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Simplified Method to Study Stability of Pharmaceutical Systems

To the Editor:

A recent study (1) reported a simplified method to study the stability of pharmaceutical preparations. According to this method, shelflife or $t_{0.9}$, the time required for 10% degradation, is determined at elevated temperatures, and, by plotting log $t_{0.9}$ against the reciprocal of the absolute temperature, the shelflife at room temperature can be calculated by extrapolation of the apparent straight line. This approach is suggested (1) to be applicable to all orders of reactions since the initial decay of up to 10% can be fitted by a first-order equation regardless of the actual order of reaction.

Although some limited academic applications of this method (1) can be demonstrated, it has little utility because of erroneous assumptions inherent in the approach and the unfeasible experimental methods suggested.

This study suggests the use of the Arrhenius approach for all orders of reactions, an erroneous assumption. In fitting a straight line through a log $t_{0.9}$ and reciprocal absolute temperature profile, the intercept on log $t_{0.9}$ can be obtained only if $1/T$ approaches zero or T approaches infinity. Thus, no significance should be attached to such intercepts since they represent only a mathematical treatment parameter.

Although Amirjahed (1) tried to prove that, for up to 10% degradation, the concentrations can be fitted by straight lines, no correlation was made between the calculated rate constants reported in the literature. For example, no correlation exists between the rate constants calculated for zero-order reactions ($r = 0.078$) as reported in Table VI of Ref. 1.

Even in those instances where a straight line can be fitted to the log $t_{0.9}$–temperature profile, the slope of the line will be highly dependent on the initial concentration except for a first-order reaction. For example, an allowable (±5%) content variation will result in a 10% variation in the calculated shelflife of a zero-order reaction. Thus, the

statement made by the author that "the present method does not depend on x and k" is misleading. Briefly, therefore, a shelflife obtained at one concentration level cannot be extrapolated to other levels and is only valid for the sample studied, making it an evasive method with little practical utility.

The conclusions drawn (1) were based on either theoretically generated curves or published data obtained by more rigorous methods. It would have been more convincing if the author had used actual laboratory data for decompositon up to 10% to calculate the stability at room temperature, since this approach will require extremely sensitive analytical techniques to obtain concentration profiles. Generally, the techniques available for the analysis of dosage forms are not sensitive enough to detect small variations accurately. Thus, unless appropriate analytical techniques are available, the suggested method (1) has little utility, especially in "small laboratories and hospital pharmacy manufacturing units" as recommended by the author (1).

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Use of Area under the Curve to Estimate Absolute Bioavailability of Digoxin

To the Editor:

The absolute bioavailability of digoxin from tablets has been discussed widely with respect to the actual numerical value as well as the most appropriate method of measurement. Reported values are based on the use of the area under the serum digoxin concentration–time curve from 0 to a finite time, such as 24 or 72 hr, and range from 55 to 65% (1–6). These areas for a finite time approximate the theoretically correct area from zero to infinity (7). This communication compares the approximate method of estimating the absolute bioavailability of a digoxin tablet[1] using the area under the curve from 0 to 24 hr and from 0 to 72 hr and the theoretically correct method using the area under the curve from 0 to infinity.

The absolute bioavailability of a digoxin tablet[1] was measured in 12 normal volunteer subjects. The tablet was given at doses of 0.5 and 1.0 mg (two or four 0.25-mg tab-

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[1] Lanoxin Tablet, 0.25 mg, lot 022-1, Burroughs Wellcome and Co.