menten equation to be evaluated quickly without the use of tables, numerical integration, or iterative techniques.

The solution to the Michaelis–Menten equation:

$$\frac{dC}{dt} = -V_m C/(K_m + C) \qquad \text{(Eq. 1)}$$

is accurately evaluated using the algorithm:

$$C(t) = K_m G(x) \qquad \text{(Eq. 2)}$$

where: $x = V_m t/K_m - C(0)/K_m + \ln [K_m/C(0)]$ (Eq. 3)

The G function in Eq. 2 is for $x \leq -1.9$ evaluated as:

$$G(x) = -x - \ln\left[-x + \frac{a_1 x}{a_2 - x} \ln(-x)\right] \qquad \text{(Eq. 4)}$$

$$a_1 = 0.99419 \qquad \text{(Eq. 5)}$$

$$a_2 = 1.1195 \qquad \text{(Eq. 6)}$$

and for $x > -1.9$:

$$G(x) = \exp\{-x - b_1 \exp(-b_2 x)/[b_3 + \exp(-b_4 x)]\} \qquad \text{(Eq. 7)}$$

$$b_1 = 1.1249 \qquad \text{(Eq. 8)}$$

$$b_2 = 1.0250 \qquad \text{(Eq. 9)}$$

$$b_3 = 0.98405 \qquad \text{(Eq. 10)}$$

$$b_4 = 0.76577 \qquad \text{(Eq. 11)}$$

The maximum global error in the evaluation of the Michaelis–Menten equation using Eq. 2 is 0.078% which is more than sufficient for practical applications.

Derivation—The Michaelis–Menten equation given by Eq. 1 can be transformed by setting:

$$C = K_m y(x) \qquad \text{(Eq. 12)}$$

with x given by Eq. 3. Then:

$$\frac{dC}{dt} = K_m \frac{dy}{dx}\frac{dx}{dt} = K_m \frac{dy}{dx}\frac{V_m}{K_m} = -\frac{V_m K_m y}{K_m + K_m y} \qquad \text{(Eq. 13)}$$

The last equality of Eq. 13 simplifies to:

$$\frac{dy}{dx} = -\frac{y}{1+y} \qquad \text{(Eq. 14)}$$

Separating variables and integration of Eq. 14 gives:

$$\ln y - \ln y_0 + (y - y_0) = -(x - x_0) \qquad \text{(Eq. 15)}$$

or

$$\ln y + y + x = \ln y_0 + y_0 + x_0 \qquad \text{(Eq. 16)}$$

The right-hand side of Eq. 16 is zero since according to Eqs. 12 and 3:

$$\ln y_0 + y_0 + x_0 = \ln [C(0)/K_m] + C(0)/K_m + (-C(0)/K_m + \ln [K_m/C(0)]) = 0 \qquad \text{(Eq. 17)}$$

Thus, Eq. 16 becomes:

$$\ln y(x) + y(x) = -x \qquad \text{(Eq. 18)}$$

Exponentiating both sides yields:

$$y(x) \exp[y(x)] - exp(-x) = 0 \qquad \text{(Eq. 19)}$$

The function $y(x)$ is the same as Toothill's function ϕ and Beal's function F with a change in sign of x; *i.e.*, $y(x) = F(-x) = \phi(-x)$ (1, 2). The implicit, parameterless function $y(x)$ can be approximated in many ways using various standard transcendental functions. The approximation $y(x) \simeq G(x)$ presented (Eqs. 4 and 7) appears to be a reasonable compromise between simplicity and accuracy. It is derived from the following considerations. From Eq. 18 it follows that:

$$y = -x - \ln y \qquad \text{(Eq. 20)}$$

by substituting the right-hand side expression for y on the right-hand side yields:

$$y = -x - \ln(-x - \ln y) \qquad \text{(Eq. 21)}$$

This equation can be used as an approximation for $y(x)$ if a sufficiently accurate approximation for $\ln y$ is used. By empirical numerical means it was found that for $x < 0$ $\ln y$ is quite well approximated by the function:

$$\ln y \simeq \frac{a_1 x}{a_2 - x} \ln(-x) \qquad \text{(Eq. 22)}$$

with a_1 and $a_2 \simeq 1$. Inserting this equation into Eq. 21 yields Eq. 3.

For positive values of x it is more accurate to use Eq. 19 in rearranged form:

$$y = \exp[-x - y] \qquad \text{(Eq. 23)}$$

This equation (Eq. 19) can be used to approximate $y(x)$ when a sufficiently accurate approximation for $y(x)$ is substituted on the right-hand side of Eq. 23. Previous research by the investigators involving empirical approximations of drug level profiles in Michaelis–Menten kinetics suggests that an empirical function of the form:

$$y \simeq b_1 \exp(-b_2 x)/[b_3 + \exp(-b_4 x)] \qquad \text{(Eq. 24)}$$

should be a suitable approximation to use. This was indeed the case. Inserting Eq. 24 into Eq. 23 yields Eq. 7.

The strategy above of expanding and rearranging the functional relationship to be approximated serves the purpose of producing an expression for y which is very little sensitive to errors in the "primary approximation" (*i.e.*, errors in Eqs. 22 and 24). For example, substituting Eq. 22 into Eq. 21 leads to better approximations than substituting into Eq. 20. Similarly the "primary approximation" Eq. 24 may not give sufficiently accurate results by itself. However, when substituted into Eq. 23 an excellent approximation can be obtained.

The constants a_1 and a_2 of Eq. 4 were obtained using FUNFIT (3) by minimizing the sum of squares expression:

$$ss = \sum_i [y(x_i) - G(x_i)]^2 \qquad \text{(Eq. 16)}$$

with x_i ranging from −1.9 to −8.0 in steps of 0.1. The $y(x)$ function was evaluated to an accuracy of at least six significant digits from Eq. 15 using Brent's numerical root-solving algorithm (4). The constants $b_1 - b_4$ of Eq. 7 were similarly evaluated with x_i ranging from −1.9 to 8.0 in steps of 0.1. The switch point $x = -1.9$ in the formula for $G(x)$ was derived empirically from preliminary observations which showed Eq. 4 starts to deviate significantly from $y(x)$ for $x > -1.9$, and the same is the case for Eq. 7 for $x < -1.9$. The maximum relative error $\epsilon = |y(x) - G(x)|/y(x)$ of Eq. 4 with the constants given is 0.078% ($x = -1.9$) in the range $x = -1.9$ to −8.0. From a mathematical analysis of Eq. 4 it can be shown that the relative error will continue to decrease beyond $x = -8$. This was confirmed by evaluating ϵ for $x = -8$ to −20. The maximum relative error for Eq. 7 with the constants given is 0.064% ($x = 2.2$) in the range −1.9–8. The relative error continues to decrease beyond $x = 8$ as expected from Eq. 7, and at about $x = 14$ reaches convergence and starts to oscillate tightly around the "machine precision value."

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Pan Abrasion and Polymorphism of Titanium Dioxide in Coating Suspensions

Keyphrases □ Tablet-coating suspensions—titanium dioxide, pan abrasion from abrasive components □ Titanium dioxide—in coating suspensions, polymorphic modifications

To the Editor:

It is not generally recognized that aqueous tablet-coating suspensions may contain abrasive components which can cut into the surface of the coating pan causing deposition of metallic particles onto the tablets. Subsequent to a series of film-coating operations in a 24-in. coating pan[1], black specks were observed on the white tablet film coats derived from a commercial batch of color concentrate (Batch A)[2]. This phenomenon was not observed, however, when another batch of color concentrate (Batch B)[2] was employed. Isolation of the foreign material gave a positive test for iron, and it was confirmed that the actual rubbing of tablets coated with either batch against the pan surface produced black smudges. The streaks were, however, less intense on tablets coated with Batch B.

Titanium dioxide, an opacifier used in these aqueous film solutions, can exist in several polymorphic modifications, each with a different hardness (1). Anatase, for example, has a hardness on the Mohs' scale of 5.5–6, whereas rutile is in the range 6–6.5. For comparison, the common oxide of iron, hematite, gives values of 5–6 and magnetite, 5.5–6.5. The pan material itself, stainless steel 304, has a hardness range of 160–400 Brinnell (2). Conversion of the latter scale to the Mohs' scale (3) shows that the upper range lies somewhat below 6 on the Mohs' scale.

The Mohs' scale is a semiquantitative scale of hardness, which is a function of the elastic, plastic, and frictional properties of the surface. Materials with higher Mohs' numbers will scratch or abrade those with lower numbers.

In the range of Mohs' numbers considered here, the scale is linear and relatively sensitive, although hardness values tend to cluster at the high end. Abrasion or wear of the coating pan is essentially a surface phenomenon involving the removal of oxide films. A comparison of the Mohs' numbers shows that rutile is the harder of the two titanium dioxide polymorphs and would be expected to remove material through abrasion more readily than anatase. To confirm whether this could explain the observations, titanium dioxide was extracted from both batches of color concentrate and analyzed by X-ray powder diffraction. Batch A was found to contain 60:40 anatase/rutile in contrast to Batch B which was composed of 90:10 anatase/rutile.

Differences in surface roughness should theoretically not play a major role since, as the number of asperities in the film coating is increased, the number of contacting points would be increased proportionately. More scratches would be produced, but each would be of smaller cross-sectional area. This point was checked by measuring the advancing and receding contact angles of a series of liquids of varying surface tension on the film-coated tablet surfaces (4). There was no significant difference in surface roughness of films produced from either batch.

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