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Nonisothermal Kinetics with Programmed Temperature Steps

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Abstract □ Data required for predicting the stability of an active principle in solution can be obtained by two kinetic methods. With the isothermal method, the degradation rate constants are determined at different temperatures, which are kept constant throughout the experiment. With the nonisothermal method, the temperature is increased with time. This paper describes a nonisothermal kinetic method in which the temperature is increased in consecutive equal steps. The results are compared with those obtained by the conventional isothermal method. The values for the activation energy are approximately the same by both methods. Although the technique of nonisothermal kinetics demands sophisticated equipment and high experimental accuracy, it provides a continuous picture over a wide temperature range.

Keyphrases □ Stability—prediction, nonisothermal kinetic method, programmed temperature steps, comparison with isothermal kinetic method □ Drug degradation kinetics—nonisothermal method, programmed temperature steps, comparison with isothermal kinetic method □ Kinetics, degradation—nonisothermal method, programmed temperature steps, comparison with isothermal kinetic method

Degradation kinetics usually are studied under isothermal conditions by determining the reaction rate constant at different temperatures. These temperatures generally are fairly high and are kept constant throughout the experiment; in nonisothermal kinetic studies, the temperature changes continuously with time. Several such methods have been described, with the essential difference between them being the equation for the time–temperature relationship (1–3).

Calculations using a continuous temperature increase were carried out previously *via* a multistep model (3). Study of an experimental model with a stepwise temperature profile then was desired. This paper describes the application of nonisothermal kinetics in which the temperature is raised discontinuously in consecutive equal steps, whose number and duration are predetermined. The results are compared with those obtained in conventional isothermal kinetic studies.

EXPERIMENTAL

The investigation was carried out using an active principle, a substituted benzazepine, as a 0.2% solution in pH 5 buffer–ethanol (60:40). This pH was chosen to give appreciable degradation in a relatively short time[1].

The solution of the active principle was introduced into ampuls, which then were sealed and immersed in a thermostatically controlled bath[2] of glycerol–water. At predetermined times coinciding with the end of a temperature stage, ampuls were removed to determine the remaining amount of active ingredient. This determination was done by high-performance liquid chromatography (HPLC) or by spectrophotometry after separation by TLC followed by elution.

TLC—Plates precoated with silica gel and an indicator[3] were used as the stationary phase. The mobile phase was chloroform—ethanol–concentrated ammonia (90:10:0.8). The plates were developed to 12 cm. UV detection was performed at 254 nm with the use of Dragendorff's reagent and peroxide for visualization of degradation after elution.

The R_f values were 0.5 for the active principle and 0.4, 0.7, and 0.9 for the degradation products. After development, the spot corresponding to the unchanged active principle was eluted[4] with 2.50 ml of solvent

[1] M. O. Baltzer, unpublished results.
[2] Model FP thermostat, Haake.
[3] G 1500/LS 254, Schleicher and Schuell.
[4] Eluchrom apparatus, Camag.

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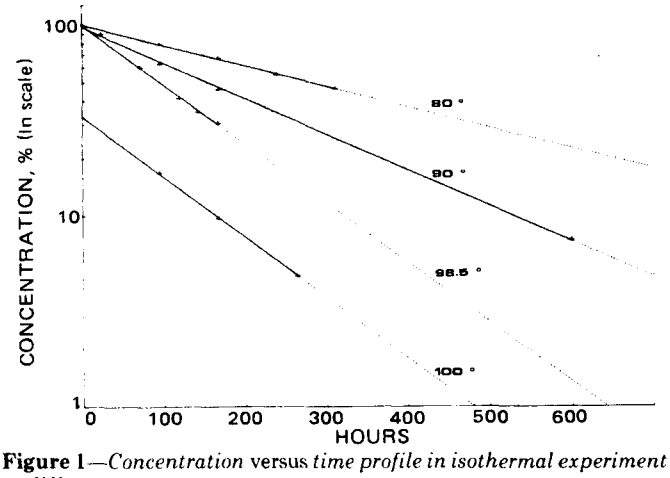

Figure 1—*Concentration* versus *time profile in isothermal experiment at different temperatures.*

(methanol–10% concentrated ammonia). A UV absorption spectrum of this solution was recorded between 200 and 320 nm with a spectrophotometer[5] linked to a recorder[6]. The value was measured at the extinction maximum of 230 nm. The recovery was 97%.

The values are the means of five samples from one ampul. A calibration curve was prepared under the same conditions. The equation was $y = 0.0726x + 0.0111$ ($r = 0.9995$) for concentrations between 1 and 9.5 μg/ml.

HPLC[7]—The stationary phase was Lichrosorb Si 100, 5 μm in a column of 10 cm length and 0.46 i.d. The mobile phase was 95% ethanol–methanol–saturated ammonium carbonate solution (900:100:0.4). A pump[8] maintained the flow rate at 1.5 ml/min with a pressure of ~175 × 10^5 Pa. The chart speed of the recorder[9] was 1 cm/min. The UV detector[10] wavelength was set at 230 nm. The sample loop of the injector[11] had an injection volume of 20 μl. The peak area was obtained by an integration system[12] connected to the detector.

The values are the means of three injections obtained after diluting the sample to give a concentration of unchanged active principle approximating that of the calibration curve. The equation was $y = 0.0258x + 0.0174$ ($r = 0.9999$) for injections from 0.2 to 6 μg.

The kinetic test at 100° carried out using TLC also was performed using HPLC and gave concentrations of 33.7, 19.6, 10.68, and 5.2% at 0, 96, 168, and 264 hr, respectively. These values are close to those shown in Fig. 1. This fact indicates the equivalence of the two methods.

Nonisothermal Temperature Programming—A programmer[13] was used to control the rise of temperature in the bath. This system enables the bath temperature to be altered automatically stepwise from a preset starting temperature over a range of 115° at 10 rates. The kinetic experiments were carried out between 40 and 97.6° in consecutive equal steps, which in this case were temperature changes, ΔT, of 0.3° every 3 hr (Fig. 2). The temperature was increased by 0.3° quickly at the beginning of each step and was kept constant for the remainder of the step time.

RESULTS

Nonisothermal Kinetics—Zoglio *et al.* (3) used a linear progression for temperature. The degradation curve, $f(C)$, is described by a series of straight lines (where the time interval during which the temperature remains constant is reduced) whose individual slopes (or rate constants), k_i, represent the instantaneous degradation rate at a given moment (or temperature). The shorter this time interval, the greater is the chance of the curve being linear in this interval. (For first-order reactions, the curve is log concentration as a function of time.)

This method is based on the hypothesis that the arithmetic mean of these rate constants is equal to the ratio of total degradation, $f(b) - f(a)$,

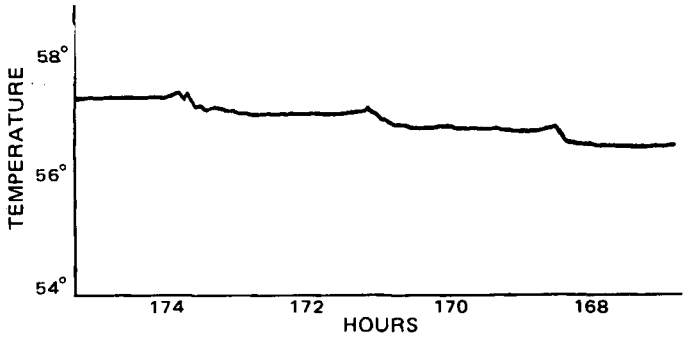

Figure 2—*Section of the experimental temperature profile.*

for the duration of the experiment, $b - a$:

$$\frac{f(b) - f(a)}{b - a} = \frac{k_1 + k_2 + \ldots + k_i + \ldots + k_n}{n} \qquad \text{(Eq. 1)}$$

The size of n is fixed to minimize the error.

The temperature programming in the present experiment represents a special case of this theory. The hypothesis according to which each interval can be described by a straight line becomes a reality. Each temperature stage can be regarded as a miniature isothermal kinetic model. For each step, the degradation is represented by a straight line whose slope corresponds to the rate constant at that temperature. The error due to the time required to raise the temperature between each stage can be regarded as negligible. The equation for the degradation is:

$$\ln C - \ln C_0 = \frac{t}{n}(k_1 + k_2 + \ldots + k_i + \ldots + k_n) \qquad \text{(Eq. 2)}$$

To solve this equation for any rate constant, the constant must be expressed in terms of all of the other constants in the equation. For constant k_i:

$$k_i = Ae^{-E(RT_i)^{-1}} \qquad \text{(Eq. 3)}$$

For constant $k_i + 1$:

$$k_{i+1} = Ae^{-E(RT_{i+1})^{-1}} \qquad \text{(Eq. 4)}$$

By dividing Eq. 4 by Eq. 3, the following expression is obtained:

$$k_{i+1} = k_i e^{E/R[(T_{i+1}-T_i)(T_iT_{i+1})^{-1}]} \qquad \text{(Eq. 5)}$$

Because the increment $T_{i+1} - T_i$ is constant and equal to ΔT, the solution for k_{i+2} with respect to k_i becomes:

$$k_{i+2} = k_i e^{E/R[\Delta T(T_{i+1}T_i)^{-1}]}\, e^{E/R[\Delta T(T_{i+2}T_{i+1})^{-1}]} \qquad \text{(Eq. 6)}$$

In the same way, each constant can be expressed with respect to k_i. The corresponding expressions can be substituted for the values of k_1 to k_n in Eq. 2.

If $k_1 = k_i$, then:

$$\ln C - \ln C_0 = k_1 \frac{t}{n}(1 + e^{E/R[\Delta T(T_1T_2)^{-1}]} + e^{E/R[\Delta T(T_1T_2)^{-1} + \Delta T(T_2T_3)^{-1}]} + \ldots + e^{E/R[\Delta T(T_1T_2)^{-1} + \ldots + \Delta T(T_{n-1}T_n)^{-1}]}) \qquad \text{(Eq. 7)}$$

or:

$$\ln C - \ln C_0 = k_1 \frac{t}{n}\left(1 + \sum_{m=1}^{n-1} \exp\left[E/R\ \Delta T \sum_{i=1}^{m} (T_iT_{i+1})^{-1}\right]\right) \qquad \text{(Eq. 8)}$$

Once the values of $\ln C - \ln C_0$ and t/n are determined experimentally, k_1 can be calculated for any activation energy.

Equations similar to Eq. 8 can be derived and solved for the constants k_2 to k_n in the same way. These constants then are used to plot the theoretical curves [$\ln C = f(t)$] for different activation energies using a scale that corresponds to the order of the degradation reaction (which must be determined).

Since extremely lengthy calculations are needed to solve these equations, a program was elaborated that enables the problem to be solved on a computer[12]. (Automatic calculation takes ~6 hr.) For a first-order reaction and for a particular activation energy, this program calculates (with the aid of Eq. 8) the k' value corresponding to the first temperature stage. With this value, it then is possible to determine the theoretical concentration at the end of this stage, which also is the concentration at the beginning of the next stage. By substituting the values of the con-

[5] Model SP 1800, Pye Unicam.
[6] Model AR 25, Pye Unicam.
[7] J. Meier and C. Morin, Sandoz Ltd., Basel, Switzerland, personal communication.
[8] Model 110, Altex.
[9] Model 312, W + W.
[10] Model LC 55, Perkin-Elmer.
[11] Model 7120, Rheodyne.
[12] System 3354, Hewlett-Packard.
[13] Model PG 12, Haake.

Table I—Values Obtained by Nonisothermal Conditions [a]

Hours	Percent of Unchanged Substance	ln C
0	100	4.60517
72	97.47	4.57954
144	94.95	4.55335
192	93.95	4.54276
240	91.60	4.51743
312	85.59	4.44957
360	73.06	4.29128
408	71.70	4.27249
480	58.37	4.06680
528	48.36	3.87867
576	35.61	3.57263

[a] Number of stages, n, = 576/3 = 192.

centration and initial temperature in the first stage with those in the second stage and by substituting n with the number of stages remaining, an analogous computation gives the k value corresponding to the second stage and so on to the last one.

The concentrations calculated theoretically are compared with the concentrations obtained experimentally. The value taken for the activation energy then is altered until the calculated concentrations approach the experimental data. Progressively smaller adjustments evaluate the activation energy at best fit to the nearest 100 J. When the sum of the squares of the difference between the experimental values and the theoretical values at the same moment is a minimum, the corresponding activation energy is regarded as the activation energy of the reaction. The constant of the Arrhenius equation is determined at the same time.

Quantitative analysis of the ampul produced the results shown in Table I over 576 hr. Automatic computation of the activation energy after scanning between 40,000 and 70,000 J yielded E = 62.2 kJ/mole. Although this value is purely arbitrary since the n value used corresponds to an actual number of temperature stages during which it remained constant, the same calculation also was performed with n twice the size, and there was no appreciable modification in the activation energy.

The theoretical degradation curves for each activation energy (Fig. 3) were plotted with the concentration values for each ΔT interval given by the computer. The points corresponding to experimental values also were plotted on the graph. One point is marked to show the considerable effect that an error of ±1% can have on the concentration at a given moment.

Isothermal Kinetics—Degradation kinetics were performed isothermally at 80, 90, 98.5, and 100° (Fig. 1). The reaction order was checked in each case as a function of time; the graph of C, ln C, and C^{-1} *versus* t is a straight line for zero-, first-, and second-order reactions, respectively, where C is the concentration of unaltered active ingredient.

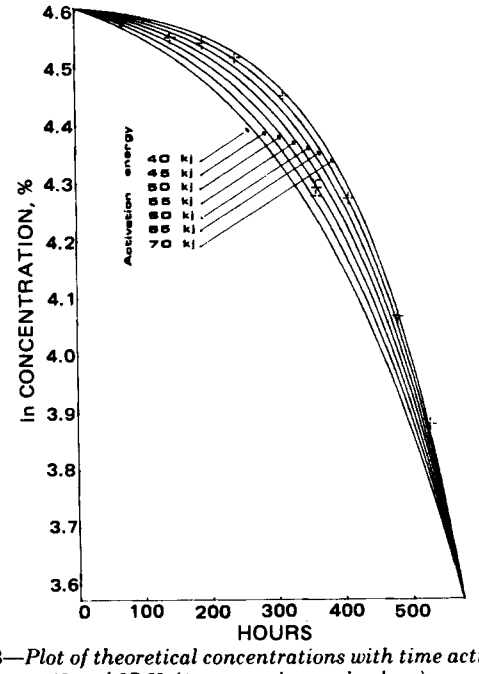

Figure 3—*Plot of theoretical concentrations with time activation energy between 40 and 97.6° (+ = experimental values).*

Table II—Correlation and k Values at Different Temperatures

Parameter	80°	90°	98.5°	100°
Correlation	0.9992	0.9994	0.9989	0.9997
$k \times 10^5$, hr^{-1}	248	431	716	728

When the linear regression was calculated on a programmable computer[14], the best correlation coefficient was obtained for a first-order reaction at the four temperatures. Therefore, the equation for calculating the degradation rate constant is:

$$C = C_0 e^{-kt} \qquad \text{(Eq. 9a)}$$

or:

$$\ln C = \ln C_0 - kt \qquad \text{(Eq. 9b)}$$

where k is the slope of the regression line (Table II).

With the Arrhenius equation, $k = Ae^{-E/RT}$, the graph of ln k as a function of T^{-1} is a straight line with a slope of $-E/R$ (Fig. 4). Calculation of the regression line of ln k as a function of T^{-1} at 80, 90, 98.5, and 100° gave a correlation coefficient of 0.9999. The equation for the straight line was ln k = 14.6 − 7290 T^{-1} in which ln A = 14.6 and E/R = 7290 °K. The activation energy was E = 60.6 kJ/mole.

DISCUSSION AND CONCLUSION

The value for activation energy obtained by the nonisothermal method was similar to that obtained by the isothermal method (62.2 and 60.6 kJ/mole). Therefore, the two methods may be regarded as equivalent with respect to their results. However, they generally are suitable only when the activation energy and the reaction order remain constant throughout the experiment, *i.e.*, the Arrhenius relationship is valid in the particular case.

Given these conditions, the major limitation of the nonisothermal procedure seems to be the experimental accuracy. This limitation is demonstrated by the fact that if the experimental points are measured inaccurately, the experimental and the theoretical degradation curves intersect in too broad a range of activation energies and this effect soon leads to a considerable scattering of the results. To control the experimental accuracy, it is essential to complement the computation by plotting the theoretical curves corresponding to each activation energy to compare them with the experimental curve. It also is necessary to have a prior idea of the degradation rate to select a suitable temperature program; this planning avoids alteration during the experiment.

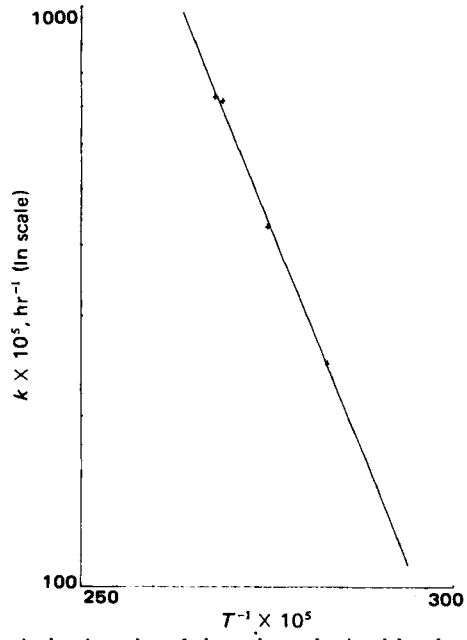

Figure 4—*Arrhenius plot of the values obtained by the isothermal experiment.*

[14] Model 9810 A, Hewlett-Packard.

One advantage of the method is that it examines a wider temperature range than does the isothermal kinetic method. Provided that the tests are sufficiently accurate, it is possible to detect any activation energy change.

Since three temperatures stages and three durations for each stage generally are considered as a minimum for isothermal kinetic studies, the nonisothermal method does not appear to offer any decisive advantage. The definitive need for more sophisticated equipment (temperature programmer, computer, and plotter) is a disadvantage. On the other hand, the nonisothermal method may lead to more precise results with less experimental effort, *e.g.*, data points. Furthermore, it requires only a fraction of the time an isothermal experiment does. Selection of a method depends on the equipment and the time available.

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Time and Temperature Dependence of Disintegration and Correlation between Dissolution and Disintegration Rate Constants

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Abstract □ Commercial prednisone tablets were subjected to dissolution tests by USP basket and paddle methods. It was found experimentally that disintegration adheres to an exponential decay law: $\ln(W/W_0) = -d(t - t_i)$, where W is the nondisintegrated weight, d is a disintegration constant, t is time, and t_i is a lag time. Dissolution has been reported to adhere to a similar law, where the dissolution constant, K, follows a pseudo-Arrhenius relationship with changing temperature. Within a certain temperature range, this relationship also exists for the disintegration rate constant, d. A correlation exists in these tablets between K and d. The shaft length in the dissolution apparatus plays a part in the disintegration (and hence dissolution) rate and, therefore, is an important apparatus parameter affecting reproducibility.

Keyphrases □ Disintegration—commercial prednisone tablets, time and temperature dependence, correlation between dissolution and disintegration rate constants □ Prednisone—commercial tablets, time and temperature dependence of disintegration, correlation between dissolution and disintegration rate constants □ Dissolution—commercial prednisone tablets, time and temperature dependence of disintegration, correlation between dissolution and disintegration rate constants

Several recent articles correlated two- or three-component dissolution model parameters with those of disintegration in the same apparatus. These studies were aimed at elucidation of the type of dissolution curve obtained in dissolution experiments both for control and for research purposes. The curves usually are *s*-shaped. Wagner (1) and Wood (2) first recognized the importance of this type of curve, and a probit and a Weibul function were suggested later as a descriptive means (1–4).

Several investigators demonstrated that disintegration and dissolution in an apparatus can be correlated and that these factors lead to *s*-shaped curves (5–11). Carstensen *et al.* (7, 8) suggested that the best general trial function is one in which the weight of undisintegrated tablet is monitored as a function of time. The dimensions of the tablets remaining (such as thickness) as a function of time can be useful in certain cases; but since many tablets swell on contact with water, the functions become complicated. Furthermore, the thickness of a swelling, disintegrating tablet is difficult not only to monitor but also to define.

The simplest model of weight *versus* time that appears compatible with experimental data (8) is a simple exponential decay function. Double exponentials may apply in more complicated systems. This model has been recognized in compendial work, and disintegrating dissolution calibrators have been suggested. This article presents data showing the disintegration–dissolution behavior of a conventional prednisone tablet.

Excellent research and review articles regarding the mechanism of disintegration have been published (12–14), and the effect of temperature on dissolution has been elucidated (15). This article reports the dependence of tablet disintegration on temperature and also the effect of the length of the stirring shaft on dissolution.

EXPERIMENTAL

Commercial prednisone tablets were assayed and found to contain starch, lactose, metallic stearate, and prednisone. Two 20-mg tablets were placed in the basket of a USP basket dissolution apparatus in a thermostated bath. The apparatus was operated at 150 rpm. This agitation speed was chosen because problems with liquid homogeneity exist at lower rotational speeds (9). Samples were taken routinely at appropriate time intervals and, after filtration[1], were assayed using the spectrophotometric absorbance at 242 nm. The amount of prednisone then was determined by comparison with a standard curve of prednisone obtained with a USP reference standard. The experiment was repeated using a different shaft length (Fig. 1), *i.e.*, assembling the shaft onto the motor such that the length of free shaft was different from that first used. The two shaft "lengths" used are denoted as positions I and II (Fig. 1).

A set of experiments was performed (in both positions) to establish the disintegration rate of the tablets in the apparatus. These experiments were done as follows (6, 7). An experiment was carried out for t_i min and then was stopped. The basket was lifted out, and the tablets were removed and dried to constant weight, W, at 100°. This weight was compared with the weight, W_0, of a similarly dried tablet prior to the dissolution test. The experiment then was repeated for other t_i values.

The experiments were repeated using a USP paddle apparatus at 150 rpm. Experiments were carried out at 10, 20, and 30° for the paddle apparatus and at 0, 5, 10, 15, 20, 30, and 37° for the basket apparatus.

[1] Millipore filter.

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