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A. M. Wahbi ˣ
H. Abdine
M. A. Korany
F. A. El-Yazbi
Faculty of Pharmacy
University of Alexandria
Alexandria, Egypt

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Simplified Method to Study Stability of Pharmaceutical Systems

Keyphrases □ Stability—pharmaceutical preparations, criticism of previously reported method relating plot of log $t_{0.9}$ and reciprocal of absolute temperature to shelflife □ Shelflife—pharmaceutical preparations, criticism of previously reported method of prediction by relating to plot of log $t_{0.9}$ and reciprocal of absolute temperature

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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S. Bakar
S. Niazi ˣ
Department of Pharmacy
College of Pharmacy
University of Illinois at the Medical Center
Chicago, IL 60612

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

Keyphrases □ Digoxin—bioavailability estimated using area under the curve from 0 to 24 and 0 to 72 hr and 0 to infinity □ Bioavailability—digoxin, estimated using area under the curve from 0 to 24 and 0 to 72 hr and 0 to infinity □ Cardiotonic agents—digoxin, bioavailability estimated using area under the curve from 0 to 24 and 0 to 72 hr and 0 to infinity

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-

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

lets), and the intravenous bolus dose[2] was 1.0 mg. Serum samples were collected through 72 (oral) or 96 (intravenous) hr and analyzed by radioimmunoassay (8). The area under each curve from 0 to 24 or 72 hr was calculated using the trapezoidal method. Areas under the curve from 0 to infinity were calculated using the trapezoidal method from 0 to the final data point and by extrapolation from the final point to infinity (9). Absolute bioavailability (B) was calculated for each subject according to:

$$B = \frac{(AUC_{0\to t}/D)_{\text{oral}}}{(AUC_{0\to t}/D)_{\text{iv}}} 100\% \qquad \text{(Eq. 1)}$$

where AUC is the area under the serum digoxin concentration–time curve from 0 to t = 24 or 72 hr and D is dose; B also was calculated according to:

$$B = \frac{(AUC_{0\to\infty} \times \beta/D)_{\text{oral}}}{(AUC_{0\to\infty} \times \beta/D)_{\text{iv}}} 100\% \qquad \text{(Eq. 2)}$$

where β is the apparent terminal log–linear slope. The values for β varied randomly between the intravenous and oral treatments. Therefore, the areas under the curve, from 0 to infinity, were corrected for these changes (9).

The estimates of the absolute bioavailability of digoxin calculated using the areas under the curve from 0 to 24 hr (Eq. 1), from 0 to 72 hr (Eq. 1), and from 0 to infinity (Eq. 2) were 59.0, 72.6, and 79.7%, respectively, for the 0.5-mg oral dose and 49.4, 59.8, and 85.8%, respectively, for the 1.0-mg oral dose (numbers are the means of individual values for the 12 subjects). Use of the truncated areas underestimated bioavailability by 26 and 9% (0.5-mg dose) and by 42 and 30% (1.0-mg dose) for the 24- and 72-hr areas, respectively.

These results indicate that the estimation of the absolute bioavailability of digoxin from serum level measurements is dependent on the extent of time that sampling is carried out and that the calculation probably becomes more accurate as time approaches infinity. These differences, particularly between the 24-hr and infinity calculations, may be due to slow or prolonged absorption of drug over a portion of the first 24 hr. Consequently, the area under the curve from 0 to 24 hr for the oral preparation may represent a smaller fraction of the area to infinity than that for the intravenous dose, yielding an apparently low estimate of absolute bioavailability. The error introduced by use of a finite area is, naturally, reduced as the final sampling time is increased.

The absolute bioavailability of digoxin tablets may be underestimated by the use of finite areas under the curve and may actually exceed 80% for the brand tested rather than the much lower values previously accepted.

[2] Lanoxin Injection, lot 644-G, Burroughs Wellcome and Co.

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William G. Kramer ˣ

Department of Pharmaceutics
College of Pharmacy
University of Houston
Houston, TX 77004

Richard H. Reuning

Division of Pharmaceutics and Pharmaceutical Chemistry
College of Pharmacy
Ohio State University
Columbus, OH 43210

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