DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 7(5), 539-561 (1981)



# THE APPLICATION OF NON-ISOTHERMAL ACCELERATED KINETIC STUDY IN PHARMACEUTICAL PRODUCT DEVELOPMENT

Wu-huang Yang*
Department of Industrial Pharmacy
Massachusetts College of Pharmacy
Boston, Massachusetts 02115

## ABSTRACT

A non-isothermal kinetic study allows the determination of the important kinetic parameters in a single experiment and thus is useful for the quick assessment of stability characteristics of the pharmaceutical prototypes during the development stage. The applicability and limitations of two non-isothermal accelerated kinetic methods in the pharmaceutical product development are discussed. Both methods are simple and no sophisticated calculation is necessary. These methods, however, fail to provide a unique reaction order for the pharmaceutically acceptable systems. The method is applicable only to those systems which obey the Arrhenius relationship.

*Present address: Pharmaceutical Product Development, Mead Johnson & Company, Evansville, Indiana 47721.

## INTRODUCTION

In a non-isothermal accelerated kinetic study the degradation of a drug substance is monitored when the temperature of the system is being increased at a predetermined rate. This makes it possible, from a single experiment, to determine the important kinetic parameters which are normally obtained from the isothermal kinetic studies at several temperatures. Both isothermal and non-isothermal accelerated kinetic methods are based on the Arrhenius relationship.

Different temperature-time programs have been used in the non-isothermal kinetic study (1-5). However, all the systems chosen to demonstrate the non-isothermal methods were relatively unstable when compared to the pharmaceutical products. It is desirable to analyze and compare these methods for their applicability in developing the pharmaceutical products. The goal of this paper is to search a non-isothermal accelerated kinetic method which 1) is mathematically simple; 2) requires only simple tools normally immediately available in a laboratory, such as calculators as opposed to the computers, for the data treatment; 3) is realistic to fit into the time frame of the pharmaceutical industry (i.e., 8 working hours per day).

## THEORETICAL

Three temperature-time programs were used for the non-isothermal accelerated kinetic studies (1-3):

$$1/T_o - 1/T = b \ln(1+t) \qquad \text{Eq.1}$$

$$1/T_o - 1/T = at \qquad \text{Eq.2}$$

$$T - T_o = ct \qquad \text{Eq.3}$$

where $T_o$ is the initial temperature, T is the temperature at time t, and a, b and c are heating rate constants.

The temperature-time program shown in Eq.1 together with the Arrhenius relationship result in an analytical solution (1):

$$\log f = \log k_o - \log\left[1+(Eb/R)\right] + \left[1+(Eb/R)\right] \log(1+t) + \log\left[1-(k_o/k)^{1+(R/Eb)}\right] \qquad \text{Eq.4}$$

where the function f is defined in Table I for different kinetic orders, $k_o$ and k are rate constants at the initial temperature $T_o$ and at the temperature T (thus also at time t) respectively, E is the activation energy, and R is the gas constant.

When

$$\log\left[1-(k_o/k)^{1+(R/Eb)}\right] \ll \log f \qquad \text{Eq.5}$$

Eq.4 can be simplified to:

$$\log f = \log k_o - \log\left[1+(Eb/R)\right] + \left[1+(Eb/R)\right] \log(1+t) \qquad \text{Eq.6}$$

Plotting log f vs log(1+t) should give a straight line. The values of the parameters $k_o$ and E can be obtained from the slope and the intercept of the straight line.

Similarly, when the temperature-time program shown in Eq.2 is used an analytical solution can also be obtained. The equations corresponding to Eq.4, 5 and 6 are (2):

$$f = (Rk_o/aE)e^{aEt/R} - Rk_o/aE \qquad \text{Eq.7}$$

$$Rk_o/aE \ll f \qquad \text{Eq.8}$$

$$\log f = \log(Rk_o/aE) + (aE/2.303R)t \qquad \text{Eq.9}$$

Another mathematical manipulation of Eq.7 leads to (2):

$$\log g = \log\left[(e^{aE\Delta t/R}-1)(Rk_o/aE)\right] + (aE/2.303R)t \qquad \text{Eq.10}$$

where the function $g$ is defined in Table I for different kinetic orders, $\Delta t$ is a constant time interval employed to obtain the function $g$. No assumption, such as shown in Eq.8, is made in deriving Eq.10. Note that plotting log f vs t in Eq.9 and log g vs t in Eq.10 result in straight lines from which values of $k_o$ and E can be computed.

One of the attributes of Eq.6, 9 and 10 is the ability to determine the reaction order. This is accomplished by substituting the appropriate function f or g as defined in Table I to obtain the best straight line.

No analytical solution, similar to Eq.4 and Eq.7, can be obtained when the temperature-time program shown in Eq.3 is used. Data treatment is more complicated in this case.

TABLE I

Function f and g for Different Kinetic Orders

| Kinetic Order | f | g |
|---|---|---|
| 0 | $A_o - A_t$ | $A_t - A_{t+\Delta t}$ |
| 1 | $\ln(A_o/A_t)$ | $\ln(A_t/A_{t+\Delta t})$ |
| 2 | $1/A_t - 1/A_o$ | $1/A_{t+\Delta t} - 1/A_t$ |

$A_o$, $A_t$ and $A_{t+\Delta t}$ are drug levels at time 0, t and $t+\Delta t$ respectively.

The application of the non-isothermal accelerated kinetic method based on Eq.1 and Eq.2 in the pharmaceutical product development is discussed in this paper. Pharmaceutically acceptable values of the kinetic parameters E and $k_o$ (expressed indirectly in terms of the shelf life at 25°, $t_{90}$) are used in the calculation. Suitable temperature-time programs which are realistic and acceptable to be used in the industry are employed. Data are then calculated using a suitable sampling schedule (discussed later). Finally data are treated according to Eq.6, 9 or 10 to generate $k_o$ and E and tested for the ability to determine the reaction order. Only zero order and the first order are discussed in this paper.

## RESULTS AND DISCUSSION

Typical temperature-time programs described by Eq. 1-3 are shown in Figure 1. The heating curve based on

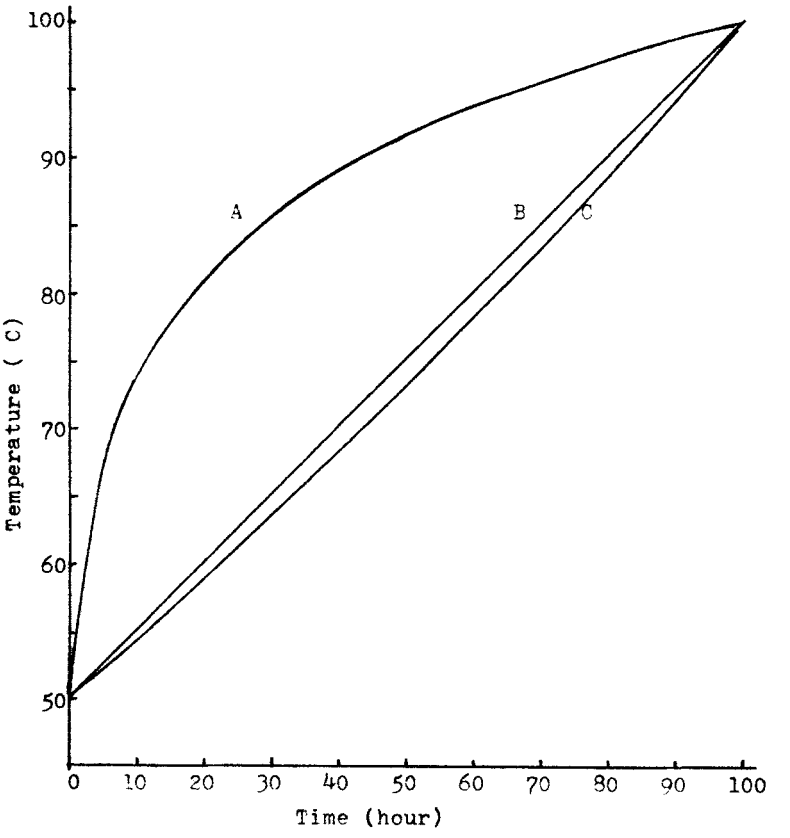


Figure 1

Temperature-time programs used in the non-isothermal study. A: Eq.1; B: Eq.3; C: Eq.2.

Eq.1 is convex, while the heating curve from Eq.2 is concave. The heating curve using Eq.3 is of course a straight line. This basic difference is reflected in the kinetic profiles. This is best illustrated using Figure 2 when the same pharmaceutical system is studied under non-isothermal conditions having the same initial and terminal temperature and the same duration of the study[1]. As anticipated, the extent of the degradation at any time is the greatest for the temperature-time program described by Eq.1, followed by those for Eq.3 and Eq.2. Another major difference lies in the early time of the study. Drug degradation becomes substantial at the early time when Eq.1 and Eq.3 are used, while the same is not true for Eq.2.

Note that a calculator with simple linear regression capacity is sufficient to manipulate the kinetic data using Eq.6, 9 or 10. A digital computer (3-5, 7) and an analog computer (8) must be used to generate $k_o$ and E when Eq.3 is used. Because of the involvement with a computer the non-isothermal method based on Eq.3 is excluded from the discussion in this paper.

When Eq.6 and Eq.9 are used for the data treatment the assumptions shown in Eq.5 and Eq.8 must be met. A 2%

---

1. Eq.4 and Eq.9 are used to compute these theoretical degradation curves. A numerical integration method is used for the non-isothermal study employing Eq.3 (6).

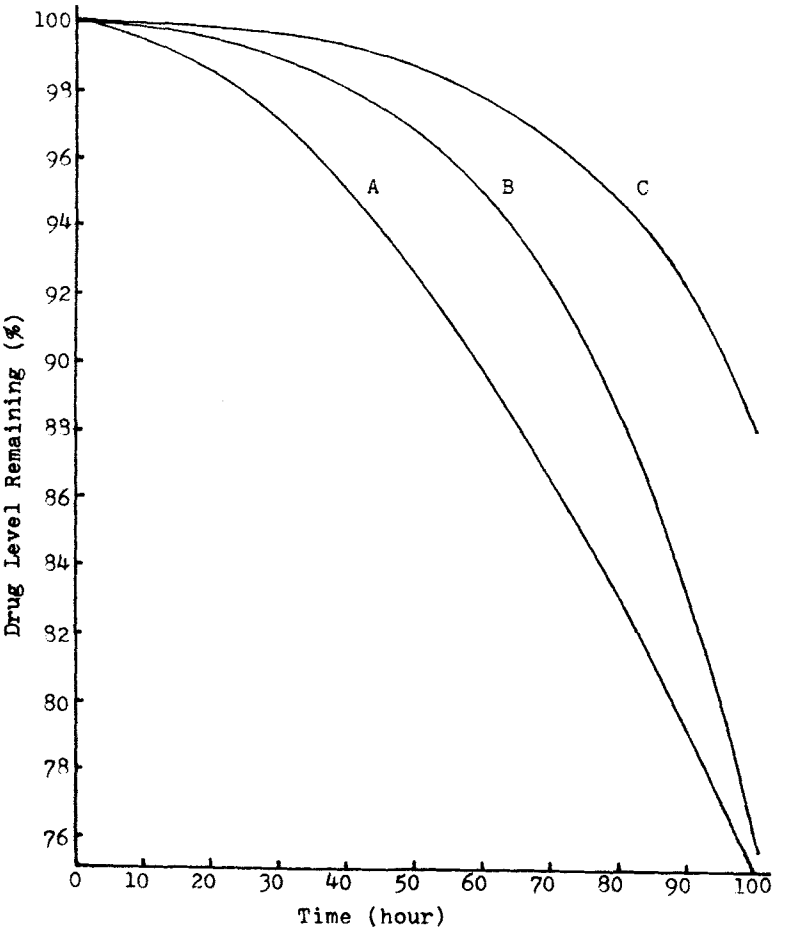


Figure 2

Kinetic profiles of a formulation having a shelf life of 24 months and degradation activation energy of 20 kcal/mole under the non-isothermal conditions described in Figure 1. First order kinetics is used in the calculation. A: Eq.1; B: Eq.3; C: Eq.2.

cut-off was used (9) for the method using Eq.6, i.e.:

$$\log\left[1-(k_o/k)^{1+(R/Eb)}\right] = 2\% \log f \qquad \text{Eq.11}$$

Therefore only those data collected after the cut-off time, $t_c$, are usable in the data treatment. This cut-off time is a complex function of E, b and $k_o$ and it can be determined by solving the following equation:

$$\left[1-(1+t_c)^{-\left[1+(Eb/R)\right]}\right] 50 - \left[k_o/1+(Eb/R)\right](1+t_c)^{1+(Eb/R)} = 0 \qquad \text{Eq.12}$$

When the same cut-off is adopted for Eq. 9:

$$Rk_o/aE = 2\% f \qquad \text{Eq.13}$$

the cut-off time, $t_c'$, is:

$$t_c' = R \ln 50/aE \qquad \text{Eq.14}$$

Preliminary calculation shows that for most pharmaceutically acceptable systems the non-isothermal kinetic method must span for a period of several days, rather than for a few hours as already reported (1-5, 7,9),to provide reasonable extent of degradation.

The kinetic profiles under different non-isothermal conditions (based on Eq.1) are shown in Figures 3-6. Briefly, the following observations are found:

1) Figure 3 indicates that raising the initial temperature increases the extent of degradation when the same formulation is studied.

2) With the same initial and terminal temperature, increasing the duration of the study increases the extent of degradation when the same formulation is studied

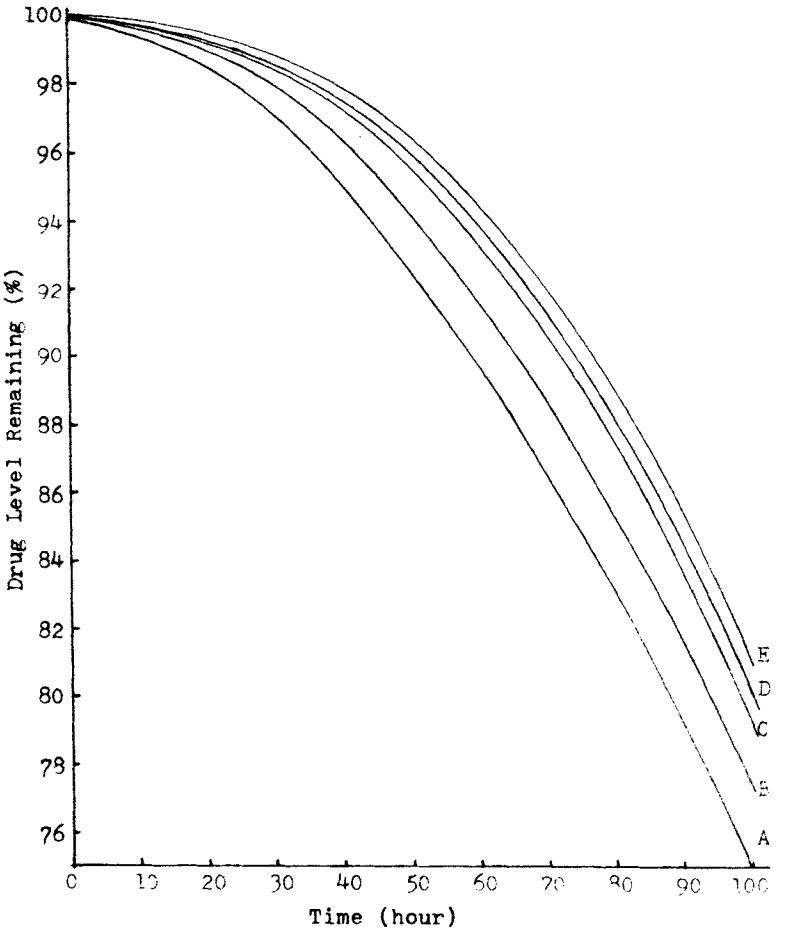


Figure 3

Kinetic profiles of a formulation having a shelf life of 24 months and degradation activation energy of 20 kcal/mole under different non-isothermal conditions having $T_f$= 100° and $t_f$= 100 hours and various initial temperatures ($T_o$). $T_o$: A=50°, B=40°, C=30°, D=25°, E=20°. First order kinetics is used in the calculation.

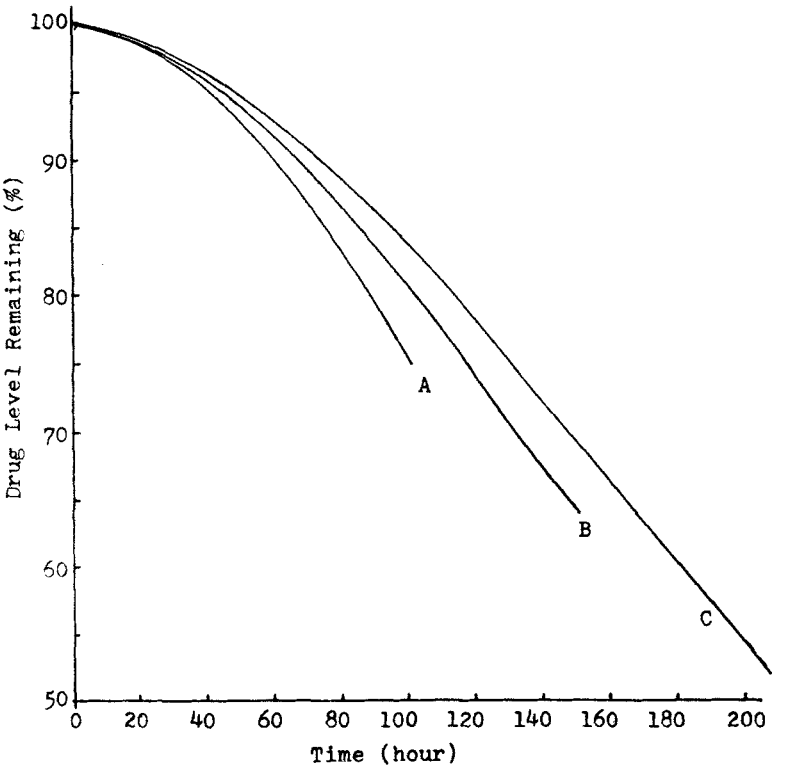


Figure 4

Kinetic profiles of a formulation having a shelf life of 24 months and degradation activation energy of 20 kcal/mole under different non-isothermal conditions having $T_0$=50°, $T_f$=100° and various duration of the study ($t_f$). $t_f$: A=100 hours; B=150 hours; C=200 hours. First order kinetics is used in the calculation.

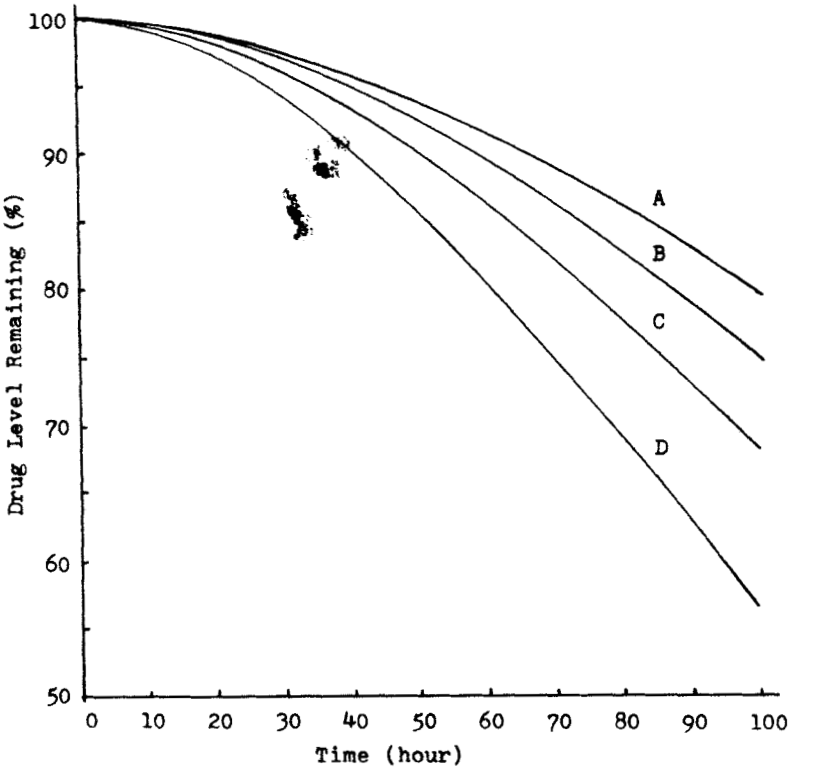


Figure 5

Kinetic profiles of the formulations with different shelf lives, but the same degradation activation energy (20 kcal/mole), under the same non-isothermal condition ($T_o$=50°, $T_f$=100° and $t_f$=100 hours based on Eq.1). $t_{90}$: A= 30 months; B= 24 months; C= 18 months; D= 12 months. First order kinetics is used in the calculation.

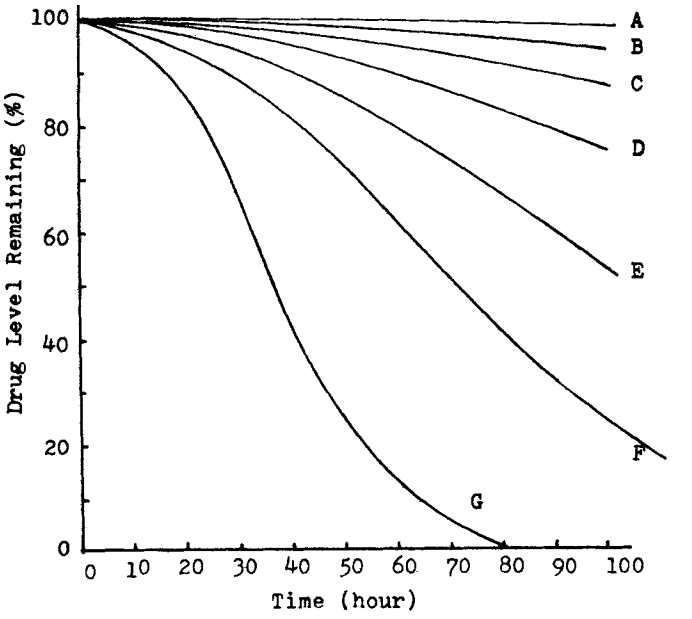


Figure 6

Kinetic profiles of the formulations with different degradation activation energy, but the same shelf life (24 months), under the same non-isothermal condition ($T_o$=50°, $T_f$=100°, $t_f$=100 hours based on Eq.1). E: A=10 kcal/mole; B=15 kcal/mole; C=17.5 kcal/mole; D=20 kcal/mole; E=22.5 kcal/mole; F=25 kcal/mole; G=30 kcal/mole. First order kinetics is used in the calculation.

3) Under the same non-isothermal condition, less stable formulation (smaller $t_{90}$ value) exhibits greater extent of degradation (Figure 5).

4) Figure 6 shows that under the same non-isothermal condition, a greater activation energy results in a greater extent of degradation when formulations having the same shelf life are studied.

These conclusions are of course anticipated. Figures 3-6 are presented mainly to show the degradation pattern under different situations. For most pharmaceutically acceptable systems, the conditions in which the temperature is raised from an initial temperature ($T_o$) of 20-50° to a terminal temperature ($T_f$) of 100° in a period ($t_f$) of 100 hours seem appropriate. The cut-off times ($t_c$) for those degradations described in Figures 3-6 are less than 5 hours. The sampling schedule shown in Table II can be used for the minimum inconvience in an industrial situation. As shown in Table III, the generation of $k_o$ and E according to Eq.6 for the stability assessment is quite satisfactory. It should be emphasized that these represent the best situations obtainable. Experimental variation will be inevitably involved in real situations.

The kinetic profile pattern when the temperature-time program Eq.2 is used is generally similar to Figures 3-6. However, as shown in Figure 1. the extent

TABLE II

A Possible Sampling Schedule When the Temperature-Time Program Eq.1 Is Employed

| Sampling Time | | Time Elapsed (hr) |
|---|---|---|
| Monday | 8AM (Study initiated) | 0 |
| Tuesday | 8AM | 24 |
| | 4PM | 32 |
| Wednesday | 8AM | 48 |
| | Noon | 52 |
| | 4PM | 56 |
| Thursday | 8AM | 72 |
| | Noon | 76 |
| | 4PM | 80 |
| Friday | 8AM | 96 |
| | Noon (Study terminated) | 100 |

of degradation is generally much diminished as can be seen from the drug levels remaining at the terminal temperature shown in Table IV. The cut-off times are also shown in Table IV when Eq. 9 is used for the data treatment. In general $t_c'$ is much greater than $t_c$ for the same system when subjected to the non-isothermal conditions with the same initial and terminal temperatures and the same duration of the study. As shown in Table IV, there are two instances in which $t_c'$ is greater than $t_f$, thereby invalidate the use of Eq.9 in the data treatment. In most other instances the extent of degradation between

TABLE III

Calculation Using Equation 6

| Parameters Used for Calculation | | | | Data Treatment Using Eq.6[a] | |
|---|---|---|---|---|---|
| $t_{90}$ (Month) | E (kcal/mole) | $T_o$ (°C) | $t_f$ (hr) | $t_{90}$ (Month) | E (kcal/mole) |
| 24 | 20 | 20 | 100 | 23.99 | 20.08 |
| 24 | 20 | 25 | 100 | 23.80 | 19.95 |
| 24 | 20 | 30 | 100 | 24.52 | 20.09 |
| 24 | 20 | 40 | 100 | 24.70 | 20.10 |
| 24 | 20 | 50 | 100 | 25.0 | 20.14 |
| 24[b] | 20 | 50 | 100 | 25.0 | 20.14 |
| 24[c] | 20 | 50 | 150 | 25.44 | 20.20 |
| 24 | 20 | 50 | 200 | 24.36 | 20.06 |
| 24 | 10 | 50 | 100 | [d] | |
| 24 | 15 | 50 | 100 | [d] | |
| 24 | 17.5 | 50 | 100 | 25.8 | 17.66 |
| 24 | 20 | 50 | 100 | 25.0 | 20.14 |
| 24 | 22.5 | 50 | 100 | 23.46 | 22.48 |
| 24 | 25 | 50 | 100 | 24.93 | 25.13 |
| 24[e] | 25 | 50 | 100 | 22.9 | 15.96 |
| 24[f] | 30 | 50 | 100 | 24.29 | 30.04 |
| 12 | 20 | 50 | 100 | 13.14 | 20.33 |
| 18 | 20 | 50 | 100 | 18.78 | 20.16 |
| 24 | 20 | 50 | 100 | 25.0 | 20.14 |
| 30 | 20 | 50 | 100 | 31.32 | 20.16 |

a. In all cases, $T_f$=100° . A first order degradation is used in the calculation unless otherwise stated. The sampling schedule shown in Table II is employed in the data treatment. All $r^2$=0.99 - 0.9999.
b. Sampling times: 64, 72, 88, 92, 96, 112, 116, 120, 136, 140, 144 hours (study beginning at 4PM Friday)
c. Sampling times: 64, 72, 88, 92, 96, 112, 116, 120, 136, 140, 144, 160, 168 hours (study beginning 4PM Friday)
d. The active ingredient does not degrade sufficiently ( < 10%)
e. The function f for the zero order is used in the calculation.
f. Sampling times: 16, 18, 20, 22, 24, 40, 42, 44, 46, 48 hours (study beginning 8AM Monday)

TABLE IV

The Cut-off Times And The Drug Levels at Cut-off Times And Terminal Temperature When Temperature-Time Program Eq.2 Is Used

| $t_{90}$ (Month) | E (kcal/mole) | $T_o$ (°C) | $t_f$ (hour) | $t_c'$ (hour) | $A_{t_c'}/A_o$ (%) | $A_{t_f}/A_o$ (%) |
|---|---|---|---|---|---|---|
| 24 | 20 | 20 | 100 | 54 | 99.76 | 92.93 |
| 24 | 20 | 25 | 100 | 58 | 99.55 | 92.35 |
| 24 | 20 | 30 | 100 | 63 | 99.16 | 91.70 |
| 24 | 20 | 40 | 100 | 76 | 97.08 | 90.13 |
| 24 | 20 | 50 | 100 | 94 | 90.59 | 88.03 |
| 24 | 20 | 50 | 100 | 94 | 90.59 | 88.03 |
| 24 | 20 | 50 | 150 | 141 | 86.23 | 82.59 |
| 24 | 20 | 50 | 200 | 188 | 82.07 | 77.49 |
| 24 | 10 | 50 | 100 | 188 | a | 93.33 |
| 24 | 15 | 50 | 100 | 125 | a | 91.53 |
| 24 | 20 | 50 | 100 | 94 | 90.59 | 88.03 |
| 24 | 25 | 50 | 100 | 75 | 86.04 | 56.96 |
| 24 | 30 | 50 | 100 | 63 | 77.98 | 7.64 |
| 12 | 20 | 50 | 100 | 94 | 82.07 | 77.49 |
| 18 | 20 | 50 | 100 | 94 | 87.66 | 84.36 |
| 24 | 20 | 50 | 100 | 94 | 90.59 | 88.03 |
| 30 | 20 | 50 | 100 | 94 | 92.40 | 90.30 |

In all cases, $T_f = 100°$. A first order degradation is used in the calculation.

a. $t_c' < t_f$.

$t'_c$ and $t_f$ is quite small (typically 5%). This makes the data treatment utilizing Eq.9 rather difficult and the prediction based on this narrow range is questionable in the real situations.

Eq.10 provides an alternative method for the data treatment which eliminates the restraint of the cut-off time. However, a constant time interval ($\Delta t$) is required in the data treatment. A sampling schedule can not be arranged without difficultyin an industrial situation. For this reason, the non-isothermal kinetic method based on Eq.2 is not recommended.

It was suggested (9) that it would be impossible to determine the reaction order when the degradation was not monitored far enough. However, for pharmaceutically acceptable systems discussed in this paper, even when the degradation is allowed to proceed considerably Eq.6 is still unable to differentiate first order from zero order. Calculation shows that substituting the function f for first order or zero order in Eq.6 leads to equally acceptable straight line (Table III). Despite this shortcoming it is generally a good idea to follow the degradation sufficiently far to obtain more representative data. This can be achieved by careful selection of the non-isothermal condition.

Some practical consideration and limitations merit further discussion. All non-isothermal accelerated kinetic

methods are based on the Arrhenius relationship. Therefore these methods are applicable only for those systems which obey the Arrhenius relationship.

Perhaps the major reason that the non-isothermal accelerated kinetic method did not enjoy widespread use is the lack of the hardware to provide the desired temperature-time program easily. Manually adjusted thermoregulator in the water bath (1, 3-5) and variable transformer-controlled heater in the oil bath (9) have been used. No detail was given for a water bath whose temperature was stated to be controlled by a variable speed programmer (2). Manual adjustment of the temperature is undoubtly tedious. However, it can still be accomplished if only a few hours are involved in a study, which is the case for the papers published thus far. For a study which must span a few days, any manually adjusted device would not be applicable for obvious reason. At least one microprocessor-controlled mechanical convection oven is available to provide the desirable non-isothermal condition (Eq.1-3) automatically for the time period discussed in this paper[2].

The container and the closure are integral parts of the stability characteristics of a pharmaceutical

---

[2] Blue M Micro Might Microprocessor-Controlled Mechanical Convection Oven, Blue M Electric Company, Blue Island, Illinois 60406.

product and should be used in the test if possible. The smallest possible containers are preferred to ensure quick response to the temperature change of the environment. FDA's current policy allows the container size be expanded up to 8 times of the size tested (10).

## REFERENCES

1. A.R. Rogers, J. Pharm. Pharmac., 15, 101T(1963)

2. S.P. Eriksen and H. Stelmach, J. Pharm. Sci., 54, 1029(1965)

3. M.A. Zoglio, J.J. Windheuser, R. Vatti, H.V. Maulding, S.S. Kornblum, A. Jacobs and H. Hamot, J. Pharm. Sci., 57, 2080(1968)

4. H.V. Maulding and M.A. Zoglio, J. Pharm. Sci., 59, 333(1970)

5. M.A. Zoglio, H.V. Maulding, W.H. Streng and W.C. Vincek, J. Pharm. Sci., 64, 1381(1975)

6. Wu-huang Yang, Unpublished data.

7. B.W. Madsen, R.A. Anderson, D. Herbison-Evans and W. Sneddon, J. Pharm. Sci., 63, 777(1974)

8. A.I. Kay and T.H. Simon, J. Pharm. Sci., 60, 205(1971)

9. B.R. Cole and L. Leadbeater, J. Pharm. Pharmac., 18, 101(1965)

10. Quality Control Reports, The Gold Sheets, 12(11) November 1978.

## APPENDIX

Readers who refer to reference 2 will find some equations cited therein are different from those mentioned in this paper. Errors in reference 2 are pointed

out in this appendix. All equation, table and figure numbers are those used in the original paper unless otherwise stated.

Eq.1 is true for the zero order and the first order, but is incorrect for both second orders listed in Table I. The functions $f(C_a, C_b, \ldots)$ and $f(C_a^o, C_b^o, \ldots)$ for both second orders in Table I should be interchanged.

Eq.5, 6, 7 and 8 should read as:

$$f(C_a^o, C_b^o, \ldots) = \frac{Rk_{obs}(T_o)}{aE} e^{(aE/R)t} + f(C_a, C_b, \ldots) - \frac{Rk_{obs}(T_o)}{aE} \qquad \text{Eq.5}$$

$$f(C_a^o, \ldots) - f(C_a^t, \ldots) = \frac{Rk_{obs}(T_o)}{aE} e^{aEt/R} - \frac{Rk_{obs}(T_o)}{aE} \qquad \text{Eq.6}$$

$$f(C_a^o, \ldots) - f(C_a^{t+\Delta t}, \ldots) = \frac{Rk_{obs}(T_o)}{aE} e^{[aE(t+\Delta t)]/R} - \frac{Rk_{obs}(T_o)}{aE} \qquad \text{Eq.7}$$

$$\log\left[f(C_a^t, \ldots) - f(C_a^{t+\Delta t}, \ldots)\right] = \frac{aE}{2.303R} t + \log\left\{\left[e^{(aE/R)\Delta t} - 1\right]\left[\frac{Rk_{obs}(T_o)}{aE}\right]\right\} \qquad \text{Eq.8}$$

The labels of the abscissa of Figure 3 should read 0, 0.5, 1.0 and 1.5.

No detail about the temperature-time program was given in reference 2. However the heating rate constant, a, can be estimated from the slope of the straight line in Figure 3 and the activation energy in Table II for p-nitrophenol acetate. The value of a is estimated to be 0.000079. It is interesting to note that with this a value the cut-off time ($t_c'$) is calculated to be 4.68 hours using Eq.14 in this paper. Since the kinetic experiment in reference 2 lasted for only 2.5 hours, Eq.9 in this paper is not applicable at all for the degradation of p-nitrophenol acetate with the non-isothermal condition used in reference 2.