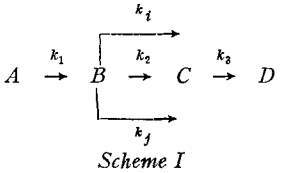
Method for Estimating Rate Constants for Absorption, Metabolism, and Elimination from Urinary Excretion Data

By JOHN G. WAGNER

A method is described for estimating the first-order rate constants for absorption, metabolite formation, and all-over loss of drug from the body if the time course of urinary excretion of the metabolite and an estimate of the rate constant for urinary excretion of the metabolite are available. The rate constants are estimated by drawing only two graphs and performing simple calculations which are described in detail. A simulation example is given where the rate constants were estimated with small errors when the rate constant for absorption was only twice the magnitude, and the rate constant for urinary excretion of metabolite only three times the magnitude of the rate constant for over-all loss of drug from the body. If the estimate of the rate constant for urinary excretion of metabolite is appreciably in error, the other rate constants are estimated with sufficient accuracy that they may be used as preliminary estimates for iterative computer programs which provide "least squares" fitting and which estimate all parameters simultaneously.

THE SAME type of equation used to construct absorption plots (1) may also be used to prepare plots of the cumulative amount or per cent of a metabolite formed as a function of time. Once such a plot is constructed, its resolution into components is the key to the complete elucidation of the kinetics of certain common pharmacokinetic models.

A common pharmacokinetic model is the catenary chain with parallel branches, such as shown in Scheme I where all the rate constants are first-order rate constants.



Scheme I

The most common situation would be the one where A represents a drug at the absorption site in the gastrointestinal tract in the case of oral administration or in the muscle in the case of intramuscular administration, B represents the drug, and C represents a metabolite (formed from the drug) in the blood and other fluids of distribution, and D represents the metabolite C in urine. The parallel paths, indicated by the arrows alongside the $B \rightarrow C$ step, represent other paths for disposal of the drug from the blood and other fluids of distribution. For example, k_i could be the first-order rate constant for urinary excretion of unchanged drug, and k_j could be the rate constant for formation of an additional metabolite. There could be other parallel paths in addition to the two shown, or there may be one or none. The number of paths does not influence the method to be described. Another possible situation equally amenable to the method is where A would represent the drug in blood and other fluids of distribution, B would represent a primary metabolite formed from A; this primary metabolite would be excreted in the urine (say the k_i path) but also would be converted to two other metabolites—one along the k_j path, the other being C; again, D represents the metabolite C in urine.

If the over-all rate constant for loss of B from the body is designated k, then, as Scheme I is written, $k = k_2 + k_i + k_j$. In other words, k is the sum of all the first-order rate constants involved in branches initiating at B. Let X_A, X_B, X_C, and X_D be the amounts in compartments A, B, C, and D, respectively, at time t and X_A^0 be the initial amount in A at time zero. The equations which give these amounts as a function of time, t, contain one exponential term for X_A, two exponential terms for X_B, and three exponential terms for X_C and X_D. The rate constants in the exponents of the exponential terms are k_1 for X_A, k and k_1 for X_B, and k, k_1, and k_3 for X_C and X_D. One can use the "feathering" or back-projection technique on a plot of the logarithm of the amount not excreted *versus* time. However, when three exponentials are involved, this method is subject to large errors; especially one often obtains very poor estimates of the larger two rate constants, which are usually k_1 and k_3.

The method to be discussed assumes there is available an approximation of the rate constant k_3; *i.e.*, the rate constant for urinary excretion of the metabolite C. This is sometimes available. For example, Levy (2) and Elliott (3) determined

Received November 16, 1966, from the Medical Research Division, The Upjohn Co., Kalamazoo, MI 49001
Accepted for publication December 20, 1966.

the first-order rate constant for urinary excretion of salicyluric acid in man, and Nelson *et al.* (4) determined the same rate constant for rats. Hence, the method to be proposed is applicable to the acetylsalicylic acid–salicylic acid–salicyluric acid system. It is always wise to estimate k_3 in a separate study since one should ensure that levels of C obtained, when A is administered, are not high enough to saturate the active secretory pathway in the kidney. One could determine k_3 for a metabolite of a drug administered to a human or animal, at the same time as the other rate constants were operative, by administering the drug in cold (nonradioactive) form and a dose of ^{14}C- or ^{3}H-labeled (radioactive) metabolite; the counting of radioactivity in the urine, and appropriate mathematical treatment, would yield the estimate of k_3; this estimate, employed with the data obtained by the normal chemical methods for C in the urine (compartment D), would provide estimates of k_1 and k.

The optimum method of estimating the constants X_A^0, k, k_1, k_2, and k_3 from a given set of X_D, t values is to estimate the constants simultaneously with an appropriate iterative digital computer program and a digital computer of sufficient capacity and speed. Such programs require preliminary estimates of the constants. The method to be proposed is an excellent one for obtaining such preliminary estimates, providing there is an adequate distribution and number of data points. A guide to obtaining an adequate distribution of data points will be the subject of a separate publication (5).

EXPERIMENTAL

Assume that $X_B = X_C = X_D = 0$ and $X_A = X_A^0$ at $t = 0$. The equations apply to all cases when no two or all of the rate constants k, k_1, and k_3 are exactly equal. Let X_D^∞ be the amount of metabolite (mass units) ultimately excreted in the urine. Urine should be collected for at least eight or nine half-lives of the drug to ensure that X_D, at this time, is close enough to X_D^∞. Then, for Scheme I, we have

$$\frac{dX_D}{dt} = k_3 X_C \qquad \text{(Eq. 1)}$$

$$X_C = X_A^0\left(\frac{k_2}{k}\right) \times \left[\frac{k_1 k e^{-kt}}{(k_1 - k)(k_3 - k)} - \frac{k_1 k e^{-k_1 t}}{(k_1 - k)(k_3 - k_1)} + \frac{k_1 k e^{-k_3 t}}{(k_3 - k_1)(k_3 - k)}\right] \qquad \text{(Eq. 2)}$$

$$X_D = X_A^0\left(\frac{k_2}{k}\right) \times \left[\frac{k_1 k_3(1 - e^{-kt})}{(k_1 - k)(k_3 - k)} - \frac{k k_3(1 - e^{k_1 t})}{(k_1 - k)(k_3 - k_1)} + \frac{k k_1(1 - e^{-k_3 t})}{(k_3 - k_1)(k_3 - k)}\right] \qquad \text{(Eq. 3)}$$

where t is time measured from time of administration, which is considered zero time. The cumulative amount of B converted to C in time T is given by

$$\frac{k_2}{k}\int_0^T \frac{dX_B}{dt}\cdot dt = X_C + X_D = \left[\left(\frac{1}{k_3}\cdot\frac{dX_D}{dt}\right) + X_D\right] \qquad \text{(Eq. 4)}$$

Substituting for X_C and X_D from Eqs. 2 and 3 into Eq. 4 and simplifying gives

$$\left[\left(\frac{1}{k_3}\cdot\frac{dX_D}{dt}\right) + X_D\right] = X_D^\infty \times \left[1 - \left\{\left(\frac{k_1}{k_1 - k}\right)e^{-kt} - \left(\frac{k}{k_1 - k}\right)e^{-k_1 t}\right\}\right]$$

when $k_1 > k$ (Eq. 5)

and $$\left[\left(\frac{1}{k_3}\cdot\frac{dX_D}{dt}\right) + X_D\right] = X_D^\infty \times \left[1 - \left\{\left(\frac{k}{k - k_1}\right)e^{-k_1 t} - \left(\frac{k_1}{k - k_1}\right)e^{-kt}\right\}\right]$$

when $k > k_1$ (Eq. 6)

where $X_D^\infty = X_A^0(k_2/k)$. It should be noted that Eqs. 5 and 6 are actually the same equation but, to avoid confusion, have been written so that the exponential terms are always positive with the given conditions.

Let

$$\%X_D = \frac{X_D}{X_D^\infty} \times 100 \qquad \text{(Eq. 7)}$$

and

$$Y = \left[\left(\frac{1}{k_3}\cdot\frac{\Delta\%X_D}{\Delta t}\right) + \widehat{\%X_D}\right] \qquad \text{(Eq. 8)}$$

$\frac{\Delta\%X_D}{\Delta t}$ represents the observed excretion rate measured over the interval $t_2 - t_1 = \Delta t$; this rate is an approximation of the derivative $\frac{dX_D}{dt}$. The $\%\hat{X}_D$, appearing in Eq. 8 is assumed to be the estimate of the cumulative per cent of metabolite excreted at the midpoint, T, of the excretion interval. In practice, it may be estimated from a smooth curve drawn through a plot of cumulative per cent excreted against time (*i.e.*, $\%X_D$ *versus* t).

Case When $k_1 > k$—From Eqs. 5 and 8, one can see that if $(100 - Y)$ is plotted on the logarithmic (base 10) scale of semilogarithmic graph paper against T, the line drawn through the terminal points will have a slope $-\frac{\hat{k}}{2.303}$. If this line is extrapolated back to $t = 0$, the intercept, I, will be (in natural numbers, not logarithms),

$$I \simeq 100\left(\frac{k_1}{k_1 - k}\right) \qquad \text{(Eq. 9)}$$

Rearrangement of Eq. 9 gives

$$\hat{k}_1 = \frac{\hat{k}}{1 - \frac{100}{I}} \qquad \text{(Eq. 10)}$$

If residuals, R, are taken, where

$$R = Ie^{-\hat{k}T} - (100 - Y) \qquad \text{(Eq. 11)}$$

and R is plotted on the logarithmic scale of the semilogarithmic graph paper against T, then the slope of the residual line will be $-\frac{\hat{k}_1}{2.303}$ and the value of R at $T = 0$ will be $I - 100$.

Case When $k > k_1$—Similarly, from Eqs. 6 and 8, the terminal line drawn through a semilogarithmic plot of $(100 - Y)$ against T will have a slope $-\frac{\hat{k}_1}{2.303}$ and an intercept, I', such that

$$I' \simeq 100\left(\frac{k}{k - k_1}\right) \qquad \text{(Eq. 12)}$$

Rearrangement of Eq. 12 gives

$$\hat{k} = \frac{\hat{k}_1}{1 - \frac{100}{I'}} \qquad \text{(Eq. 13)}$$

If residuals, R', are taken, where

$$R' = I'e^{-\hat{k}_1 T} - (100 - Y) \qquad \text{(Eq. 14)}$$

and, R is plotted on semilogarithmic paper against T, then the slope of the line will be $-\frac{\hat{k}}{2.303}$ and the value of R' at $T = 0$ will be $(I' - 100)$.

Hence, the equations provide a method of getting one estimate of the smaller of the two rate constants k and k_1, and two estimates of the larger of these two rate constants. It should be noted that one really does not know which is the smaller of the two, but the assumption is usually made that $k_1 > k$ unless there is evidence to the contrary.

The method of estimating k, k_1, and k_2 is then as follows.

(*a*) Measure urinary excretion rates long enough to obtain a good estimate of X_D^∞.

(*b*) Convert all X_D amounts to percentages according to Eq. 7.

(*c*) Calculate the percentage excretion rates, $\frac{\Delta \%X_D}{\Delta t}$, for each excretion interval.

(*d*) Estimate the $\%X_D$ values at the midpoints, T, of the excretion intervals from a $\%X_D$, t plot.

(*e*) Calculate the values of Y for each excretion interval according to Eq. 8.

(*f*) Plot $(100 - Y)$ on the logarithmic scale of semilogarithmic graph paper against T.

(*g*) Draw a straight line through the points at the tail end of this plot and extrapolate the line to $t = 0$.

(*h*) Multiply the absolute value of the slope of the line by 2.303 to obtain the estimate of the smaller of the two rate constants, k and k_1, with dimensions time^{-1}.

(*i*) Make the first estimate of the larger of the two rate constants, k and k_1, from the intercept of the terminal line using Eqs. 10 or 13.

(*j*) Estimate residuals for those points which are not on the terminal line using Eqs. 11 or 14.

(*k*) Plot the residuals on the logarithmic scale of the semilogarithmic graph paper against T.

(*l*) Either graphically determine the slope of the residual line to obtain the second estimate of the larger of the two rate constants, k and k_1, or, more elegantly, calculate the slope of the least squares line forced through the point at $t = 0$ by means of the formula

$$|\text{slope}| = \frac{\Sigma[\log_{10}(I - 100) - \log_{10}R] \cdot T}{\Sigma T^2} \qquad \text{(Eq. 15)}$$

(*m*) If all metabolites and unchanged drug have been measured in urine to "infinite time" (*i.e.*, for at least eight to nine half-lives, $0.693/k$, assuming k is smaller than k_1 and k_3), then k_2 may be estimated. Convert all the amounts of metabolites and unchanged drug excreted to "infinite time" to mass units equivalent to metabolite C; then the sum of these amounts is $\widehat{X_A^0}$. Or, if absorption is complete, then X_A^0 is equal to the dose administered, but this is not a good assumption in the usual case. Estimate k_2 from the relationship

$$\hat{k}_2 = \frac{X_D^\infty}{\widehat{X_A^0}} \cdot \hat{k} \qquad \text{(Eq. 16)}$$

The method is illustrated by simulations based on Scheme I.

Example 1—Assignments made were $X_A^\circ = 100$ units, $k_1 = 0.500$ hr.$^{-1}$, $k_2 = 0.150$ hr.$^{-1}$, $k = 0.250$ hr.$^{-1}$, and $k_3 = 0.75$ hr.$^{-1}$. Hence, $X_D^\infty = \frac{0.15}{0.25} \times 100 = 60$ units, and $k_1/k = 2$.

Example 2—Assignments were the same as in example *1* except it was assumed there was a 25% error in k_3 on the high side; *i.e.*, $k_3 = 1.0$ hr.$^{-1}$ was used instead of $k_3 = 0.75$ hr.$^{-1}$.

Example 3—Assignments made were $X_A^\circ = 100$ units, $k_1 = 1.250$ hr.$^{-1}$, $k_2 = 0.150$ hr.$^{-1}$, $k = 0.250$ hr.$^{-1}$, and $k_3 = 1.0$ hr.$^{-1}$. Hence $X_D^\infty = 60$ units and $k_1/k = 5$.

RESULTS

Example 1—Table I gives the detailed calculations made for example *1*. The observed data are represented by the t and X_D values listed in columns 1 and 3 of this table. The $\%\widehat{X_D}$ values at the midpoints, T, may be estimated from a smooth curve drawn through the data points such as shown in Fig. 1. The semilogarithmic plot of $(100 - Y)$ *versus* T is shown in Fig. 2. Due to the data points used, and since $k_1/k = 2$, there are only two points available to draw the appropriate terminal line. The tangent line should be drawn, and not a line through the last few points which form a slight curve, since $[d \log_{10}(100 - Y)/dT]_{T \to \infty} = -k/2.303$. There will usually be few points to estimate the terminal line when $2 \leq k_1/k < 3$ if $k_1 > k$ or when $2 \leq k/k_1 < 3$ if $k > k_1$.[1] When the ratio of rate constants is greater than these ranges, there will be more points for fitting the terminal line (*e.g.*, see example *3*).

The terminal line has a slope of -0.1095; hence $\hat{k} = 0.252$ hr.$^{-1}$. The real value is 0.250 hr.$^{-1}$. The intercept of the terminal line is 200; hence, $\hat{k}_1 = \frac{0.252}{1 - \frac{100}{200}} = 0.504$ hr.$^{-1}$. The real value is 0.500 hr.$^{-1}$. The slope of the residual line, forced through $\log_{10}(I - 100)$, is 0.2214; hence, $\hat{k}_1 = 0.510$ hr.$^{-1}$. Thus, the two estimates of k_1 agree quite closely.

Figure 3 is a plot of the cumulative amount of metabolite formed as a function of time. The points are the Y,T values used to make the estimates above. The line shown on the plot is the theoretical line obtained from

$$100 - \left[1 - \left(\frac{k_1}{k_1 - k}\right)e^{-kt} - \left(\frac{k}{k_1 - k}\right)e^{-k_1 t}\right]$$

[1] The method is practically useless when $1 < k_1/k < 2$, if $k_1 > k$, or when $1 < k/k_1 < 2$ if $k > k_1$ unless an extraordinarily good analytical method is available for the drug.

TABLE I—DETAILS OF ESTIMATION FOR EXAMPLE WHEN $k_1 = 0.50$ hr.$^{-1}$, $k = 0.25$ hr.$^{-1}$, AND $k_3 = 0.75$ hr.$^{-1}$

Time, hr. t	Mid-point Time, hr. T	X_D (units)	$= \frac{X_D}{X_D^\infty} \times 100$	$\frac{\Delta\%X_D}{\Delta t}$	Y[a]	$100 - Y$	$Ie^{-\hat{k}T}$[b]	R[c]	$\log_{10}R$	$\log_{10}(I - 100) - \log_{10}R$[d]
0		0	0		0	100.0	200.0	100.0	2.0000	0.
0.2	0.2	0.006	0.01	0.225	0.310	99.69	191.48	91.79	1.9628	0.0372
0.4		0.054	0.09							
0.6	0.6	0.162	0.27	0.775	1.303	98.697	171.56	72.86	1.8625	0.1375
0.8		0.240	0.40							
1.0	1.0	0.642	1.07	3.35	5.536	94.464	155.44	60.98	1.7852	0.2148
1.2		1.044	1.74							
1.6	1.6	2.148	3.58	5.4625	10.863	89.137	133.48	44.34	1.6428	0.3532
2.0		3.666	6.11							
2.2	2.2	4.560	7.60	7.950	18.20	81.80	114.88	33.08	1.5195	0.4805
2.4		5.574	9.29							
2.6	2.6	6.556	10.93	8.650	22.463	77.537	103.86	26.32	1.4203	0.5797
2.8		7.650	12.75							
3.2	3.2	10.03	16.716	10.1625	30.266	69.734	89.240	19.51	1.2902	0.7098
3.6		12.53	20.88							
3.8	3.8	13.85	23.08	10.875	37.58	62.42	76.78	14.36	1.1571	0.8429
4.0		15.14	25.23							
4.5	4.5	18.47	30.78	11.100	45.58	54.42	...	...	...	...
5.0		21.80	36.33							
5.5	5.5	25.03	41.71	10.570	58.80	41.20	...	...	...	...
6.0		28.14	46.90							
7.0	7.0	33.84	56.40	8.880	68.24	31.76	...	...	...	...
8.0		38.80	64.66							
10.	10.	46.40	77.33	5.285	84.376	15.624	...	...	...	...
12.		51.48	85.80							
14.	14.	54.73	91.21	2.200	94.143	5.857	...	...	...	...
16.		56.76	94.60							
18.	18.	58.03	96.71	0.850	97.843	2.157	...	...	...	...
20.		58.80	98.00							
22.	22.	59.28	98.80	0.315	99.22	0.780	...	...	...	...
24.		59.56	99.26							
∞	$X_D^\infty =$	60.00	100.00							

[a] $Y = \left[\frac{1}{k_3} \cdot \frac{\Delta\%X_D}{\Delta t} + \%\hat{X}_D\right]$. [b] $Ie^{-\hat{k}T}$ are the line values obtained from the terminal linear segment extrapolated to $t = 0$. (See Fig. 1.) In Fig. 1 the value of I is 200. [c] R is the residual, *i.e.*, $R = Ie^{-\hat{k}t} - (100 - Y)$. [d] The absolute value of the slope of the residual line (Fig. 1) is given by $|\text{slope}| = \frac{\hat{k}_1}{2.303} = \frac{\Sigma[\log_{10}(I-100) - \log_{10}R]T}{\Sigma T^2}$, where $\hat{k}_1 = (2.303)(|\text{slope}|)$ in hr.$^{-1}$.

which after substitution of the given constants yields

$$100 - [1 - \{2e^{-0.25t} - e^{-0.50t}\}]$$

One can see, indirectly, that with adequate and frequent sampling, the estimation of the derivatives, $\frac{d\%X_D}{dt}$, by the "excretion rates," $\frac{\Delta\%X_D}{\Delta t}$, is excellent except for the very initial part of the plot.

Example 2—This example was a test to see what the effect of a relatively large error in k_3 would be. From the terminal line a value of $\hat{k} = 0.254$ hr.$^{-1}$ was obtained. The intercept, I, was 234 from which $\hat{k}_1 = 0.449$ hr.$^{-1}$. Hence, use of a value of k_3, which was 25% higher than the true value, gave a value of $\hat{k}$ which was 1.6% higher than the true value, and a value of $\hat{k}_1$ which was 10.2% lower than the true value.

Example 3—In this example $k_1/k = 5$ and there are 11 points to determine the terminal line shown in Fig. 4. The least squares line for the $\log_{10}(100 - Y)$, T points in the range $2.2 \leq T \leq 22$ has a slope of -0.110 and an intercept of 127.6. Hence $\hat{k} = 0.253$ hr.$^{-1}$, obtained from the slope, and $\hat{k}_1 = 1.16$ hr.$^{-1}$, obtained from the intercept. The slope of the least squares line, forced through $\log_{10}(I-100)$, from residuals, corresponding to $T = 0.2$, 0.6, 1.0, and 1.6 hr., is -0.489; hence, $\hat{k}_1 = 1.13$ hr.$^{-1}$. The true values were $k = 0.250$ hr.$^{-1}$ and $k_1 = 1.25$ hr.$^{-1}$.

DISCUSSION

The method gives two estimates of the larger of the two rate constants k and k_1. Usually, but not always in pharmacokinetics, $k_1 > k$ and $k_3 > k$. In the absence of additional information, these are reasonable assumptions. Frequently in pharmacokinetic studies in which Scheme I applies, blood is sampled also and the blood and urine are analyzed for unchanged drug in addition to measurement of metabolite in urine as assumed in this report. If k is smaller than k_1 and k_3, the terminal linear segments of a plot of the logarithm of the plasma concentration of total (free and protein bound) unchanged drug against time and a plot of the logarithm of amount of unchanged drug not excreted *versus* time will also yield estimates of $k/2.303$.

If unchanged drug is measured in the urine, then application of the method of Wagner and Nelson (1) to these data should yield the same estimate of k_1, within error, as that obtained from the above method using data derived from measuring the metabolite in urine. A result such as this was found with the data of Levy (2).

When applying the above method to data derived from urine assays care must be taken in drawing the line through the terminal points of the semilogarithmic $(100 - Y)$, T plot. Terminal points

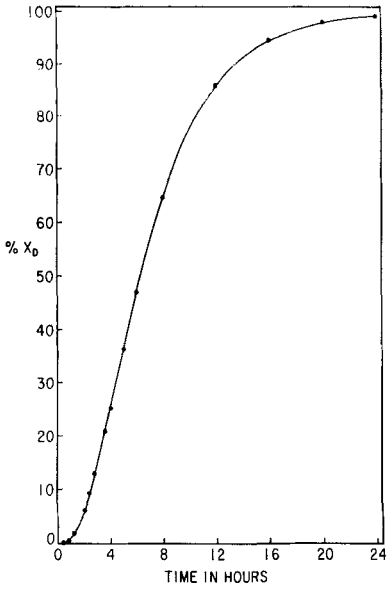


Fig. 1—The $\%X_D$ against time, t, plot for example 1. The points correspond to the cumulative per cent of the metabolite excreted to the end of the simulated urine collection periods at 0.4, 0.8, 1.2, 2, 2.4, 2.8, 3.6, 4, 5, 6, 8, 12, 16, 20, and 24 hr.

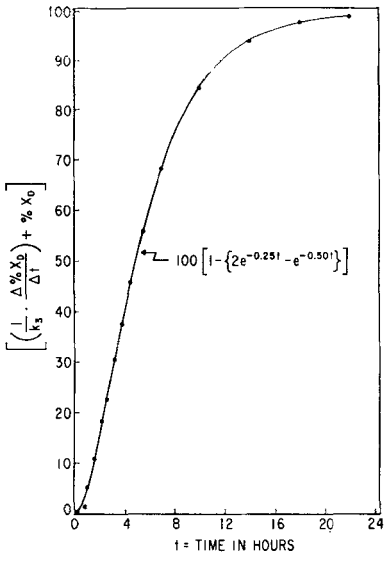


Fig. 3—A plot of the cumulative amount of metabolite formed against time for example 1. The points are the Y,T values listed in Table I from which the estimates of the rate constants were made. The line shown on the plot is the theoretical line for the model and assignments of the rate constants.

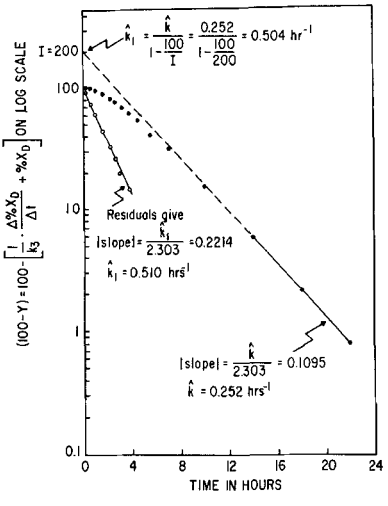


Fig. 2—Illustrating the semilogarithmic plots of (100−Y) and the residuals, R, against the midpoint, T, for example 1.

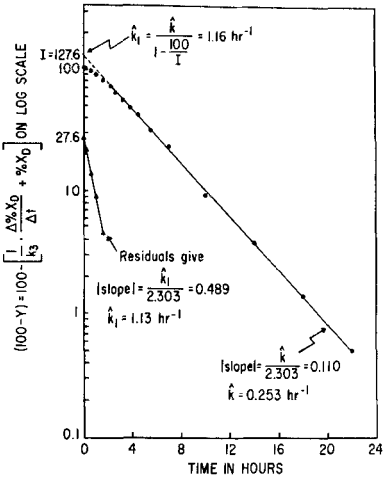


Fig. 4—Illustrating the semilogarithmic plots of (100−Y) and R against T for example 3.

on this plot will be derived from excretion rates which are relatively small in magnitude and which arise from urine collections obtained very late in the study and, hence, contain very little metabolite, if the ratio of the rate constants k_1 and k is between 1 and 3. The curvature of the points on the plot will indicate when this is the case. Assay error and the sensitivity of the assay will greatly affect the terminal points in these cases. The tendency will be for these inaccurate points to lie below the proper terminal line. The same problem exists in estimating the smallest of any two or more rate constants from the tail and of any type of semilogarithmic plot when the rate constants are within a factor of about 3 of each other. When applying the method to semilogarithmic $(100 - Y),T$ plots which have significant curvature, it is wise to make one, two, or more estimates of where the terminal line should be drawn and compare the results with other knowledge available about the particular system with which one is working.

It should be noted that the cumulative curves of

Figs. 1 and 3 arise from exponential equations only, *i.e.*, there are no zero-order rate constants involved. The curves are nearly linear for almost 50% of the ordinate scale. This phenomenon, and its implications in relation to recent publications concerning parallel zero-order and first-order kinetics (2, 4) will be the subject of a separate publication (6).

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Quantitative Evaluation of the Heat-Stabilizing Properties of Organotin Compounds in Rigid Polyvinyl Chloride Using Differential Thermal Analysis

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Rigid polyvinyl chloride bottles are in current use in Europe for a host of products including foods, drugs, and cosmetics. In this country, a number of pharmaceutical and cosmetic firms are exploring the possibilities of this plastic container for packaging of one or more products. Presently, a number of vinyl systems are effectively stabilized against thermal and radiation degradation by the use of organotin compounds. In order to ascertain the efficiency of organotins to stabilize rigid vinyls, a quantitative study was undertaken on a series of vinyl formulations containing various organotin compounds using differential thermal analysis. These techniques proved to be extremely helpful in evaluating the materials from both a qualitative and quantitative point of view. Furthermore, the same techniques appear to have great promise in predicting the most suitable plastic formula for achieving the most stable plastic item when thermal or radiation damage becomes a potential problem.

ONE OF THE most widely used polymers in the medical science field is polyvinyl chloride (PVC). Its primary application has been in the construction of blood bags, surgical tubings, containers for biological products, catheters, and a host of other items. As is well established, vinyl resins are inherently unstable materials and are prone to thermal and oxidative degradation (1). This instability is primarily due to the imperfections and anomalies on the polymer chain, such as unsaturated chain endings and chain branching and to certain incorporated oxygen functions such as hydroperoxy groups. During the heat processing and throughout the active life of the polymer, these structural abnormalities will be the initiating points of the degradation process. In 1936, Yngve discovered that certain organotin compounds proved effective in minimizing the deterioration of PVC (2). During the past 20 years hundreds of structurally modified organotin compounds have been used as PVC heat and light stabilizers. Much has been written on their mode of action, but even up to the present time no generally agreed theory has evolved.

Within the past several years, great commercial interest has been shown in the development of the clear, colorless, rigid polyvinyl chloride bottles which now enjoy a great deal of success in Europe as food and drug containers. Generally, it has been found that the organotin compounds are the most efficient stabilizers for the clear, colorless bottles, even though some question of toxicity may be raised if the organotin compound would be leached into a product (3). Extraction tests following generally accepted procedures, however, have demonstrated that the rigid vinyls have little propensity to release a constituent to an extracting medium, and thus the safety of the bottle may be quite acceptable for any intended drug or cosmetic use.

Since the stabilizers play a key role in producing an acceptable rigid polyvinyl chloride, and since the organotins appear to be in general the most suitable stabilizers, it was decided to undertake a study using differential thermal analysis to evaluate which of a group of organotin compounds might give the greatest protection against thermal degradation. As will be demonstrated, differential thermal analysis proved

Received October 4, 1966, from the Drug-Plastic Research and Toxicology Laboratories, College of Pharmacy, University of Texas, Austin, TX 78756
Accepted for publication December 15, 1966.
Presented to the Drug Standards, Analysis and Control Section, A.PH.A. Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.
This investigation was supported by contract PH 43-64-557 from the Division of Biologics Standards, National Institutes of Health, U.S. Public Health Service, Bethesda, Md.