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*Research Article*

# Nonisothermal Stability Assessment of Stable Pharmaceuticals: Testing of a Clindamycin Phosphate Formulation

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The stability of an antibiotic formulation (clindamycin phosphate in dextrose), which is stable at room temperature, was assessed by nonisothermal kinetic analysis at elevated temperatures. A preliminary study, conducted to establish apparent rate order, verified the appropriateness of a first-order kinetic model. The test formulation was then heated linearly from 70 to 90°C over 12 hr. Data (drug concentration, temperature, and time) were fitted to the first-order model using nonlinear least-squares regression. Arrhenius parameter estimates obtained from three nonisothermal trials, and rate constants at 25°C derived by extrapolation, demonstrated acceptable reproducibility and were in agreement with values derived from isothermal experiments at 30, 45, 55, 65, and 75°C. First-order rate constants obtained from studies conducted for 20 months at 25°C were in accord with isothermal and nonisothermal results.

KEY WORDS: nonisothermal kinetics; sequential simplex optimization; numerical integration; Arrhenius study; stability prediction; clindamycin phosphate.

## INTRODUCTION

There has been considerable interest (1–21) in the use of nonisothermal accelerated testing to estimate formulation stability. The goal is to reduce experimental effort; in many cases, an experiment can be conducted in one apparatus on the same solution within a day. All reports have, in general, either demonstrated this methodology using drugs that are somewhat unstable at room temperature at moderate pH in aqueous solution, such as β-lactam antibiotics (13,17), or chosen stringent conditions to facilitate acid or base hydrolysis (4–7,9–12,16,18). In this manner an entire study could be conducted in 1 day at moderately elevated temperatures. In contrast, the shelf life of an injection preparation was estimated to be 211 days, based on nonisothermal data collected over a 10-week period (21).

We wished to determine whether a short-term (1-day) nonisothermal test could be applied to a stable pharmaceutical formulation (i.e., less than 10% degradation at room temperature after 2 years), yet obtain reasonably accurate, reproducible shelf-life estimates. To this end, a parenteral formulation consisting of clindamycin-2-phosphate in 5% dextrose monohydrate was chosen for investigation. It has been shown (22) that decomposition of clindamycin-2-phosphate follows first-order kinetics in the pH region 6–8. In this study, we have verified this apparent rate order at pH 6 in a separate isothermal experiment.

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## MATERIALS AND METHODS

Three nonisothermal experiments and two isothermal Arrhenius studies were carried out. The drug preparation consisted of clindamycin phosphate, equivalent in potency to 600 mg of the active dephosphorylated compound, clindamycin, per 50 ml of 5% dextrose monohydrate. In addition, samples of clindamycin phosphate formulation were stored in plastic i.v. containers for 20 months at 25°C. The pH of all solutions was adjusted to 6.

### Nonisothermal Studies

As in previous investigations (16,17), it was considered important that all sampling occur from the same vessel, rather than from multiple samples. In this manner, the potential for sample-to-sample temperature variation would be minimized. The apparatus shown in Fig. 1 was used. The digital control programmer (Honeywell 770111) was set to hold the solution at an initial temperature of 70°C for a half-hour to enable thermal equilibration and then linearly increase the solution temperature from 70 to 90°C over 12 hr. After the vessel was brought to the initial program temperature, 800 ml of formulation was added. Some of this solution was saved as a standard in the drug assay. The formulation in the vessel was allowed to equilibrate thermally with stirring (approximately 30 min), after which the programmed temperature increase commenced. The test solution was stirred vigorously throughout the entire experiment. Samples were removed from the reaction vessel through a sampling port, consisting of a section of Teflon tubing terminating in a three-way stopcock with a Luer-Lok fitting. Samples could be removed by syringe and injected directly into a

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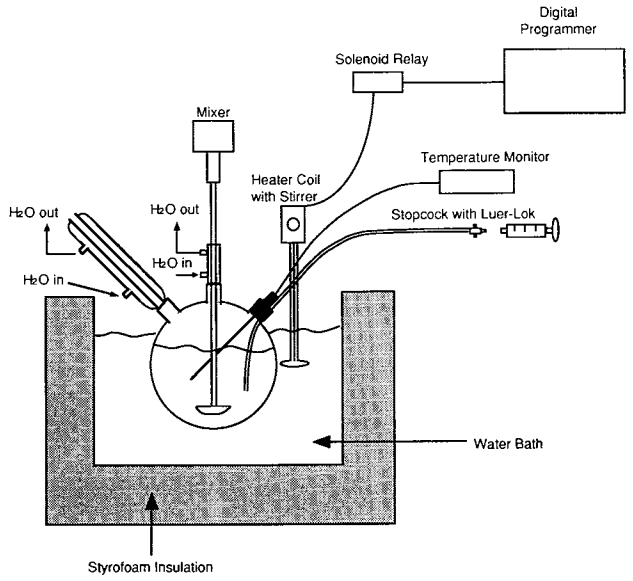


Fig. 1. Schematic of apparatus used in nonisothermal kinetic experiments.

sample vial, without any moisture loss. To verify that no water loss was occurring, a control experiment was run on a potassium chloride solution (see below) prior to actual testing of the formulation. For all nonisothermal runs, 2-ml aliquots were removed at 20- to 30-min intervals. In all, 30–40 samples were collected. At the moment of sample removal, the readout on the digital thermometer (Sensortek BAT-12, with Type T thermocouple) was recorded, and the corresponding time was noted. After removal, each vial was immediately refrigerated for later analysis. All samples were assayed for drug by HPLC. Solution pH was also measured at selected intervals using a Beckman Φ71 pH meter. Variation of pH over an entire run was consistently within 0.2 pH unit.

### Isothermal Studies

Type I glass ampoules were filled with the test formulation and stored at 30, 45, 55, 65, and 75°C. Samples were removed at various intervals (up to 22 months at 30°C) and assayed for drug by HPLC. In addition, the formulation in plastic i.v. containers, stored for 20 months at 25°C, was assayed for clindamycin phosphate at various intervals.

The rate-order determination was carried out on formulations at five different concentrations (0.6, 1.2, 3.0, 6.0, and 12.0 g of clindamycin phosphate, clindamycin equivalent, per liter). All solutions were adjusted to pH 6. Type I glass serum bottles (50 ml) were filled with these solutions, and were heated in a thermostated water bath at 90°C. Sample aliquots (2 ml) of each solution were removed by syringe at each hour up to 6 hr. Drug concentration was measured by HPLC. Duplicate injections were made.

### HPLC Assay for Clindamycin Phosphate

Samples were assayed without dilution using a C8-reverse phase column (Zorbax). An HPLC system with autosampler (Hewlett–Packard 1050) was used. An injection volume of 10 μl was used. The mobile phase consisted of 77.5% phosphate buffer (1.3% potassium phosphate monobasic in water, adjusted to pH 2.5), and 22.5% acetonitrile. Solvent was delivered at a flow rate of 2.0 ml/min. The effluent was monitored at 210 nm. Chromatographic data were collected and processed on a Hewlett–Packard 3396A integrator.

Before analysis, linearity of detector response was checked in the analytical region of interest and was found to be linear ($r^2$ = 0.999), with an intercept not significantly different from zero. Reproducibility was checked by making six replicate injections of the standard. The relative standard deviation was 0.53%.

During assay, every set of five experimental samples was bracketed with vials containing the initially prepared formulation as a standard. Two injections per vial were made. The residual drug fraction was determined by dividing the average peak area of the drug by that of the standard.

### Control Study

Prior to nonisothermal testing, the possibility of water loss during an experiment had to be ruled out. A 5 m*M* solution (800 ml) of potassium chloride was tested under the same conditions used for testing the clindamycin phosphate formulation. Samples were assayed for potassium using flame photometry (Instrumentation Laboratory Inc., Model 343). Results showed no significant change in potassium concentration throughout the 12-hr test period.

### Estimation of Kinetic Parameters

The method for analyzing the nonisothermal data generated in this study has been previously described (16,17). The data (time, temperature, and fraction of initial drug concentration) were fitted to the integral form of the first-order rate equation:

$$C = C_0 \exp\left\{-Z \int_0^t \exp\left[-E/RT(t)\right]dt\right\} \quad (1)$$

Parameters $Z$ and $E$ are the empirical preexponential factor and activation energy and are dependent on the rate model chosen. Integration of the appropriate differential equations over the interval zero to time $t$ affords the following equations for apparent zero- and second-order decomposition.

Zero order:

$$C = C_0 - Z \int_0^t \exp\left[-E/RT(t)\right]dt \quad (2)$$

Second order:

$$1/C = 1/C_0 + Z \int_0^t \exp\left[-E/RT(t)\right]dt \quad (3)$$

Least-squares optimization was accomplished by use of the sequential simplex algorithm of Nelder and Mead (23). Standard deviations of the parameters were estimated by the Gauss–Newton method (24,25). The nonlinear optimization routine required evaluation of the integral in Eqs. (1)–(3). This was done numerically using Simpson's approximation without end correction (26).

The rate constant estimate at 25°C was obtained by substitution of the optimal $Z$ and $E$ values into the Arrhenius expression. The variance of this estimate ($s_k^2$) was determined by a Taylor-series approximation (6,25):

$$s_k^2 = s_Z^2\left(\frac{dk}{dZ}\right)^2 + s_E^2\left(\frac{dk}{dE}\right)^2 + 2\,\mathrm{cov}(Z,E)\left(\frac{dk}{dZ}\right)\left(\frac{dk}{dE}\right) \quad (4)$$

where $s_Z^2$ and $s_E^2$ are the variances of parameters $Z$ and $E$, and cov($Z$,$E$) is the covariance of $Z$ and $E$ as determined by the Gauss–Newton method. The period required for 10% drug degradation ($\tau_{0.90}$), or shelf life, was estimated using the rate constant ($k_{25}$) predicted from the Arrhenius equation at 25°C. For a first-order reaction,

$$\tau_{0.90} = -\ln(0.9)/k_{25} \quad (5)$$

Likewise,

$$\tau_{0.90} = 0.1\ C_0/k_{25} \quad \text{(zero order)} \quad (6)$$

$$\tau_{0.90} = 1/(9k_{25}C_0) \quad \text{(second order)} \quad (7)$$

The computer program used by us previously (16,17) was rewritten in Turbo PASCAL (Borland International, Inc. version 5.0), and modified to include error estimation as described above. Programs were run on a Compaq Deskpro 386S microcomputer equipped with an Intel 80387 (16 MHz) math coprocessor.

To execute the program, a polynomial order is chosen (1st through 20th order). A polynomial least-squares fit affords a regression curve which interpolates temperature between experimental values for the purpose of numerical integration. The number of terms was varied to produce the best fit to the rate model chosen. The integration procedure also required a convergence criterion to enable escape from the integration routine. Successive interval halving (16) was employed until the absolute value of the difference between two consecutive integral estimates was less than a certain fraction (tolerance value) of the first estimate. A tolerance of $10^{-5}$ was used in this experiment. Decreasing this value further resulted in no changes in the final parameters to a precision of at least four significant figures.

Data obtained from the isothermal experiments were treated by nonlinear regression using the following first-order model:

$$C = C_0 \exp\,[-t Z \exp(-E/RT)] \quad (8)$$

The above expression or variants have been discussed by various authors (19,25). The regression parameters $E$ and $Z$ were then used to estimate $k$ at 25°C, $k_{25}$. Errors in $Z$, $E$, and $k_{25}$ were calculated by the Gauss–Newton and error propagation methods described earlier.

## RESULTS AND DISCUSSION

At the outset of this study, the apparent rate order for loss of drug was estimated by the initial rate method (27). The experimental procedure is described under Materials and Methods. After 6 hr at 90°C, less than 20% drug loss was observed for all five formulations. The average rate of drug loss over the 6-hr interval for each solution was estimated from a linear least-squares regression of concentration on time. A graph of the logarithm of estimated rate versus the logarithm of initial drug concentration is presented in Fig. 2. The slope of the graph, 0.85 (SD = 0.02), indicates that, to the closest integer approximation, drug decomposition is pseudo-first order.

Isothermal data, representing one of two trials, collected at 30, 45, 55, 65, and 75°C, are presented in Fig. 3.

The results of a typical nonisothermal run are graphed in Fig. 4, which shows the fraction of drug remaining as a function of time. Superimposed is a plot of measured temperature versus time.

Shelf life was not estimated directly from the kinetic model as has been done by previous workers (19–21). Implicit in the error treatment for the first-order model derived in those studies is the assumption that the distribution of estimated shelf life corresponding to a normal distribution in potency is also symmetric and normal. It is readily shown (25) that the distribution of shelf-life estimates so obtained must be skewed and non-Gaussian. Use of the least-squares method and error treatment by the Gauss–Newton approach requires an assumption of asymptotic normality in all parameters (24).

In this study, statistics of the shelf-life estimates were determined from those of the rate constants, which must be asymptotically normal (25). Table I lists the kinetic parameter estimates computed for the three nonisothermal trials and the averages for all trials. In comparison, the values computed from the isothermal rate studies (30–75°C) and the first-order rate constants determined from storage of the formulation in i.v. containers for 20 months are presented. The agreement of data between nonisothermal experiments is excellent and in close agreement with the isothermal results (30–75°C). Moreover, the rate constant and shelf life estimated from room-temperature storage of formulation in i.v. containers agree well with the other results. This consistency indicates that variations in the Arrhenius parameters ($E$ and $Z$) over the temperature range included in this study (25–90°C) are insignificant. Therefore, estimates obtained at high temperatures (nonisothermal at 70–90°C or isothermal at 30–75°C) are in accord with the results from 25°C storage.

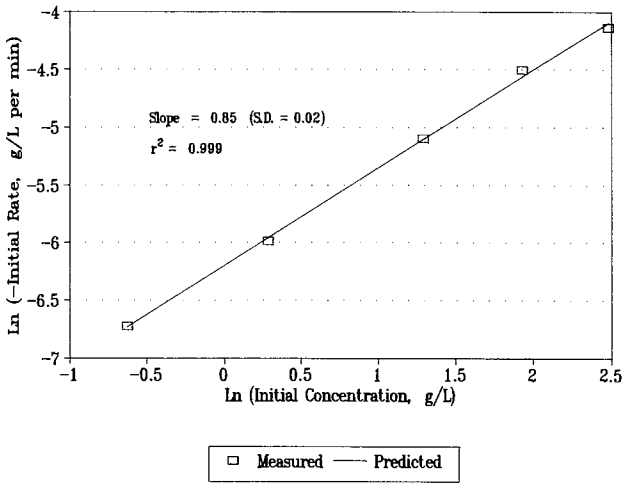


Fig. 2. Logarithm of initial decomposition rate at 90°C versus logarithm of initial concentration. Formulations: clindamycin-2-phosphate (0.6, 1.2, 3.0, 6.0, and 12.0 g/L) in 5% dextrose monohydrate (pH 6).

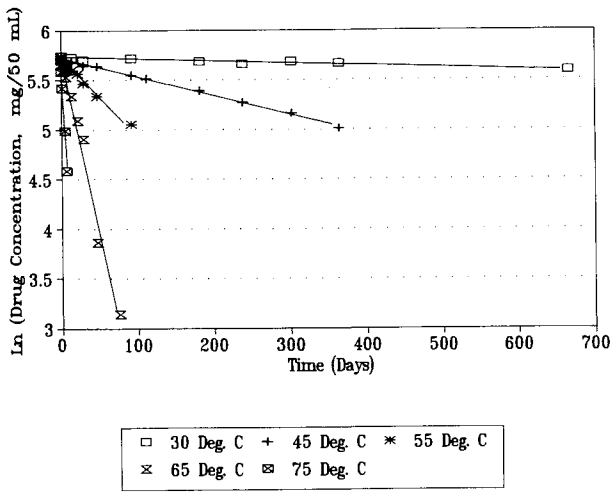


Fig. 3. Isothermal decomposition of clindamycin-2-phosphate formulation (pH 6) at 30, 45, 55, 65, and 75°C.

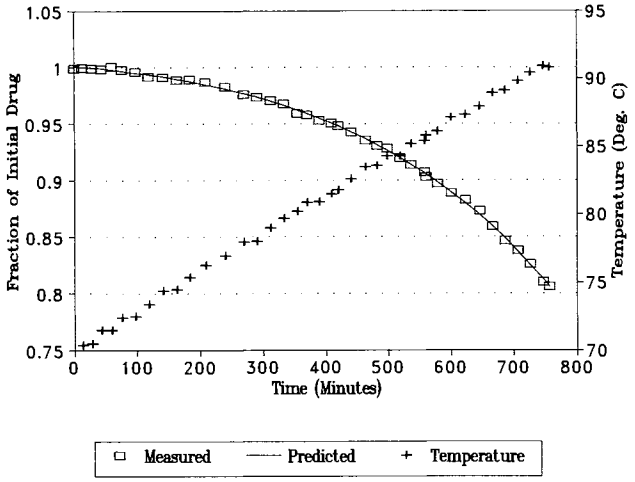


Fig. 4. Nonisothermal decomposition of clindamycin-2-phosphate (12 g/L) in dextrose monohydrate (pH 6). Temperature program: 70–90°C over a 12-hr period.

This is in contrast to other nonisothermal kinetic studies (21) which have shown deviations between nonisothermal and isothermal results depending upon the temperature range chosen for analysis.

From Table I, it is apparent that the standard errors for $k_{25}$ and shelf life, determined from the isothermal data (30–75°C), are consistently lower than those corresponding to the nonisothermal experiments. This is partly a reflection of the greater confidence afforded by sampling over a larger

**Table I.** Kinetic Parameter Estimates—Nonisothermal and Isothermal Stability Testing of Clindamycin Phosphate in 5% Dextrose Monohydrate (A First-Order Kinetic Model Is Assumed)

| Trial | $E$ (kcal/mol) | $Z$ (1/hr, × $10^{-18}$) | $k_{25}$ (1/hr, × $10^6$) | $\tau_{0.90}$ at 25°C (months) |
|---|---|---|---|---|
| Nonisothermal trial 1 (70–90°C, $n$ = 33) | 32.5 (0.2)[a] | 1.54 (0.03)[a] | 2.28 (0.61)[b] | 63.3 (49.9–86.7)[c] |
| Nonisothermal trial 2 (70–90°C, $n$ = 37) | 32.3 (0.2) | 1.19 (0.02) | 2.38 (0.77) | 60.5 (39.7–69.2) |
| Nonisothermal trial 3 (70–90°C, $n$ = 40) | 32.5 (0.1) | 1.45 (0.02) | 2.33 (0.47) | 61.9 (51.5–77.8) |
| Average | 32.4 (0.1)[e] | 1.39 (0.2)[e] | 2.33 (0.58) | 61.9[d] (49.7–82.2) |
| Isothermal trial 1 (30–75°C, $n$ = 124) | 32.6 (0.2) | 1.66 (0.18) | 2.18 (0.16) | 66.3 (61.7–71.8) |
| Isothermal trial 2 (30–75°C, $n$ = 124) | 31.9 (0.2) | 0.659 (0.300) | 2.52 (0.16) | 57.2 (53.8–60.9) |
| Average | 32.3 (0.5) | 1.16 (0.71) | 2.35 (0.16) | 61.4 (57.5–65.8) |
| Storage at 25°C for 20 months, trial 1 ($n$ = 25) | — | — | 2.50 (0.63) | 57.8 (46.1–77.4) |
| Storage at 25°C for 20 months, trial 2 ($n$ = 25) | — | — | 2.60 (0.41) | 55.5 (47.9–66.0) |

[a] Standard error, determined by Gauss–Newton method.
[b] Standard error of rate constant, approximated by Taylor series.
[c] Shelf-life limits corresponding to ±1 SD about the mean estimated rate constant. Values determined by Eq. (5).
[d] As explained in the text, the average shelf life is determined from the mean predicted rate constant.
[e] Standard error of averages determined from the weighted sum of the variances in each parameter.

temperature range. Furthermore, the error contributed by extrapolation of the Arrhenius model from 52.5°C (midpoint of 30–75°C) to 25°C is considerably less than that obtained upon extrapolation of the nonisothermal data from 80°C (midpoint of 70–90°C) to room temperature.

One objective of this study was to determine how much kinetic information on a stable formulation could be gathered from short-term nonisothermal experiments. Yang (8) demonstrated, in a theoretical investigation of simulated nonisothermal data, the inability to determine the rate order for degradation of stable drugs. For a hypothetical drug having an activation energy of 30 kcal/mol and a shelf life ($\tau_{0.90}$) of approximately 24 months, it was impossible to distinguish predictions based on a first- versus zero-order model using the correlation coefficient ($r^2$) as a measure of goodness of fit. This deficiency is not demonstrated when less stable drug formulations are investigated (6,13,16,17). In these examples, a larger extent of drug degradation can be obtained in a relatively short time (1 day). In another article by Cole and Leadbeater (4), it was found that the hydrolysis of sucrose could be verified as being first order with respect to the sugar if decomposition was followed to completion. If only the first 20% of decomposition was used in the analysis, determination of order was not possible.

Data from the three trials were fitted to all three kinetic models [Eqs. (1)–(3)], and the standard errors of the residuals were compared. Results are given in Table II. The standard deviations for all three models were too close to allow assessment of rate order. In fact, the best fit in each trial resulted in an incorrect estimate. The coincidence of all three rate models through 12 hr can be seen in Fig. 5, which was generated by solving Eqs. (1)–(3) using parameters $E$ and $Z$ obtained in nonisothermal experiment 3. At the end of the experiment (80.6% of initial drug after 12.6 hr), differences between the residual drug levels predicted from each model are similar to the standard deviations of the residuals for the three models ($1.7 \times 10^{-3}$, from Table II). Assuming the same rate of temperature increase over 21 hr, the zero-order model should be distinguishable (see Fig. 5) from first or second order, because nearly 100% degradation should occur by a zero-order rate, as opposed to 72% by first-order and 62% by second-order decomposition. Distinction between first- and second-order models may be difficult, however, even after 21 hr—a difference of less than 10% in percentage of initial drug level (28 vs 38%) is expected. This strengthens the argument that screening studies must be run prior to nonisothermal testing if drug decomposition is not followed to near-completion. This inability to detect the empirical reaction order based on decomposition through less than one half-life is not a unique limitation of the nonisothermal approach, but applies to isothermal studies as well (25).

Table II. Regression Error as a Function of Kinetic Model (Zero, First, or Second Order with Respect to Drug)

| Experiment | Rate order | SD of residuals ($\times 10^3$) | Best model |
|---|---|---|---|
| 1 | 0 | 3.3429 | |
| | 1 | 3.2558 | |
| | 2 | 3.1942 | X |
| 2 | 0 | 3.2151 | |
| | 1 | 3.1214 | |
| | 2 | 3.0572 | X |
| 3 | 0 | 1.6618 | X |
| | 1 | 1.6688 | |
| | 2 | 1.7479 | |

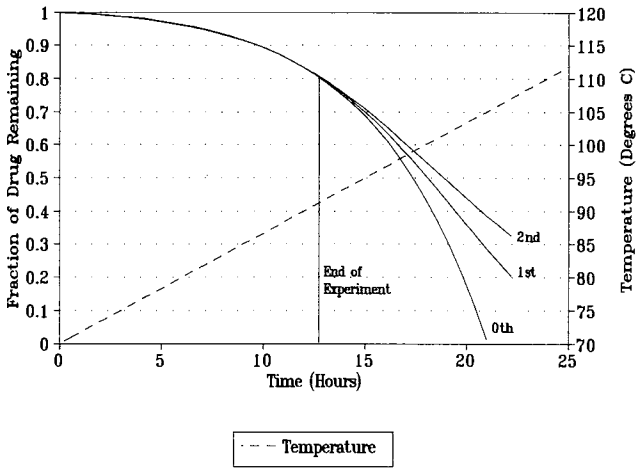


Fig. 5. Predicted drug fraction as a function of rate order (0, 1, or 2). $E$ = 29.5 kcal/mol and $Z = 2.01 \times 10^{16}$ fraction $hr^{-1}$ for zero order; $E$ = 32.5 kcal/mol and $Z = 1.45 \times 10^{18}$ $hr^{-1}$ for first order; $E$ = 35.5 kcal/mol and $Z = 1.09 \times 10^{20}$ fraction$^{-1}$ $hr^{-1}$ for second order. The dashed line indicates the temperature program employed: $T$ = 70°C + 1.67 (time, hr).

In summary, nonisothermal testing of a clindamycin phosphate formulation has provided reproducible estimates of empirical first-order activation energy and the Arrhenius preexponential factor. This study has shown that confidence in the extrapolated rate constant is sacrificed at the expense of shortened experimental time, because of the higher temperatures necessary to effect significant degradation. These results also validate those from earlier work indicating that apparent reaction order may be very difficult to ascertain in cases in which drug concentration is not followed to nearly complete degradation. In such cases, additional studies are imperative for determining reaction order.

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