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THE CONCEPT OF EQUILIBRIUM TEMPERATURE TIME EQUIVALENTS IN ACCELERATED STABILITY TESTING: A NEW MATHEMATICAL FORMULATION AND ITS EFFECT IN PHARMACEUTICAL PRODUCT DEVELOPMENT

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ABSTRACT

Borrowing the mathematics used in the nonisothermal kinetic method, a new and simpler mathematical treatment of the concept of the Equilibrium Temperature Time Equivalents (ETTE) is presented. The effect of the ETTE in the pharmaceutical product stability assessment is discussed. The analysis shows that due to the stability characteristics of most drug candidates, the ETTE has very little effect on the stability data treatment.

INTRODUCTION

During the early stage of the product development process, accelerated stability testing at high temperature is usually employed to access the stability characteristics

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of the prototypes and/or to establish an appropriate overage. It is not uncommon in an industrial situation that the samples, after being placed in an oven, are allowed to be gradually heated up before reaching the oven temperature. A gradual cooling is experienced by the samples after they are withdrawn from the oven at the appropriate sampling times before the analysis. The concept of the Equilibrium Temperature Time Equivalents (ETTE) was developed (1) to correct the initial heating period and the subsequent cooling time period.

This paper describes a new and simpler mathematical treatment of the ETTE and investigates its effect in the pharmaceutical product development.

THEORETICAL

The following situation is considered. Packaged samples at room temperature are placed in an oven at time zero. The temperature of the samples gradually increases from the room temperature (T_o) and reaches the oven temperature (T_{ov}) at time t*. Let the drug level at t* be C*. Samples are withdrawn from the oven at time t_i ($i = 1, 2, \ldots, n$). Let the drug level at t_i be C_i. Prior to the assay, the samples are allowed to cool to the room temperature at time t_i*. Let the drug level at t_i* be C_i*.

The ETTE at each sampling time is composed of three parts:

$$(ETTE)_i = t_h + (t_i - t^*) + (t_c - t_i) \qquad \text{Eq.1}$$

The term $t_i - t^*$ accounts for the time period when the temperature of the samples actually remains at the oven temperature.

The term t_h is called "heating time equivalent" and can be calculated as follows for a first order degradation:

$$t_h = \ln(C_o/C^*) \; / \; k_{ov} \qquad \text{Eq.2}$$

where C_o is the initial drug level and k_{ov} is the rate constant at the oven temperature. Thus t_h accounts for time equivalent at the oven temperature for the extent of degradation incurred during the heating period.

The term $t_c - t_i$ is called "cooling time equivalent" and is expressed as:

$$t_c - t_i = \ln(C_i/C_i^*) \; / \; k_{ov} \qquad \text{Eq.3}$$

The term $t_c - t_i$ has a similar meaning as t_h.

In actual practice, only C_o and C_i^* are determined. Therefore Eq.2 and Eq.3 must be further treated in order to calculate t_h and $t_c - t_i$.

During the heating and the cooling period, the samples undergo degradation when the temperature is changing. The mathematical treatment for nonisothermal kinetic study (2) can thus be applied to these situations. Eq.2 and Eq.3 can be expressed as (see Appendix for the derivation):

$$t_h = \int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_{ov}} - \frac{1}{T_h(t)}\right)\right] dt \qquad \text{Eq.4}$$

$$t_c - t_i = \int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_{ov}} - \frac{1}{T_c(t)}\right)\right] dt \qquad \text{Eq.5}$$

where $T_h(t)$ and $T_c(t)$ are the temperature-time relationship experienced by the samples during the heating and the cooling period respectively. The time scale in Eq.5 is counted from the time the samples are withdrawn from the oven.

Numerical integration method can be employed to evaluate the finite integrals in Eq.4 and Eq.5.

RESULTS AND DISCUSSION

It was suggested that the samples were subjected to an exponential temperature increase or decrease during the heating and the cooling period:

$$T = T_{ov} - (T_{ov} - T_o) \exp(-Z_h t) \qquad \text{Eq.6}$$

$$T = T_o - (T_o - T_{ov}) \exp(-Z_c t) \qquad \text{Eq.7}$$

where T is the sample temperature at time t, Z_h and Z_c are the heating rate coefficient and the cooling rate coefficient respectively.

With these two temperature-time functions, Eriksen et al. (1) employed the following equations to calculate t_h and $t_c - t_i$:

$$t_h = (A/Z_h k_{ov}) \int_{T_o}^{T_{ov}} [\exp(-E/RT)]/(T_{ov} - T)\, dT \qquad \text{Eq.8}$$

$$t_c - t_i = (A/Z_c k_{ov}) \int_{T_{ov}}^{T_o} [\exp(-E/RT)]/(T_o - T)\, dT \qquad \text{Eq.9}$$

where A is the preexponential factor in the Arrhenius relationship. It can be easily proved that Eq.8 and Eq.9 are equivalent to Eq.4 and Eq.5 respectively. Eq.8 and Eq.9 were used since the integrals in both equations are independent of the nonisothermal conditions during the heating and the cooling period.

The advantages of Eq.4 and Eq.5 over Eq.8 and Eq.9 are twofold. Firstly, only the activation energy is needed in order to evaluate the integrals in Eq.4 and Eq.5. While the values of A, E and k_{ov} are required when using Eq.8 and Eq.9 to calculate t_h and t_c-t_i. Secondly, as shown in Figure 1 and Figure 2, the integrands in both Eq.8 and Eq.9 increase quite rapidly when the sample temperature approaches the final temperature. Therefore the values of the integrals (area under curve) are extremely sensitive to the final temperature used. By comparison, the exponential functions in Eq.4 and Eq.5 are much smoother and easier to manipulate using a numerical integration method.

Since the exponential functions are used for the temperature-time relationship during the heating and the cooling period, the sample never reaches the final temperature theoretically. The time t* and t_i* were approximated (1) by the time when the reaction rate had reached 95% of its final value at the final temperature.

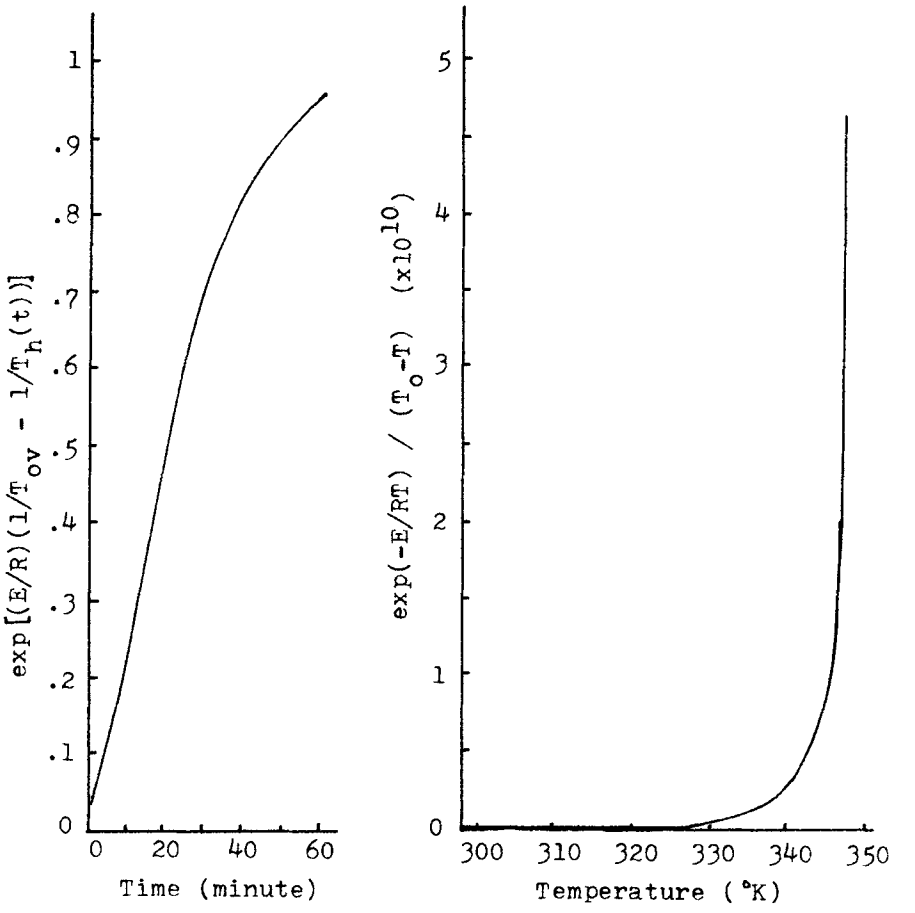

Figure 1

Graphical representation of the exponential functions in Eq.4 and Eq.8 using the condition in the example in reference 1.

Using this criterion and the example in reference 1, the integrals in Eq.4, 5, 8 and 9 are numerically integrated using the trapezoidal rule. The results are shown in Table I. Using the results in Table I, the values of t_h and t_c-t_i are calculated and are shown in

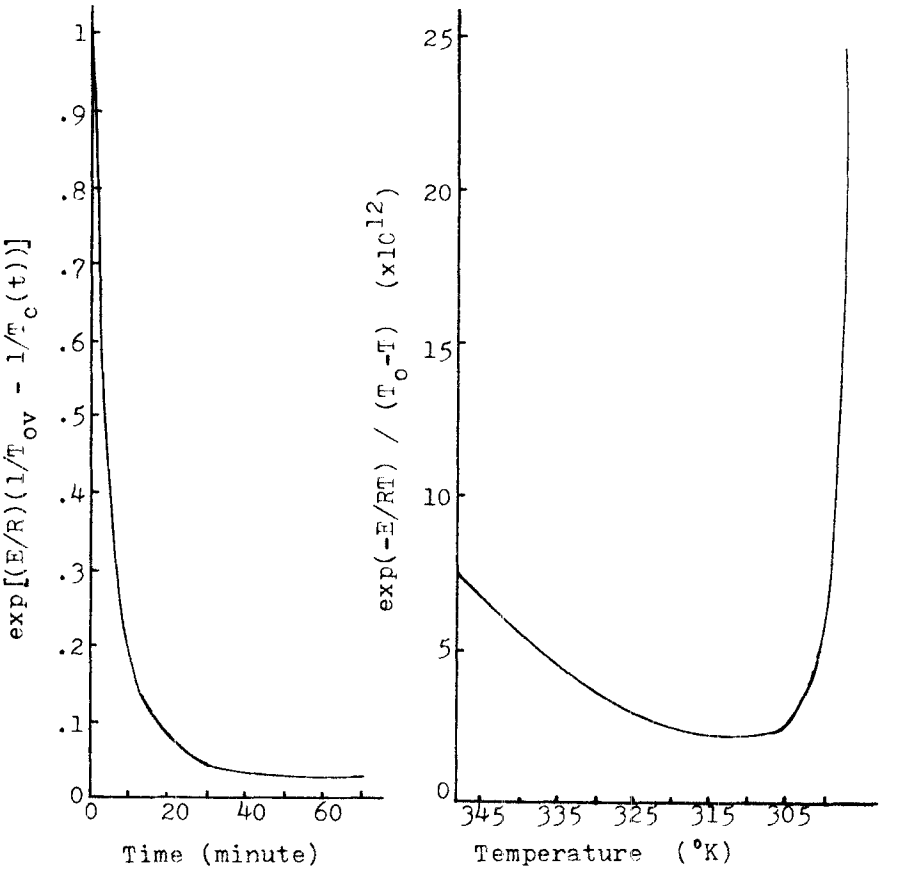

Figure 2

Graphical representation of the exponential functions in Eq.5 and Eq.9 using the condition in the example in reference 1

Table II. Comparable results are obtained. The discrepancy may lie in the different choice of the final temperature.

With the validity of Eq.4 and Eq.5 documented, let us turn to a real world situation. Most drug candidates

TABLE I

The values of the integrals in Eq.4, 5, 8 and 9 at 75° when $A=10^{10}$, E=15 kcal/mole, $Z_h=0.0313\times 2.303$ and $Z_c=0.0295\times 2.303$

	This paper*	Reference 1
$\int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_{ov}}-\frac{1}{T_h(t)}\right)\right]dt$	34.24 minutes	-
$\int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_o}-\frac{1}{T_c(t)}\right)\right]dt$	7.67 minutes	-
P_h**	2.538	2.423
P_c**	0.5209	0.5080

*During the heating period, the rate constant reaches 95% of the rate constant at 75° at 58 minutes (or 347.2°K). During the cooling period, the rate constant reaches 95% of the rate constant at 25° at 70 minutes (or 298.4°K) after the samples are withdrawn from the oven.

**See reference 1 for definition.

TABLE II

The values of t_h, t_c-t_i and $(ETTE)_i$ after 4-hour storage at 75° when the condition of Table I applies

	This paper		Reference 1
	Eq.4 or Eq.5	Eq.8 or Eq.9	
t_h (minutes)	34.24	35.21	33.61
t_c-t_i (minutes)	7.67	7.67	7.48
$(ETTE)_i$ (minutes)	223.91	224.88	171.09*

* A t*=110 minutes was used in the calculation in reference 1. This is probably in error. Using t*=58 minutes, this $(ETTE)_i$ is equal to 223.09 minutes which is then consistent with the values obtained in this paper.

are relatively stable. More often than not, an accelerated stability test usually takes weeks or even months to accomplish. It is also not unusual for the samples, after being removed from the oven, to be placed on a shelf for a week or so before the analysis is performed. It is desirable to investigate the effect of the heating, cooling and waiting period on the prediction power of such an accelerated stability test for a pharmaceutically acceptable system. Stated generally, the problem to be investigated is as follows. A packaged prototype, after being entered in an oven, goes through the heating period and reaches the oven temperature at time t*. Samples are withdrawn at time t_i (i=1,2,..., n) and then go through the cooling and the waiting period before the analysis is made at time t_i'. Let the drug level at t_i be C_i, and the drug level at t_i' be C_i'. Note that C_i' is determined, but not C_i. Data pairs (t_i, C_i') are then used for mathematical treatment using an appropriate rate equation.

The problem is best illustrated using an example. A prototype having an expected shelf life (t_{90}) of 12 months at 25° is tested at 75°. Let the first order degradation activation energy of the active ingredient be 20 kcal/mole. The samples are subjected to the heating and the cooling period according to the Z_h and Z_c in Table I. One week at 25° is elapsed between the end of the cooling period and the time when the analysis is made.

A defferent criterion for the terminal temperature in the heating and the cooling period will be used. Since most ovens (or oven rooms) have temperature variation of typically $\pm 0.5^{\circ}$, a terminal temperature will be defined as the temperature when the sample temperature reaches this range. In this example, the terminal temperature is 74.5° for the heating period and 25.5° for the cooling period. Using the Z_h and Z_c values in Table I, the samples reach the terminal temperature at 64 minutes after the samples are placed in the oven and at 68 minutes after the samples are removed from the oven.

An accelerated stability test allows the formulator an oppotunity to determine the reaction order unequivocally by allowing the degradation to proceed to a sufficient extent. When a 80% degradation is desired, a 6-week stability study is required for the example under investigation. An adequate sampling schedule would be withdrawing samples every week for the 6-week period, thus providing six data points.

Table III lists the theoretical drug level remaining at each sampling time and the values of C_i' after correcting for the degradation incurred during the heating, cooling and waiting period.

Data treatment using (t_i, C_i'), excluding the initial data point (0, 100), with a first order rate equation gives an initial drug level of 99.69% which is equivalent to 100% for all practical purposes. Using a

TABLE III

Theoretical drug level remaining and C_i' at various sampling times

Time (week)	Drug level remaining (%)	
	theoretical	C_i'
0	100	-
1	76.99	76.75
2	59.27	59.09
3	45.63	45.49
4	35.13	35.02
5	27.05	26.96
6	20.82	20.76

very unstable system, Scott and Lachman (3) concluded that while satisfactory rate constant could be determined from the data even after the samples are subjected to the heating and the cooling period, the use of $t_{x\%}$ would be inappropriate since the intercept of the straight line at time zero would not be 100%. It is seen from the analysis in this paper that the error is small enough to be ignored when a pharmaceutically acceptable system is studied. For the relatively unstable system, such as the one used by Scott and Lachman, instaneous heating and cooling of the samples as described in Experiment A in reference 3 is considered as a standard procedure in performing a kinetic experiment.

Eriksen et al. (1) suggested that the sampling time be long enough to minimize the magnitude of the error caused by the heating and the cooling period. This paper concludes that this is actually an inherent characteritics when a very stable system is studied.

REFERENCES

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3. M.W. Scott and L. Lachman, J. Pharm. Sci., 51, 125 (1962)

APPENDIX

Using the mathematical treatment in reference 2, Eq.2 can be expressed as:

$$t_h = k_o \int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_o} - \frac{1}{T_h(t)}\right)\right]dt \;/\; k_{ov} \qquad \text{Eq.A1}$$

Using the Arrhenius relationship, the ratio k_o/k_{ov} can be expressed as:

$$k_o/k_{ov} = \exp\frac{E}{R}\left(\frac{1}{T_{ov}} - \frac{1}{T_o}\right) \qquad \text{Eq.A2}$$

Substitution of Eq.A2 to Eq.A1, followed by rearrangement results in Eq.4.

Eq.3 can be expressed as:

$$t_c - t_i = k_{ov} \int_0^t \exp\left[\frac{E}{R}\left(\frac{1}{T_{ov}} - \frac{1}{T_c(t)}\right)\right]dt \;/\; k_{ov} \qquad \text{Eq.A3}$$

The elimination of k_{ov} from Eq.A3 gives Eq.5.