as the labeled concentration and C_2 = 90% of this, then $-G/k_a$ is the shelf-life at temperature T_a (assuming no overage in the product).

An advantage of this method is that the activation energy and shelf-life can be estimated without assuming a particular reaction order. An average value for E can be estimated by appropriately grouping data into sets with each set having a different α value, then solving them simultaneously by weighted nonlinear regression to estimate an average E across sets and a $-G/k_a$ for each set.

An analogous technique has been used in thermogravimetric analysis (4–6), in which a number of nonisothermal experiments were performed at different linear heating rates. The logarithm of the reaction rate at a selected percentage decomposition *versus* $1/T$ was plotted using this technique. The reaction rate at a specific fraction of decomposition was estimated by linear interpolation. In the method suggested previously, t_α can be estimated similarly by linear interpolation, by alternative methods (*e.g.*, cubic splines, polynomial regression), or by assuming knowledge of the functional relationship [$f(C)$] as was done previoulsy (1).

(1) A. K. Amirjahed, *J. Pharm. Sci.*, **66**, 785 (1977).
(2) N. G. Lordi and M. W. Scott, *ibid.*, **54**, 531 (1965).
(3) S. Baker and S. Niazi, *ibid.*, **67**, 141 (1978).
(4) H. C. Anderson, *J. Polym. Sci., Part C*, **6**, 175 (1964).
(5) H. L. Friedman, *ibid.*, **6**, 183 (1964).
(6) J. Leyko, M. Maciezowski, and R. Szuniewicz, *J. Thermal Anal.*, **17**, 263 (1979).

Ian G. Tucker
Pharmacy Department
University of Queensland
St. Lucia 4067
Australia

Received October 15, 1981.
Accepted for publication January 13, 1982.

Simplified Method to Study Stability of Pharmaceutical Systems: A Response

Keyphrases □ Decomposition—determination of shelf-life using analytic methodologies, response □ Kinetics—decomposition, determination of shelf-life using analytic methodologies, response □ Stability—simplified method of study in pharmaceutical systems, response

To the Editor:

The preceding paper (1) discusses my earlier criticism, based on pragmatic reasons, of the paper (2) published by Amirjahed (3). It was suggested by Amirjahed (3) that if only 10% decomposition of a product is monitored, it is possible to ascertain the shelf-life, while using less than sophisticated analytic methodologies such as may be available in small institutional settings. My criticism that the initial concentration of the sample is important is still valid regardless of how the kinetic equation is manipulated such as reported by Tucker (1):

$$\ln(t_\alpha) = \ln(-G/k_a) + E\,(1/T - 1/T_a)/R \qquad \text{(Eq. 1)}$$

where t_α is the time to decompose from concentration C_1 to C_2, and $-G/k_a$ becomes the shelf-life at temperature T_a for a 10% concentration change. However, the assumptions involved here are self-defeating. It assumes that all preparations have similar initial concentrations and that there is no overage in the product (1). It should be reiterated that a ±5% variation in the content is routinely acceptable. This alone will discard the calculations that require identical starting concentrations. Furthermore, obtaining sufficient data points during 10% decomposition of the product (which may have several excipients) is a difficult, but not impossible, task and requires sophisticated analytic technology. Together, these arguments make such exercises as reported by Amirjahed (3) and Tucker (1) of merely academic interest and could be misleading if their use is suggested in those instances where operators may not be fully aware of these pitfalls. I would highly recommend that the authors (1, 3) use these equations with actual data collected in the laboratory and show their validity. It is only when such studies are reported that the validity of the interesting concept reported by Amirjahed (3) can be ascertained.

(1) I. G. Tucker, *J. Pharm. Sci.*, **71**, 599 (1982).
(2) S. Bakar and S. Niazi, *ibid.*, **67**, 141 (1978).
(3) A. K. Amirjahed, *ibid.*, **66**, 785 (1977).

Sarfaraz Niazi
Department of Pharmacy
College of Pharmacy
University of Illinois at
the Medical Center
Chicago, IL 60612

Received October 30, 1981.
Accepted for publication January 13, 1982.

Use of Unbound Drug Concentration in Blood to Discriminate Between Two Models of Hepatic Drug Elimination

Keyphrases □ Plasma protein binding—effect on systemic unbound blood drug concentration of orally administered drug □ Hepatic drug clearance—discrimination between two models, venous equilibrium model, sinusoidal perfusion model

To the Editor:

Two well-defined models have been proposed to describe the hepatic elimination of drugs and other compounds. These models differ in their basic hypotheses and in some of their quantitative predictions, *e.g.*, concerning the influence of blood flow, protein binding, and drug metabolizing activity on extraction ratio and hepatic clearance.

Model 1 (the equilibrium or well-stirred model) assumes that the liver is a single, well-stirred compartment, and that the concentration of unbound drug in hepatic venous blood is in equilibrium with unbound drug throughout the liver (1). Model 2 (the sinusoidal perfusion or parallel tube model) assumes that at any point along the hepatic sinusoid, the concentration of drug in the liver cell will equal

0022-3549/82/0500-0600$01.00/0