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LINEAR NONISOTHERMAL ACCELERATED KINETIC STUDY: A NEW DATA TREATMENT METHOD

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ABSTRACT

A new data treatment method for the linear non-isothermal accelerated kinetic study is presented and discussed. Besides being simple and straightforward, the method involves no assumptions. Important kinetic parameters can be rapidly determined for stability assessment purpose. When this method is compared with two other data treatment methods, while being able to provide equally satisfactory results, this new method offers the advantages of placing equal weights on all data points and requiring only a single numerical integration.

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INTRODUCTION

A linear nonisothermal accelerated kinetic study is a study in which drug degradation is monitored when the temperature of the system is being increased at a predetermined constant rate. This method was first developed by Zoglio et al. (1). The method provides, in a single experiment, important kinetic parameters for the stability characterization of the system. The disadvantage of using a linear temperature-time program in such a study is that the rate equation does not provide an analytical solution after integration for easy data treatment. Rather, the method resorts to the computer for data treatment. In this aspect, this method is inferior to the nonisothermal kinetic methods using nonlinear temperature-time programs (2-4).

This paper describes an alternative rapid data treatment method for the linear nonisothermal kinetic method.

THEORETICAL

In a linear nonisothermal accelerated kinetic study, the temperature of the system is increased at a predetermined constant rate according to the following temperature-time program:

$$T = T_o + ct \qquad \text{Eq.1}$$

where T_o is the initial temperature, T is the temperature at time t, and c is the heating rate constant.

For a first order degradation,

$$-dC/dt = kC \qquad \text{Eq.2}$$

where C is the drug level at time t and k is the rate constant. The rate constant in a nonisothermal kinetic study is no longer a constant. Rather, it is a function of time t. When the Arrhenius relationship is applicable, k can be expressed in terms of the rate constant at T_o (k_o):

$$k = k_o \exp\left[\frac{E}{R}\left(\frac{1}{T_o} - \frac{1}{T}\right)\right] \qquad \text{Eq.3}$$

where E is the activation energy of the degradation and R is the gas constant.

Subsitution of Eq.1 and Eq.3 into Eq.2, followed by rearrangement and integration:

$$\ln\frac{C_o}{C} = k_o \int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_o} - \frac{1}{T_o+ct}\right)\right]dt \qquad \text{Eq.4}$$

where C_o is the initial drug level. Eq.4 is the basis of the method to be discussed in this paper. The integral in Eq.4 can be solved, but the solution does not provide a basis for easy data treatment such as demonstrated by Rogers (2) and Eriksen et al. (4). Rather, this integral can be evaluated by a numerical integration method for a known temperature-time program and an E value. A set of k_o values can be computed for the corresponding experimentally determined C values. Different E values are

used until the calculated k_o values are relatively constant.

A general expression of Eq.4 can be given to accommodate different kinetic orders:

$$f = k_o \int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_o} - \frac{1}{T(t)}\right)\right] dt \qquad \text{Eq.5}$$

where T(t) is the temperature-time program and the function f is C_o-C for the zero order, $\ln(C_o/C)$ for the first order and $1/C - 1/C_o$ for the second order.

Data reported previously were used to demonstrate the validity and the application of this new data treatment method.

RESULTS AND DISCUSSION

Figure 1 shows the exponential expression in Eq.4 as a function of time. The trapezoidal approximation method was found to be appropriate to estimate the integral (area under curve) in Eq.4.

Table I lists the results obtained using Eq.4. The arithmetic means of the calculated k_o values are presented or are used to calculate the rate constant at other temperature in conjunction with the calculated activation energy. As shown, the values of k_o and E calculated using Eq.4 agree well with previously published results.

Eq.4 is applicable not only to the nonisothermal study employing the linear temperature-time program

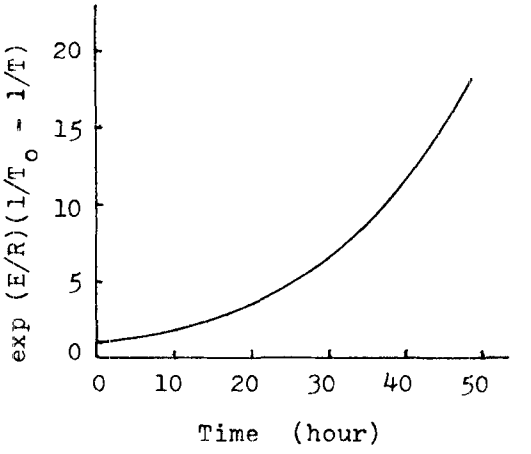

FIGURE 1

The exponential term in Eq.4 as a function of time. Shown here is for the degradation of procainamide HCl under the nonisothmal condition in reference 1 with E=13 kcal/mole.

(N-acetyl-p-aminophenol and procainamide HCl), but also to a special case of the linear nonisothermal study (substituted benzazepine) and a nonisothermal study employing a nonlinear temperature-time program (riboflavin).

Three data treatment methods have been previously described. Zoglio et al. (1) used the following equation for the data treatment:

$$\frac{g(t_f)-g(t_o)}{t_f-t_o} = \frac{k_i}{n}\left\{1+\sum_{\substack{j=0\\ j\neq i}}^{n-1} \exp\left[\frac{Ec}{R}\sum_{\substack{m=0\\ m\neq i}}^{j}(T_m T_{m+1})^{-1}\right]\right\} \qquad \text{Eq.6}$$

where i=0,1,...,n-1 and n is the number of the time intervals between t_o(initial time) and t_f(final time).

TABLE I

Estimated Kinetic Parameters from the Nonisothermal Study

Compound[a]	$k_o(hr^{-1})$	E(kcal/mole)	Reference
N-acetyl-p-aminophenol	0.000178 (35°)	17	This paper
	0.000195 (35°)	17	1(Nonisothermal)
	0.000252 (35°)[b]	16.7	5(Isothermal)
Procainamide HCl	0.0000113 (35°)	27	This paper
	-	29	1(Nonisothermal)
	-	27	1(Isothermal)
Substituted Benzazepine	0.000183 (40°)	14	This paper
	-	14.8	6(Nonisothermal)
	0.000168 (40°)[b]	14.5	6(Isothermal)
Riboflavin	0.017 (20°)[c]	21	This paper
	0.017 (20°)[d]	21	This paper
	0.018 (20°)[e]	20.4	7(Nonisothermal)

a. All compounds undergo first order degradation.
b. Calculated from isothermal data.
c. Calculation was based on a liear temperature-time regression function:
$T = 295.381 + 22.841t$ (r=0.999)
d. Calculation was based on a polynomial temperature-time regression function:

$$T = 294.15 + 41.807t - 126.215t^2 + 350.1095t^3 - 464.398t^4 + 316.695\ t^5 - 107.325t^6 + 14.304t^7.$$

e. Calculated from the data in reference 7.

The function g is defined as C for the zero order and ln C for the first order. The values of k_o through k_{n-1} can be calculated using Eq.6 for a particular n value. The appropriate n value is determined by a convergence test. These k values can then be employed to construct a family of theoretical degradation curves against which the experimental data are compared. No criterion for judging the fitness betwwen the experimental and the theoretical was mentioned by Zoglio et al. (1). Edel et al. (6), employing the same data treatment method, used the least sum of square of the difference between the experimental values and the theoretical values as a criterion. It was shown (Figure 2 and 3 in reference 1) that the theoretical degradation curves are close to each other, especially for those curves with larger activation energy. Without such a criterion, it may be difficult to treat the data objectively. When Eq.4 is used, the standard deviation of the calculated k_o values is found to be an appropriate criterion for such purpose. A minimum standard deviation is sought. Figure 2 shows a typical plot of the standard deviation of the calculated k_o values against the activation energy. Outside the activation energy range plotted, the trend of increasing or decreasing k_o values is quite apparent. These data are therefore not included in the figure.

The computation time using Eq.6 is long. Six hours were required as reported by Edel et al. (6). Since all

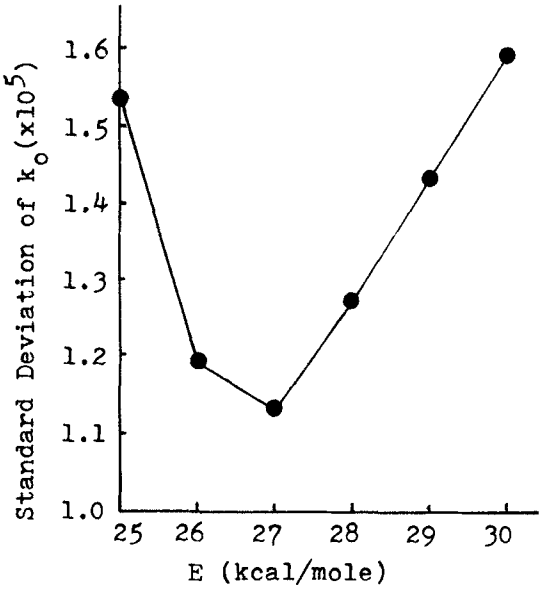

FIGURE 2

The standard deviation of calculated k_o values as a function of the activation energy. Shown here is for the degradation of procainamide HCl under the nonisothermal condition in reference 1.

k values are calculated based on the initial and the final assay results according to Eq.6, the method therefore suffers by placing heavy weights on these two data points. A later publication (8) has simplified the method by obtaining only k_o value using Eq.6 and calculating the remaining k values by the Arrhenius relationship. However, it still suffers the same problem. Kay et al. (9) suggested that an isothermal study be performed at the initial

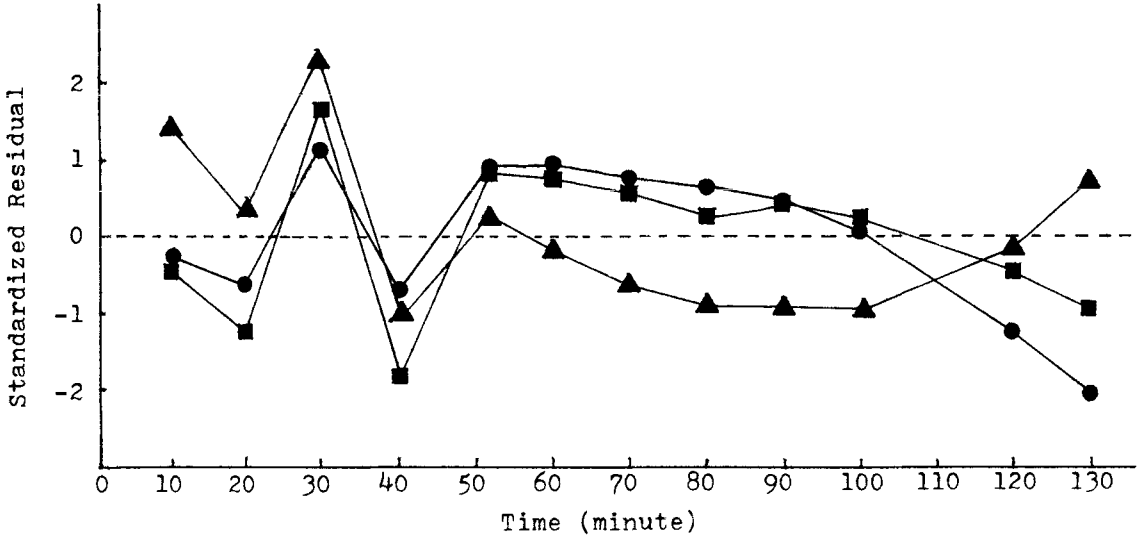

FIGURE 3

Residual plots of the hydrolysis of riboflavin for different kinetic orders. The standardized residual is calculated using : standardized residual = (calculated k_o value - mean k_o value)/(standard deviation of k_o). ● zero order ■ first order ▲ second order

temperature to derive a better estimation for k_o for the subsequent data treatment.

A data treatment method using an analog computer was demonstrated to provide results which are in excellent agreement with those reported by Zoglio et al. (9).

Madsen et al. (7) employed an iterative least-square regression method to minimize:

$$SS = \sum_{i=1}^{n} (C_i - \hat{C}_i)^2 \qquad \text{Eq.7}$$

where C_i is the observed drug level and $\hat{C}_i$ is the corresponding predicted drug level. The term $\hat{C}_i$ is defined by:

Zero oder	$\hat{C}_i = C_o - PI_i$	Eq.8
First order	$\hat{C}_i = C_o \exp(-PI_i)$	Eq.9
Second order	$\hat{C}_i = (C_o^{-1} + PI_i)^{-1}$	Eq.10

where P is the preexponential factor in the Arrhenius relationship and I_i is expressed as:

$$I_i = \int_{t_o}^{t_i} \exp(-E/RT)\, dt \qquad \text{Eq.11}$$

The integral I_i can be evaluated using the trapezoidal rule.

Note that using this mehtod, P and E are estimated. While the values of k_o and E are estimated by the new method described in this paper. However, both methods provide sufficient information for stability assessment purpose. As can be seen in Table I both methods give comparable results. In addition to the polynomial tem-

perature-time function as used by Madsen et al., the temperature-time program described in reference 7 can also be satisfactorily described by a linear function. Table I shows that data treatment using such a linear temperature-time function also gives comparable results.

One shortcoming of using Eq.7 is that initial estimates of P and E are required for the data treatment. However, this is easily compensated by the automatic computer calculation.

The method based on Eq.6 requires that the reaction order be known in advance. The method was subsequently modified to overcome this shortcoming by adding an isothermal study at the terminal temperature of the non-isothermal stage (10). This author is quick to point out such an isothermal study must be allowed to proceed over a sufficiently long period of time to enable one to unequivocally determine the reaction order. The isothermal data is Figure 2 in refernece 10 (from 2 to 3 hours) also give an equally satisfactory straight line when treated as zero order kinetics or second order kinetics.

The method based on Eq.7 was claimed to be sensitive to the reaction order (7). A residual plot was used to determine the reaction order. Figure 3 is a similar residual plot for the hydrolysis of riboflavin using the results calculated by the new method in this paper. These residual plots are essentially equivalent and thus

Table II

Estimated Kinetic Parameters Using the Method in This Paper

	Zero order	First order	Second order
k_o	$0.00000238 M \cdot hr^{-1}$	$0.0231 hr^{-1}$	$172.5 M^{-1} hr^{-1}$
E (kcal/mole)	19	21	26
P	$3.17 \times 10^{8} M \cdot hr^{-1}$	$9.45 \times 10^{13} hr^{-1}$	$3.68 \times 10^{21} M^{-1} hr^{-1}$

can not be used to determine the reaction order. Table II shows the values of the kinetic parameters calculated for degradation with different order. The same situation can also be demonstrated for the other three cases listed in Table I. This discrepancy may lie in the fact that absorbance values, instead of concentrations, were used in the calculation using Eq.7 in reference 7. The use of absorbance values or concentration is expected to give different results (except for the first order) when Eq.7 is used. This can be explained as follows. When Beer's law is applicable:

$$A = abC \qquad \text{Eq.12}$$

where A is the absorbance, a is the absorptivity, b is the path length and C is the concentration. For a given analysis, the product ab is a constant.

Subsitution of Eq.8-12 into Eq.7 results in:

$$\text{Zero order} \quad SS/(ab)^2 = \sum_{i-1}^{n} [A_i - A_o + PI_i/(ab)^2]^2 \qquad \text{Eq.13}$$

$$\text{First order } SS/(ab)^2 = \sum_{i-1}^{n} [A_i - A_o \exp(-PI_i)]^2 \quad \text{Eq.14}$$

$$\text{Second order } SS/(ab)^2 = \sum_{i-1}^{n} [A_i - (PI_i/ab + 1/A_o)^{-1}]^2 \quad \text{Eq.15}$$

where A_i is the absorbance at time t and A_o is the initial absorbance. When dealing with the first order, the use of absorbance or concentration should give the same results since when $SS/(ab)^2$ in Eq.14 is minimized so is SS in Eq.7. While the same is not true when the zero order or the second order is involved.

CONCLUSION

A new data treatment method for the linear non-isothermal accelerated kinetic study is presented. The advantages of this new method are:

1. No assumption is made.
2. All data points are equally weighed.
3. No initial estimates of kinetic parameters are required.
4. It is mathematically simple and straightforward and requires only one numerical integration step.
5. It is applicable to the nonisothermal study employing linear and nonlinear temperature-time programs.

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