by dividing the area under the concentration multiplied by time–time curve [area under the moment curve ($AUMC$)] by the area under the concentration–time curve (AUC):

$$MRT_{iv} = \frac{AUMC_{iv}}{AUC_{iv}} \quad \text{(Eq. 1)}$$

As shown previously by Benet and Galeazzi (4), a model independent distribution volume (Vd_{ss}) may be determined from the dose (D), MRT_{iv}, and AUC_{iv} as follows:

$$Vd_{ss} = \frac{D(MRT_{iv})}{AUC_{iv}} = \frac{D(AUMC_{iv})}{(AUC_{iv})^2} \quad \text{(Eq. 2)}$$

If the same dose (D) is administered as an infusion over a time (t') or is divided into increments ($D_1, D_2, \ldots D_n$) and administered as a combination of infusions and/or boluses at different times ($T_1, T_2, \ldots T_n$), the area under the curve (AUC_{total}) will equal the AUC_{iv}; but the $AUMC_{total}$ will be greater than the $AUMC_{iv}$, resulting in an overestimation of Vd_{ss} if $AUMC_{total}$ is used in Eq. 2. For a case where the drug is administered as a single infusion rather than a bolus, the MRT_{total} and the $AUMC_{total}$ are easily corrected, since the infusion will increase the MRT_{iv} by $0.5t'$ (6), and:

$$AUMC_{iv} = AUMC_{total} - AUC_{iv}(0.5t') \quad \text{(Eq. 3)}$$

When multiple dosing occurs, the correction is somewhat more complex, since there is a delay (T) in the input of a fraction of the dose. Assuming there is no previous dosing, the delay time will increase the MRT_{iv} by T if administered as a bolus and by $0.5t' + T$ if administered as an infusion, and:

$$AUMC_{iv} = AUMC_{total} - AUC_{iv}(0.5t' + T) \quad \text{(Eq. 4)}$$

The general form for n bolus and/or infusion doses then becomes:

$$AUMC_{iv} = \sum_{i=1}^{n} AUMC_i - \sum_{i=1}^{n} AUC_i(0.5t_i' + T_i) \quad \text{(Eq. 5)}$$

where: $t_i' = 0$ for a bolus dose and $T_1 = 0$.

Dividing both sides of Eq. 5 by AUC_{iv} (the total AUC calculated), and recognizing the ratio of the individual AUC_i's to AUC_{iv} is the fraction of the total dose administered (F_i), one obtains:

$$MRT_{iv} = MRT_{total} - \sum_{i=1}^{n} F_i(0.5t_i' + T_i) \quad \text{(Eq. 6)}$$

Equation 6 may be used to correct total moment data for use in Eq. 2, even when a bolus is administered during an infusion. Although it is not valid if residual drug is present prior to characterization of the concentration–time curve, corrections for the residual drug are possible in certain instances. One may be tempted to correct for oral dosing by adding $1/K_a$ to the summation term in Eq. 6, but the fraction of the oral dose absorbed must be known as well as K_a. Finally, calculation of $AUMC_{total}$ and AUC_{total} are subject to extrapolation errors as described previously (3, 4), so it is advisable to obtain data which will allow excellent characterization of the terminal elimination rate constant after the last dose increment is administered, or to collect samples until the concentration of drug is essentially zero.

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Tampon Leachable Substances: Acute Toxicity

Keyphrases □ Tampons—leachable substances, acute toxicity □ Toxicity, acute—tampon leachable substances, intramuscular implantation in rabbits □ Inhibition of cell growth—acute toxicity of tampon leachable substances □ Dehydration—tissue response, acute toxicity of tampon leachable substances

To the Editor:

The use of tampons for the control of menstrual flow has been associated with the induction of vaginal ulcerations, mucosal changes, and toxic shock syndrome. The evidence for those clinical phenomena has been reviewed recently (1), emphasizing the role of dehydration and alteration of calcium levels in the vaginal tissue as important mechanisms in the induction of vaginal ulceration. Since we are not aware of any reports on the potential toxicity of leachable substances of tampons, two acute toxicity tests were performed on regular and superabsorbant tampons available commercially. The tests performed were: a tissue culture inhibition of cell growth test on aqueous extracts (23°) of whole tampons (Table I); and a 7-day intramuscular implantation test in rabbits using (*a*) the absorbant material of the tampons (excluding the casing and fibrous material), (*b*) partially hydrated absorbant material, and (*c*) fibrous material (excluding casing and absorbant material (Table II).

The decrease in the gross rating of the muscle implant of the partially hydrated tampon material as compared to the dry material implant was consistent with the generally accepted conclusion that dehydration is a major factor in the initiation of vaginal ulceration. Also, the soluble, leachable components of the tampons tested have a significant cellular toxicity at concentrations well below that which might be expected in vaginal secretions adjacent to a tampon. The tissue culture test covers a period of time (72 hr) of usual tampon usage, and several tampons are frequently used in that period. It should also be noted that there was a significant concentration-dependent response for both extracts and that the highest concentration tested was 50% with respect to the original extract.

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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