Table I—Inhibition of Cell Growth

Extract Concentration, %[a]	Inhibition of Cell Growth, % Regular[b]	Superabsorbant[c]
10	12	5
15	18	16
20	22	24
25	28	33
30	30	42
35	39	52
40	38	57
45	47	62
50	48	64

[a] Undiluted Extract = 100%. [b] Regular tampon: extracted with 95 ml of distilled water. [c] Superabsorbant tampon: extracted with 75 ml of distilled water.

Table II—Intramuscular Implantation: Tampon Material

Implanted Material	Gross Rating[a]	Histopathologic Rating[a]
Absorbant material[b]	3	4
Absorbant material[c]	3	4
Partially hydrated absorbant material	0	4
Fibrous material[b]	0	4
Fibrous material[c]	0	4

[a] Ratings: 0, equivalent to negative control; 3, marked positive response; 4, equivalent to positive control. [b] Regular tampon. [c] Superabsorbant tampon.

Muscle tissue reaction (necrotic and inflammatory) to the absorbant and fibrous materials of tampons were the most severe of any materials tested in this laboratory, actually exceeding the positive control response in some cases. The isolated fibrous material which has lower absorbancy than the absorbant material did not show a positive gross response but had a histopathologic rating equivalent to the absorbant material, suggesting that the response was not totally due to dehydration. Fibrous material has been reported to be present in biopsies of vaginal lesions (1). Although the rabbit muscle response can not be considered to be identical to the response of vaginal tissue, the presence of fibrous material in vaginal lesions indicates that tampon material comes into intimate contact with vaginal tissue. Tissue dehydration has been demonstrated to alter calcium levels of vaginal tissue, facilitates contact of tampon material with the tissue, and undoubtedly alters cellular response to leachable toxic components of tampons. The inhibition of cell growth reported in Table I was observed in normal liquid tissue culture medium where dehydration is not a factor. The effect of leachable, soluble components of tampons on cells partially impaired or altered by dehydration is not known. The potential for the exacerbation of the ulcerative process by leachable substances of tampons is apparent.

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Simplified Method to Study Stability of Pharmaceutical Systems

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

To the Editor:

In a previous report (1), shelf-life, defined as the time for 10% decomposition at 25°, was estimated by a simplified method. The method involved carrying out a number of kinetic tests at different temperatures followed by linear regression of the logarithm of $t_{0.9}$ (the time required for the drug to decompose to 90% of its original value) on the reciprocal of absolute temperature. Simulated data were used initially to test the linearity of such plots. Since it had been reported previously (2) that it was not possible to distinguish between first-, zero-, and simple second-order kinetics when the decomposition was <10%, it was believed the plots of ln ($t_{0.9}$) *versus* $1/T$ would be linear.

In a subsequent criticism of a previous study (1), it was stated that the use of this Arrhenius approach for all orders of reaction was erroneous and that the slope of the line would be highly dependent on the initial concentration (3). For this reason, and because of analytical difficulties when decomposition is <10%, it was concluded that this method was of little use.

The problem arises because $t_{0.9}$ was defined with respect to the original concentration. It was tacitly assumed (1) that all test samples would have the same initial concentration, whereas it was implied (3) that this would not be the case necessarily.

The purpose of this communication is to point out that plots of $\ln(t_\alpha)$ (where t_α is the time to decompose from concentration C_1 to C_2) *versus* $1/T$ will be linear for all reaction orders irrespective of the α value chosen. If C_1 equals the initial concentration (C_0), and it is the same for all experiments, and C_2 is 90% of C_0, then $t_\alpha = t_{0.9}$.

Assuming the usual rate expression:

$$dC/dt = -kf(C) \qquad \text{(Eq. 1)}$$

where $f(C)$ is some function of concentration, then integrating between the limits t_2 and t_1 ($t_2 - t_1 = t_\alpha$):

$$g(C_2) - g(C_1) = -kt_\alpha \qquad \text{(Eq. 2)}$$

where $g(C)$ is the integrated form of $f(C)$. If a number of kinetic experiments are performed at different temperatures, each starting with approximately the same initial concentration, and C_1 and C_2 are chosen the same for all experiments, then $g(C_2) - g(C_1)$ is constant (G). Substituting this into Eq. 2, assuming the Arrhenius equation is applicable:

$$G = -k_a \exp[-E(1/T - 1/T_a)/R]t_\alpha \qquad \text{(Eq. 3)}$$

where k_a is the rate constant at the arbitrarily chosen temperature, T_a, and E is the activation energy. Rearranging and taking logarithms:

$$\ln(t_\alpha) = \ln(-G/k_a) + E(1/T - 1/T_a)/R \qquad \text{(Eq. 4)}$$

Thus a plot of $\ln(t_\alpha)$ *versus* $(1/T - 1/T_a)$ will be linear with slope E/R and intercept $\ln(-G/k_a)$. If C_1 is chosen

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).

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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.

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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

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