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Research Article

Kinetics of Drug Decomposition by Heat Conduction Calorimetry

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The application of heat conduction calorimetry to the determination of decomposition mechanisms and rates for drugs is shown to be a rapid and generally useful method. The application of the method to determine the nature of the decomposition reaction, sources of systematic errors in the method, the equations relating the calorimetric signal to the kinetics of the reaction, and some examples of results are presented and discussed.

KEY WORDS: microcalorimetry; Lovastatin; decomposition; thermodynamics; oxidation; kinetics.

INTRODUCTION

Determination of the kinetics of decomposition of drugs at room temperature is a difficult problem (1–5). Reaction rates as low as a few percent per year are of significance in calculating shelf life. Since it is usually impractical to wait for several years to obtain results, kinetic measurements are usually made at elevated temperatures and then the results are extrapolated to room temperature by the use of an activation energy derived from the elevated temperature data (6). This elevated temperature method is valid only if the mechanism of the reaction remains unchanged over the entire temperature range of the experimental data and the extrapolation. The major difficulty in making kinetic measurements at room temperature is that all of the current methods available depend on measuring the rate of appearance of a product of the decomposition reaction or the rate of disappearance of the drug. In these methods enough time must elapse for a measurable quantity of product to accumulate or of reactant to disappear. Since this may be of the order of a few weeks to months at room temperature, data near the beginning of the reaction are rarely obtained. Therefore, a method is needed that can measure the instantaneous rate of the reaction. Such a method would allow the determination of the rate law and the activation energy at any point in time. Since heat is a by-product of nearly all reactions, measurement of the rate of heat produced or consumed can be used to determine the kinetics of a reaction. Such a calorimetric measurement would, in many cases, produce the best data near the start of a reaction since that is the time period when the rate of heat production is the greatest.

The output signal from a heat conduction calorimeter is directly proportional to the rate of heat production in the measuring cell of the calorimeter. Thus, such an instrument can be used to obtain the instantaneous rate of a reaction. Because there is no need to wait until a measurable amount of reaction has occurred, calorimetric data can be collected on the rate as a function of time from the beginning of the reaction.

A heat conduction calorimeter having a detection limit of ± 0.1 μW was first described in the literature about a decade ago (7), and since then several calorimeter designs with similar detection limits have become commercially available (8,9). Calorimeters of this type have been utilized to investigate the thermodynamics of biological phenomena such as the association between proteins and membranes (10) and antibiotics (11) and the study of microbial metabolism and interactions with drug substances (12). Also isothermal heat conduction calorimetry has been used to study the oxidation of lipids (13).

Enthalpy changes for decomposition reactions of organic materials range up to about -600 kJ/mol and thus rates of reaction as low as 10 μmol/year could potentially be measured by the heat conduction method. Some of the commercially available calorimeters will accept samples as large as 25 g (0.1 mol assuming a molecular weight of 250) without significant degradation of the detection limit. Thus a decomposition rate of about 0.01%/year is theoretically detectable with the heat conduction calorimetric method described in this paper. The actual detection limit achievable for a given material and set of conditions will, of course, depend on the actual heat of the reaction, sample size, molecular weight, and noise in the calorimeter signal.

Because the calorimetric method can be used to make measurements on freshly formulated material, the effects of excipients, stabilizers, light, impurities, and concentrations

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of reactants (e.g., oxygen, water vapor) can be determined rapidly and information on new formulations can be developed within days instead of months.

In addition to the kinetics of the reaction, the calorimetric method can be used to determine what type of decomposition reaction is occurring. The actual decomposition reaction is often unknown for a new drug product even when the kinetics of the decomposition are known (1). This situation occurs when the potency of the drug has been measured as a function of time, often by a chromatographic or biological assay, but the products of the reaction have not been identified. In such a case the ratio of the rate of heat production (J/time) to the rate of disappearance of the drug (mol/time) at a given point in the reaction is equal to the enthalpy change for the reaction, ΔH. The value of the enthalpy change thus determined experimentally can then be compared to values calculated from bond energies. While agreement between the calculated and the experimental values of the enthalpy change is not sufficient to prove that the correct reaction has been identified, a disagreement between the calculated and experimental values is sufficient to prove that the postulated reaction is incorrect.

The purpose of this paper is to describe the experimental details of the calorimetric method, lay a theoretical foundation for the interpretation of calorimetrically obtained kinetic data, and give illustrative examples of some of the results obtained to date.

EXPERIMENTAL

The major pitfalls encountered in applying the calorimetric method to drug decomposition stem from the generality of the measurement method. Since measurable heat changes accompany nearly all chemical and physical processes, great care must be taken to ensure that the heat rate ascribed to the sample did indeed come from the sample and was due only to the process of interest. Thus, the sample container must be nonreactive with the sample, must not produce heat itself, and must be sealed to prevent loss or absorption of volatiles by the sample. For example, the evaporation of water at a rate of 10 μg/day absorbs 0.3 μW. Elastomeric seals can cause a spurious heat effect by loss or absorption of volatiles or by mechanical relaxation. Absorption or loss of volatiles from labels, fingerprints, or other materials on the outside of the sample holder must also be avoided. For this reason, glass is preferable over metals or plastics for most purposes. Actinic (brown) glass cannot be used, however, because of the slow decay of the photo active sites after the sample is placed in the calorimeter, where no light reaches the sample. Freshly machined or cleaned metal containers can produce a significant amount of heat from air oxidation of the surface. Metal containers which have been stressed by swaging, forming, or bending usually have a measurable heat output rate from release of strain energy. The thermal conductivity of the sample container material is usually not significant since the low thermal conductivity and larger mass of the sample usually determine the rate of heat transport to the calorimeter. Since the measurement is a steady-state measurement, the overall thermal conductivity of the sample and container will affect only the time required to reach the steady state, and not the measurement. The upper limit of the sample size is set by the rate of heat transport from the sample and the kinetics of the heat generation. The heat rate produced by empty sample containers can be used to identify problems associated with reactions of the container materials. Reaction of the sample with the container is, however, difficult to ascertain unless more than one material is tested for the sample container. If different results are obtained with different sample container materials, then reaction of the sample with the container is to be suspected. We have found the most reliable sample containers to be flame-sealed glass ampoules, although other containers have been used successfully at times when the all-glass ampoules could not be used.

Because sealed containers must be used to prevent heat effects from the loss or gain of volatiles, the amount of atmosphere in the sample container is limited and may become depleted in any component that reacts with the sample. For example, an organic material that reacts with oxygen may deplete the oxygen in the sample container during the course of the measurement and thus change the apparent rate of the reaction. Figure 1 shows a calculated curve giving the length of time that a typical sample can be held at various temperatures until the oxygen in the container will be depleted. This figure clearly shows that depletion of a gaseous reactant during the time span of the measurement can occur, especially at elevated temperatures. One must simply be aware of this problem and ensure that it does not compromise the data.

Most of the data reported here were collected on samples of milled and unmilled drugs sealed in glass ampoules. Some data were collected with samples sealed in a stainless-steel container with a screw cap and Teflon seal.

Three different calorimeters were used for the study reported here, a Tronac Model 350 RA, a Hart Scientific Model 7708, and an LKB Model 2277 Bioactivity Monitor. These three calorimeters are all very similar in design except for the temperature capabilities and the size of the sample

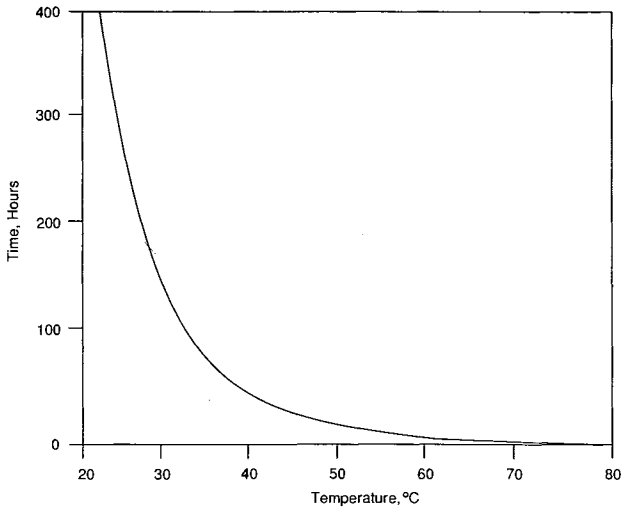

Fig. 1. The time until O_2 is depleted at various temperatures in an ampoule containing 1 cm^3 of air and 1 g of an organic compound. A molecular weight of 300 daltons, an activation energy of 94 kJ/mol, a rate of 0.2 weight%/month at 25°C, and a stoichiometry of 1 O_2 per 1 organic molecule was assumed.

chamber. The Tronac unit can be used from 5 to 45°C, the Hart unit from 25 to 180°C, and the LKB unit from 5 to 80°C. The Tronic unit has a rectangular sample chamber 1.8 × 4 × 4 cm, the Hart unit has a cylindrical sample chamber 2.5 cm in diameter and 7.5 cm deep, and the LKB unit has a cylindrical sample chamber 1.5 cm in diameter and 8 cm deep.

The baseline noise of the twin heat conduction calorimeters used for this type of study is a function of the mismatch in the sensitivities, heat capacities, and time constants of the reference and sample cells of the calorimeter. With the two cells well matched, a peak-to-peak baseline noise of ±0.1 μW is achievable. Only a slight increase in the noise figure will be found for samples sizes up to 1 to 2 g. For larger samples it is necessary to balance the cells by placing a blank sample in the reference cell.

The actual experimental procedure is very simple. It consists of enclosing a known weight of the sample in the sample container, placing the sample container in the calorimeter, and recording the rate of heat evolution or absorption by the sample as a function of time. The effective age of the sample must be known in order to analyze the data properly. The guiding principles for sample preparation and handling are that the time at which the decomposition reaction began in the sample, i.e., $t = 0$, must be known, and the temperature of the sample must be known and held constant once this reaction begins. To accomplish this, the sample must be either obtained directly from production and immediately inserted into the calorimeter or placed in storage under conditions which prevent the decomposition reaction from occurring until the measurement can begin. The sample may also be held at the same temperature as the calorimeter for a known length of time until the measurement is made. The calorimetric measurement does not need to begin at $t = 0$, but the relative time with respect to $t = 0$ at which measurements are made must be known. Continuous calorimetric measurement of the rate of heat change is not necessary. All that is required is that data be taken at frequent enough intervals to define the form of the rate law. Once the rate law is known it can be used to interpolate between existing measurements. Samples must be held at the temperature of the measurement between measurements if discontinuous data are taken.

THEORY

We begin by defining D_o as the amount of drug present in the sample at $t = 0$. Since only a fraction of a drug sample may be reactive in the solid state, we define β to be the fraction of the drug which will ultimately react. The total amount of drug that will react is then given by βD_o. The value of D_o would usually be known. However, β, and hence the amount of reactive drug in the sample, is usually an unknown. The value of β may vary from lot to lot of a drug. For some drugs β may be equal to 1, but more often β will be only a few percent. The value of β depends on the nature of the decomposition reaction. For example, if the reaction occurs only at the surface of the solid drug and produces a protective layer, then the reaction will gradually slow with time and eventually will reach an undetectable rate. Examples of other reactions which would not totally decompose a drug sample are reactions that occur only at crystal imperfections, around impurities occluded in the solid, or at other high-energy sites.

We now define α_t to be the fraction of the reaction which has occurred to time t, i.e., $\alpha_t = 0$ at $t = 0$ and $\alpha_t = 1$ at $t = \infty$. Note that the fraction of the drug which has decomposed at time t is given by $\alpha_t \beta D_o$. The value of α_t as obtained from calorimetric data is given by Eq. (1), where Q_t is the total heat produced to time t and Q_∞ is the total heat produced to $t = \infty$.

$$\alpha_t = Q_t/Q_\infty \tag{1}$$

Equation (2) expresses Q_t in terms of the enthalpy change for the reaction, ΔH, and the amount of reaction that has occurred.

$$Q_t = -\Delta H \beta D_o \alpha_t \tag{2}$$

The value of ΔH is usually an unknown. Taking the time derivative of Eq. (2) results in Eq. (3), which gives the relation between q, the rate of heat change, and the rate of the reaction.

$$dQ_t/dt = q = -\Delta H \beta D_o (d\alpha_t/dt) \tag{3}$$

Since $d\alpha_t/dt$ is equal to the product of the rate constant, k, and some function of α_t, $f(\alpha_t)$, the next part of the problem is to find the function of α_t which correctly describes the experimental q–t data for a given case. Figure 2 shows schematically the four general types of curves which will usually be obtained for data on the rate of heat production or absorption, q, as a function of the age of the sample, t. A zero-order rate law would be expected to be observed for a reaction at the surface of a solid which does not form a protective coating. The power function of time is the form of the rate law expected for reactions at the surface of a solid which result in a protective layer on the solid. In both of these cases q will be a function of the surface area of the solid, which is related to the parameter β. Autocatalytic rate

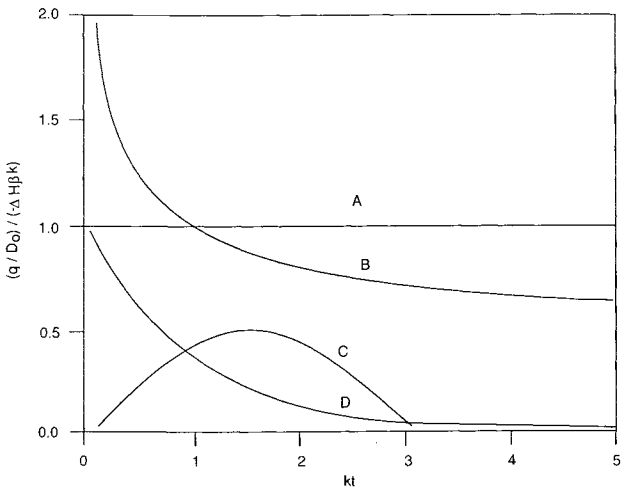

Fig. 2. Normalized plots of the rate of heat production with time for (A) a zero-order rate law, (B) a power function of time with $x = 1.5$, (C) an autocatalytic rate law with $x = y = 0.5$, and (D) a first-order rate law.

laws (4,14) are usually found for air oxidation and other free radical reactions of organic materials.

Ng (15) has shown that the rate of a reaction may be expressed in general by the function of α_t given in Eq. (4):

$$(d\alpha_t/dt) = k\alpha_t^{1-x}(1 - \alpha_t)^{1-y} \quad (4)$$

where x and y are constants characteristic of the reaction mechanism. A zero-order rate law is obtained from Eq. (4) when $x = y = 1$,

$$(d\alpha_t/dt) = k \quad (5)$$

and substitution of Eq. (5) into Eq. (3) yields q as a function of time, as given by Eq. (6).

$$q/D_o = -\Delta H\beta k = C = \text{constant} \quad (6)$$

If $x = 1$ and $y = 0$, a first-order rate law is obtained, Eq. (7), and q will decrease as an exponential in time.

$$q/D_o = -\Delta H\beta k(1 - \alpha_t) = Ce^{-kt} \quad (7)$$

Equation (7) can be written in the form

$$\ln(q/D_o) = \ln C - kt \quad (7a)$$

If $y = 1$ and $x \neq 1$, then q is given by a power function of t, Eq. (8).

$$q/D_o = -\Delta H\beta k\alpha_t^{1-x} = -\Delta H\beta k(xkt)^{(1-x)/x} = C't^{(1-x)/x} \quad (8)$$

Equation (8) in logarithmic form is

$$\ln(q/D_o) = \ln C' + [(1 - x)/x]\ln t \quad (8a)$$

The heat rate will increase or decrease with time depending on whether x is less than 1 or greater than 1, respectively.

Equation (9), which describes autocatalytic kinetics, results when $0 \leq y < 1$ and $0 \leq x < 1$.

$$q/D_o = -\Delta H\beta k\alpha_t^{1-x}(1 - \alpha_t)^{1-y} \quad (9)$$

In this case x is related to the accelerating phase of the reaction and y is related to the decelerating phase. From Eq. (9) it can be shown (15) that at q_{max}, i.e., the point in time when the maximum heat rate is observed, Eq. (10) applies.

$$\alpha_m/(1 - \alpha_m) = (1 - x)/(1 - y) = a \quad (10)$$

$$\alpha_t = \alpha_m = (1 - x)/(2 - x - y) = Q_m/Q_\infty \quad (10a)$$

Equation (10a) shows how the value of α_m is obtained from the calorimetric data. Substituting Eq. (10) into Eq. (9) results in Eq. (11).

$$q/D_o = -\Delta H\beta k[\alpha_t(1 - \alpha_t)^{1/a}]^{1-x} = C[\alpha_t(1 - \alpha_t)^{1/a}]^{1-x} \quad (11)$$

Equation (11) can be expressed in logarithmic form as

$$\ln(q/D_o) = \ln C + (1 - x)[\ln\alpha_t + 1/a\ln(1 - \alpha_t)] \quad (11a)$$

The logarithmic forms of the equations, i.e., Eqs. (7a), (8a), and (11a), all result in directly informative linear plots if $\ln(q/D_o)$ is plotted as the ordinate and the proper function of time is plotted as the abscissa. The intercept of such a plot contains information on ΔH, β, and k for the reaction, but unfortunately these constants are not separable in isothermal data. The slope of such a plot, however, contains sufficient information to quantify the rate law. The slope of the logarithmic plot for the exponential, Eq. (7a), where the abscissa is just t, is $-k$. In the case of the power function, Eq. (8a), the abscissa is $\ln t$ and the slope is equal to $(1 - x)/x$ and hence gives a value for x. The abscissa for the plot for an autocatalytic reaction is $[\ln\alpha_t + 1/a\ln(1 - \alpha_t)]$ and the slope is thus equal to $1 - x$. In order to make such a plot for an autocatalytic reaction, $\alpha_t(t)$ and the constant a must be known. Equation (10) shows that a may be calculated if α_m is known and Eq. (10a) shows that α_m can be calculated from Q_m and Q_∞. The value of Q_m can be obtained by numerical integration of q from $t = 0$ to t_m and the value of Q_∞ can be obtained likewise by integration of the entire q–t curve. In the latter case it may be necessary to fit the tail of the curve to an arbitrary power series and integrate mathematically in order to avoid excessively long experimental times. Another method of estimating Q_∞ is simply to use it as a fitting parameter and obtain the value by successive approximation or a minimization method. We note in passing that a is essentially an asymmetry factor which may be obtained by mathematical techniques which need not be detailed here.

The temperature dependence of the rate law may be obtained by determining q–t curves at several temperatures. Since a fairly narrow temperature range is all that is of interest in the application described here, the Arrhenius equation given in Eq. (12) is sufficient to describe the temperature dependence of the rate law assuming that only one rate-limiting reaction is present.

$$k = Ae^{-E^*/RT} \quad (12)$$

In Eq. (12), A is a constant, E^* is the activation energy, R is the gas constant, and T is the absolute temperature.

For a zero-order rate law the temperature dependence of q/D_o is given by Eq. (13),

$$d\ln(q/D_o)/d(1/T) = [d\ln(-\Delta H\beta A)/d(1/T)] - (E^*/R) \quad (13)$$

and the slope of a plot of $\ln(q/D_o)$ against $1/T$ is equal to $-E^*/R$ since the change in ΔH with temperature is usually negligible compared to E^*/R. The possibility that β is temperature dependent exists, but this would not be expected to be the general case since β is more likely to depend on the concentration of impurities, number of crystal imperfections, or surface area, all of which are not temperature-dependent parameters.

The exponential rate law, Eq. (7), leads to a value of k at each temperature. Thus, a plot of $\ln k$ against $1/T$ will be linear, with a slope of $-E^*/R$.

When the rate law is a power function of t, Eq. (8), a plot of $\ln\{q/D_o t^{(1-x)/x}]\}$ as the ordinate and $1/T$ as the ab-

Table I. The Effect of Atmosphere Composition and Temperature on the Rate of Heat Production of Lovastatin

Atmosphere	T(°C)	q/D_o (μW/g)
N_2	25	−0.1 ± 0.1
O_2	25	0.9 ± 0.1
N_2	50	1.1 ± 0.3
O_2	50	22.8 ± 1.1

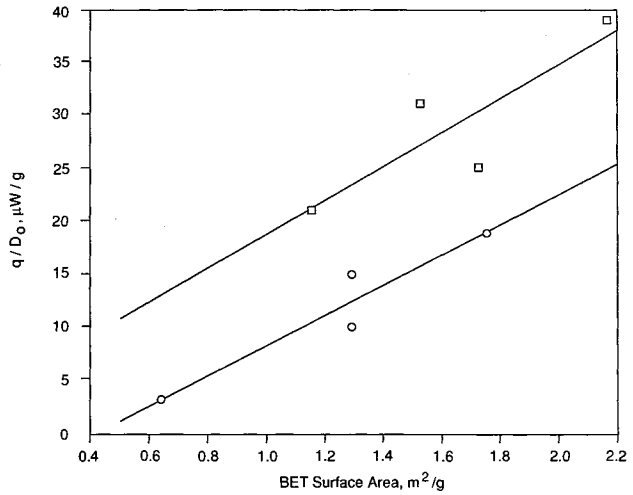

Fig. 3. The effect of surface area on the rate of heat production in two different lots of pure Lovastatin at 2 weeks of age at room temperature.

scissa will be linear, with a slope equal to $-E^*/xR$, again assuming that the change in ΔH with temperature is negligible.

The activation energy for an autocatalytic reaction may be obtained from the q_m values at different temperatures. Since α_m is independent of temperature, at $\alpha_t = \alpha_m$, $\alpha_t{}^{1-x}(1 - \alpha_t)^{1-y}$ is a temperature-independent constant and therefore $q_m/D_o = -\Delta H\beta k \times$ constant. Thus, a pilot of $\ln(q_m/D_o)$ against $1/T$ will be linear and have a slope of $-E^*/R$, again assuming that the change in ΔH with temperature is negligible.

RESULTS AND DISCUSSION

The results presented in this paper are intended to be only illustrative of the application of the methodology presented. Interpretation of the data in terms of the mechanistic details on the specific compounds studied will be presented elsewhere. The majority of the calorimetric data discussed here is for Lovastatin (Mevinolin) (16) and several derivatives of Lovastatin (17). Lovastatin is a highly potent competitive inhibitor of hydroxymethylglutaryl–coenzyme A reductase and is currently marketed as a cholesterol-lowering agent (MEVACOR).

Table I shows some representative data which were collected for Lovastatin to demonstrate that oxygen was required for reaction. The reproducibility of the data with all three of the calorimeters used in this study was about ±0.2 μW at 25°C and about ±1 μW at 50°C. The data shown in Table I were collected with 0.5-g samples sealed in glass ampoules. The Lovastatin used for these experiments was an experimental lot suspected to be subject to oxidation. All samples for measurement were taken from the same lot of drug to ensure that the samples were all at the same age when the measurements were made. The results clearly show that reaction with oxygen is the mechanism of decomposition of the material. Further evidence that this is the case was obtained by allowing the vials to stand at 50°C until the oxygen in the vial was depleted and then measuring the heat output rate. As expected, heat production fell to blank values after a few days.

The enthalpy change for the oxidation reaction can be estimated from the data in Table I and the rate of loss of potency of the same lot of drug at room temperature. The result, −400 kJ/mol, is in the range of expected values of ΔH for the oxidation of unsaturated organic compounds with oxygen. Bond energy calculations show that the reaction of O_2 with a methylene group to produce a carbonyl group and water molecule has an enthalpy change of about −600 kJ/mol. It is of interest to note in this connection that the ΔH value for the reaction of O_2 with a C—H bond to form a hydroperoxide is approximately zero. Thus, this step in the oxidation reaction will not be seen by the calorimeter. Only when the hydroperoxide decomposes to products will heat be generated.

A milling sieving study was done on two fresh lots of Lovastatin and showed that the rate of oxidation was related to the surface area (BET nitrogen adsorption method) of the material. The data presented in Fig. 3 clearly show that the

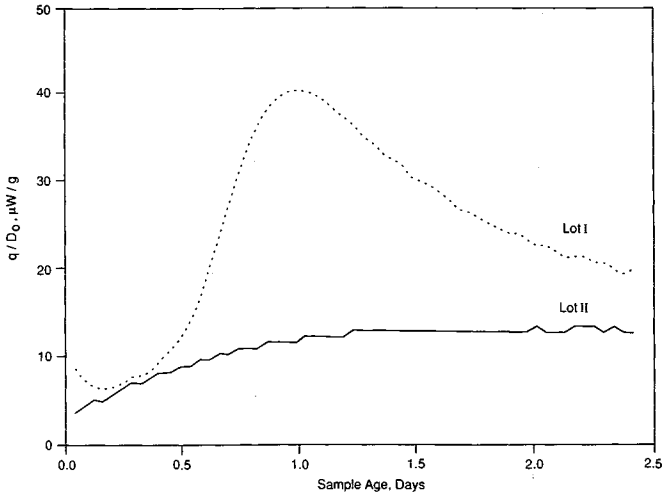

Fig. 4. Calorimetric data on two different experimental lots of Lovastatin.

surface area has a significant effect on the rate of oxidation, with the rate increasing linearly with the surface area.

Figure 4 shows the calorimetric data collected at 70°C on two additional experimental lots of Lovastatin. These results clearly demonstrate the susceptibility of lot I to an autocatalytic oxidation reaction (see Fig. 2) which does not occur with lot II. Subsequent high-performance liquid chromatographic (HPLC) analysis of room temperature-aged (approximately 6 months) samples of the same two lots showed that lot I underwent a significant amount of degradation, while lot II did not.

Figure 5 shows the effect of temperature on the kinetics of the autoxidation reaction of a given lot of Lovastatin. Figure 6 gives a plot of $\ln(q_m/D_o)$ against the reciprocal of the absolute temperature for the data in Fig. 5. The data shown in Fig. 6 fall on a straight line as suggested under Theory. The activation energy calculated from Fig. 6 is 91 kJ/mol.

Calorimetric data on a derivative of Lovastatin, also susceptible to autoxidation, were collected at four different temperatures between 40 and 70°C and are shown in Fig. 7. The same data plotted according to Eq. (8a) are shown in Fig. 8. Figure 8 demonstrates that Eq. (8a) describes the data at 60 and 70°C but does not hold for the data taken at 40 and 50°C. Therefore, we can conclude that the decomposition reaction being followed by the calorimeter changes between 50 and 60°C and that accelerated testing at elevated temperature is inappropriate for this drug. Further experiments with this same drug showed that oxygen was necessary for the reaction, i.e., $q = 0$, in an argon atmosphere. The activation energy calculated from the 60 and 70°C data according to Eqs. 8 and 12 is 105 kJ/mol.

Calorimetric data at 50°C on three different lots of yet another derivative are shown in Fig. 9. The reaction is an autocatalytic oxidation in this case. The induction period, the time to the maximum heat rate, and the heat rate at the maximum all vary from lot to lot. Although these variables all appear to be correlated, the correlation is by no means simple. The value of Q_m, however, is relatively constant and appears to be a good measure of the total amount of degradation that the material will undergo by oxidation at room temperature. We were unable to fit these data to Eq. (11). However, the lack of a fit of these data does demonstrate that a second reaction, which probably follows an exponential in time with $x < 1$, is present, i.e., the tail of the curve for lot I does not decrease rapidly enough to produce a reasonable value for Q_∞. This second reaction probably involves reaction of a product of the initial oxidation reaction.

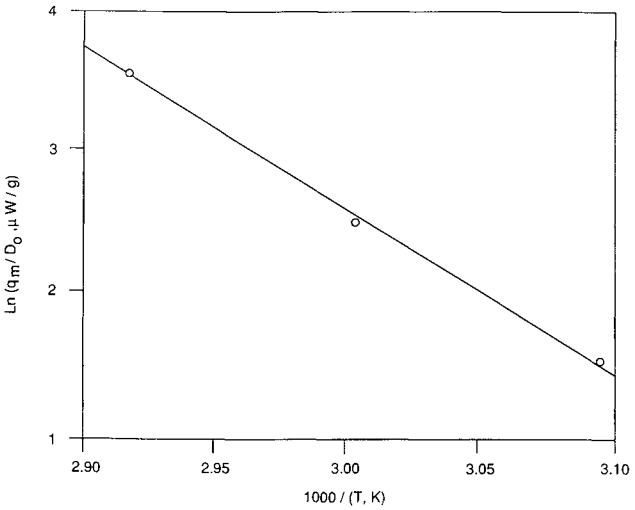

Fig. 6. A plot of $\ln(q_m/D_o)$ against $1/T$ for the data shown in Fig. 5.

One of the most significant results of this study was the realization that a single measurement of q/D_o at a known sample age can be used to predict the relative total degradation that different lots of the same material will ultimately undergo. If the age, the temperature history, the decomposition reaction, and the kinetics are the same in all of the lots, then Eq. (4) shows that $q/D_o = \beta \times$ constant, and thus q/D_o is directly proportional to the amount of drug that will ultimately decompose. The cautionary note that must be stressed, however, is that different lots of the same material

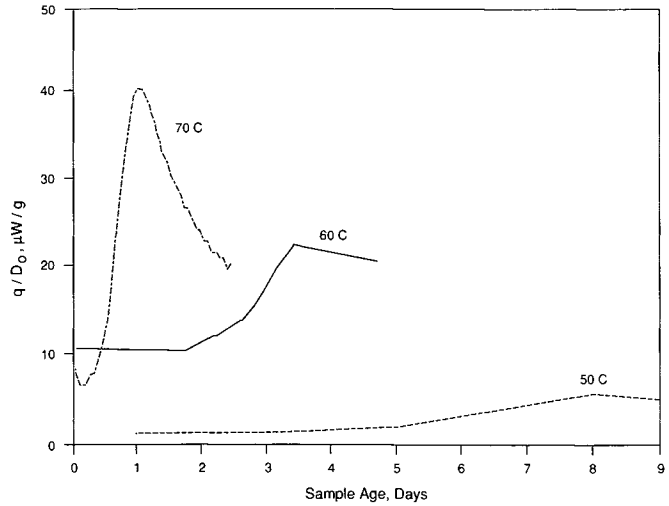

Fig. 5. The effect of temperature on the kinetics of autoxidation of a given lot of Lovastatin. The lines simply connect the data points collected.

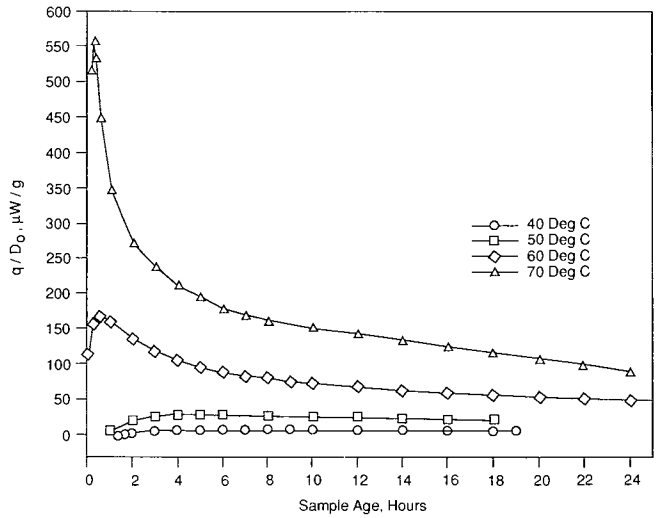

Fig. 7. Calorimetric data on one lot of a Lovastatin derivative as a function of temperature.

can have different kinetics and/or decomposition reactions as shown in Figs. 4 and 9.

CONCLUSION

This paper demonstrates the application of heat conduction calorimetry to determine the kinetics of decomposition of pharmaceutical products. We have shown, with examples, how this technique can be used to determine the nature of the reaction, the rate law, the activation energy, and the enthalpy change for the decomposition reaction. The method can be used to determine quickly if the rate law, and hence the mechanism, of a reaction changes as the temperature is increased and therefore to test the validity of temperature accelerated test methods.

No sample treatment is required in the calorimetric method. The decomposition reaction can therefore be studied directly in the actual material in which the reaction normally occurs. Since the calorimetric method is nondestructive, measurements can be made on the same sample throughout the study. Also, because the sample is not used up in the measurement, relatively small quantities of material are required.

The major advantage of the calorimetric method over other methods for measuring the rate of decomposition of organic materials is that the calorimetric method directly measures the rate of the reaction. The best data from the calorimetric method are thus obtained early in the reaction when the reaction rate is at a maximum. Most other methods depend on measuring the amount of product formed or the amount of reactant which has disappeared. In either case, these methods must wait until sufficient reaction has occurred before they can be used to produce significant data. This will often not be until the reaction has progressed into the later stages, where it is difficult to resolve differences between rate laws (see Fig. 2). A major advantage of a direct

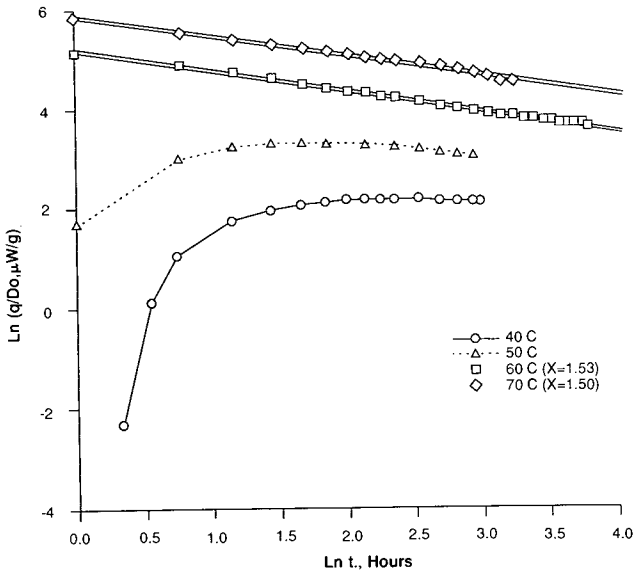

Fig. 8. Data from Fig. 7 plotted according to Eq. (8a). The x values were obtained from a linear least-squares fit of the data shown.

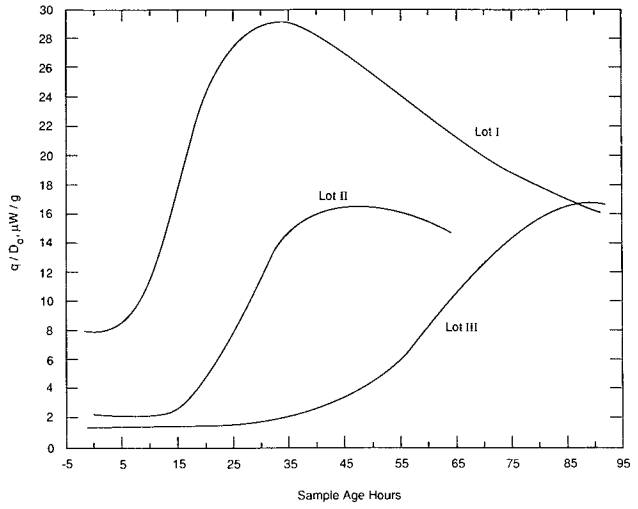

Fig. 9. Calorimetric data on three different lots of a Lovastatin derivative at 50°C.

analytical method is that measurement of the amount of product formed gives a direct measure of the fraction of the material which undergoes decomposition, while the calorimetric method gives a quantity, i.e., Q_t, which is only proportional to the amount of decomposition. Since the two methods generally complement each other, the application of both direct analytical methods and the calorimetric method to a given problem greatly increases the amount of information that can be obtained from either method alone.

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