DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 9(5), 821-835 (1983)

THEORETICAL ANALYSIS OF THE EFFECT OF THE TEMPERATURE FLUCTUATION IN AN ISOTHERMAL STABILITY STUDY

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ABSTRACT

The effect of the temperature fluctuation in a nominal isothermal stability study is theoretically analyzed using hypothesized temperature-time functions. It is concluded that for symmetrical temperature-time profiles the extent of degradation in the real nonisothermal condition is less than that in the nominal isothermal condition. However, with the temperature fluctuaction obtainable with the current thermoregulated devices, the difference between the two is usually very small and can be neglected except for extremely fast reactions.

INTRODUCTION

In an isothermal kinetic study, the system to be investigated is stored in an environment in which a constant temperature is maintained. The constant temperature is provided by a thermoregulated water or oil bath as well as an oven or oven room. Most of these

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devices employ the cycling method, i.e., turning a heating element on and off, and thus providing a temparature fluctuation around the set temperature. We are then actually dealing with a nonisothermal condition instead of the prescribed isothermal condition. The magnitude of the temperature fluctuation depends upon, to a great extent, the design charcteristics of the thermoregulator in these devices. A range of ± 0.2 to 0.5°C or less aroung the nominal temperature is typical for a water bath and a range of ± 1°C may be typical for the ovens. The duration of this temperature fluctuation is yet another characteristics of these devices.

Intuitively, it is contented that the extent of chemical degradation incurred in the real nonisothermal condition is equal to that experienced in the hypothetical isothermal condition. This paper reports a theoretical analysis of the effect of this temperature fluctuation in an isothermal kinetic study using several simulated temperature-time functions.

THEORETICAL

Consider the rate equation of a first order reaction:

$$- dA/dt = kA \qquad \text{(Eq.1)}$$

where A is the drug level at any time t and k is a rate constant at a specific temperature T.

The rate constant at any temperature in a nonisothermal condition can be obtained using the Arrhenius equation:

$$k = k_o \exp[(E/R)(1/T_o - 1/T(t))] \qquad \text{(Eq.2)}$$

where k_o is the rate constant at the nominal temperature T_o, E is the degradation activation energy, R is the gas constant and T(t) is a characteristic temperature-time function for the nonisothermal condition.

The temperature in a nonisothermal condition usually undergoes a cyclic change. For the simplicity of a mathematical analysis, it is assumed that the temperature begins with T_o, being raised to T_o+a, followed by being lowered to T_o-a and the cycle is completed when the temperature is returned back to T_o. This provides a temperature range of $T_o \pm a$ in a time period of t_c. The previously defined T(t) is sufficient to describe this temperature change over time.

Substituting Eq.2 into Eq.1 and integrating with the boundary conditions of $A=A_o$ at $t=0$ and $A=A_1$ at $t=t_c$, we obtain:

$$- \int_{A_o}^{A_1} dA/A = k_o \int_0^{t_c} \exp[(E/R)(1/T_o - 1/T(t))]dt \qquad \text{(Eq.3)}$$

Defining:

$$I_c = \int_0^{t_c} \exp[(E/R)(1/T_o - 1/T(t))] \qquad \text{(Eq.4)}$$

and solving Eq.3 lead to:

$$A_1 = A_o \exp(-k_o I_c) \qquad \text{(Eq.5)}$$

Since the temperature change in the second cycle is the same as that in the first cycle, we have:

$$A_2 = A_1 \exp(-k_o I_c) \qquad \text{(Eq.6)}$$

where A_2 is the drug level at $t=2t_c$.

The combination of Eq.5 and Eq.6 leads to:

$$A_2 = A_o \exp(-2k_o I_c) \qquad \text{(Eq.7)}$$

In general, after n temperature cycles:

$$A_n = A_o \exp(-nk_o I_c) \qquad \text{(Eq.8)}$$

It can be shown that the kinetics in an isothermal condition is a special case of that in a nonisothermal condition. When an isothermal condition is dealt with, $I_c=t_c$ since $T(t)=T_o$ at all times during the cycle in Eq.4. Substituting this relationship into Eq.8, we obtain:

$$A_n^i = A_o \exp(-nk_o t_c) \qquad \text{(Eq.9)}$$

where the superscript "i" represents "isothermal" condition. Note that the total time elapsed is:

$$t = nt_c \qquad \text{(Eq.10)}$$

therefore:

$$A_n^i = A_o \exp(-k_o t) \qquad \text{(Eq.11)}$$

Eq.11 is the integrated rate equation of a first order reaction in an isothermal condition.

The drug level at a specific time in a real nonisothermal condition can be compared with that in an isothermal condition by dividing Eq.8 by Eq.9:

$$A_n/A_n^i = \exp[-k_o t(I_c/t_c - 1)] \qquad \text{(Eq.12)}$$

Eq.14 is in a convenient form to access the effect of the temperature fluctuation.

For stable pharmaceutical systems, it is convenient to compare the drug levels at t_{90}, which is defined as the time period required for the drug level to reach 90% of the initial level. For a first order reaction:

$$k_o = 0.105/t_{90} \qquad \text{(Eq.13)}$$

Table I

Equations For The Comparison Of Drug Levels For The Nonisothermal Condition And The Isothermal Condition

Parameter	Zero Order	First Order	Second Order
A_n	$A_o - nk_oI_c$ (Eq. 8)	$A_o \exp(-nk_oI_c)$ (Eq.18)	$(A_o^{-1} + nk_oI_c)^{-1}$ (Eq.23)
A_n/A_n^i	$\frac{A_o - k_ot(I_c/t_c)}{A_o - k_ot}$ (Eq.19)	$\exp[-k_ot(I_c/t_c - 1)]$ (Eq.12)	$\frac{A_o^{-1} + k_ot}{A_o^{-1} + k_ot(I_c/t_c)}$ (Eq.24)
$\frac{A_{n,t_{1/2}}}{A_{n,t_{1/2}}^i}$	$2 - (I_c/t_c)$ (Eq.20)	$\exp[-0.693(I_c/t_c - 1)]$ (Eq.16)	$2/(1 + I_c/t_c)$ (Eq.25)
$\frac{A_{n,ht_{1/2}}}{A_{n,ht_{1/2}}^i}$	$2^h - (2^h - 1)(I_c/t_c)$ (Eq.21)	$\exp[-0.693h(I_c/t_c - 1)]$ (Eq.17)	$2^h/[1 + (2^h - 1)(I_c/t_c)]$ (Eq.26)
$\frac{A_{n,t_{90}}}{A_{n,t_{90}}^i}$	$[10 - (I_c/t_c)]/9$ (Eq.22)	$\exp[-0.105(I_c/t_c - 1)]$ (Eq.14)	$10/[9 + (I_c/t_c)]$ (Eq.27)

Thus for $t=t_{90}$, Eq.12 becomes:

$$A_{n,t_{90}}/A^{i}_{n,t_{90}} = \exp[-0.105(I_c/t_c - 1)] \qquad \text{(Eq.14)}$$

In general, after h t_{90}'s:

$$A_{n,ht_{90}}/A^{i}_{n,ht_{90}} = \exp[-0.105h(I_c/t_c - 1)] \qquad \text{(Eq.15)}$$

For fast reactions, it may be more convenient to compare the drug level at the half life ($t_{1/2}$) or at h half lives (h $t_{1/2}$). The equations for these purposes can be derived in a similar manner and are shown in Table I.

Equations for other kinetic orders can also be derived. Those for the zero order and the second order are also shown in Table I. The derivation for a mth kinetic order ($m\neq1$) is presented in Appendix 1.

RESULTS AND DISCUSSION

The numerical values of I_c are needed according to the equations listed in Table I to access the effect of the temperature fluctuation.

As defined in Eq.4, a function T(t) must be known for a numerical evaluation of I_c. Three T(t) functions (Table II) are used in this paper and are represented in Fig. 1.

Depending upon the temperature-time function employed for the nonisothermal condition, I_c can be evaluated by either an exact integration or a numerical integration as shown in Table II.

I_c is a function of T_o, a, t_c and E. Its values are evaluated using the following commonly encountered range for each parameter: T_o: 30 - 80°C; a: 0.2 - 2°C; t_c: 0.5 - 2 hours; and E: 5 - 30

Table II

Simulated Tamperature-Time Functions For The Nonisothermal Condition

Temperature-Time Function*	$T(t)=T_o+a,\ 0\le t\le t_c/2$ $T_o-a,\ t_c/2\le t\le t_c$ (Eq.28)	$T(t)=T_o+a\sin\omega t$ (Eq.31) $\omega=2\pi/t_c$ (Eq.30)	$T(t)=T_o+\alpha t, 0\le t\le t_c/4$ $(T_o+2a)-\alpha t, t_c/4\le t\le 3t_c/4$ $(T_o-4a)+\alpha t, 3t_c/4\le t\le t_c$ (Eq.33) $\alpha=4a/t_c$ (Eq.32)
I_c Evaluated By	$(t_c/2)\{\exp[(E/R)(1/T_o - 1/(T_o+a))]+\exp[(E/R)(1/T_o - 1/(T_o-a))]\}$	Numerical Integration Using Eq.4**	Numerical Integration Using Eq.4**

* In all cases, $T(t+nt_c) = T(t)$.

** The trapezoidal rule is used for the numerical integration.

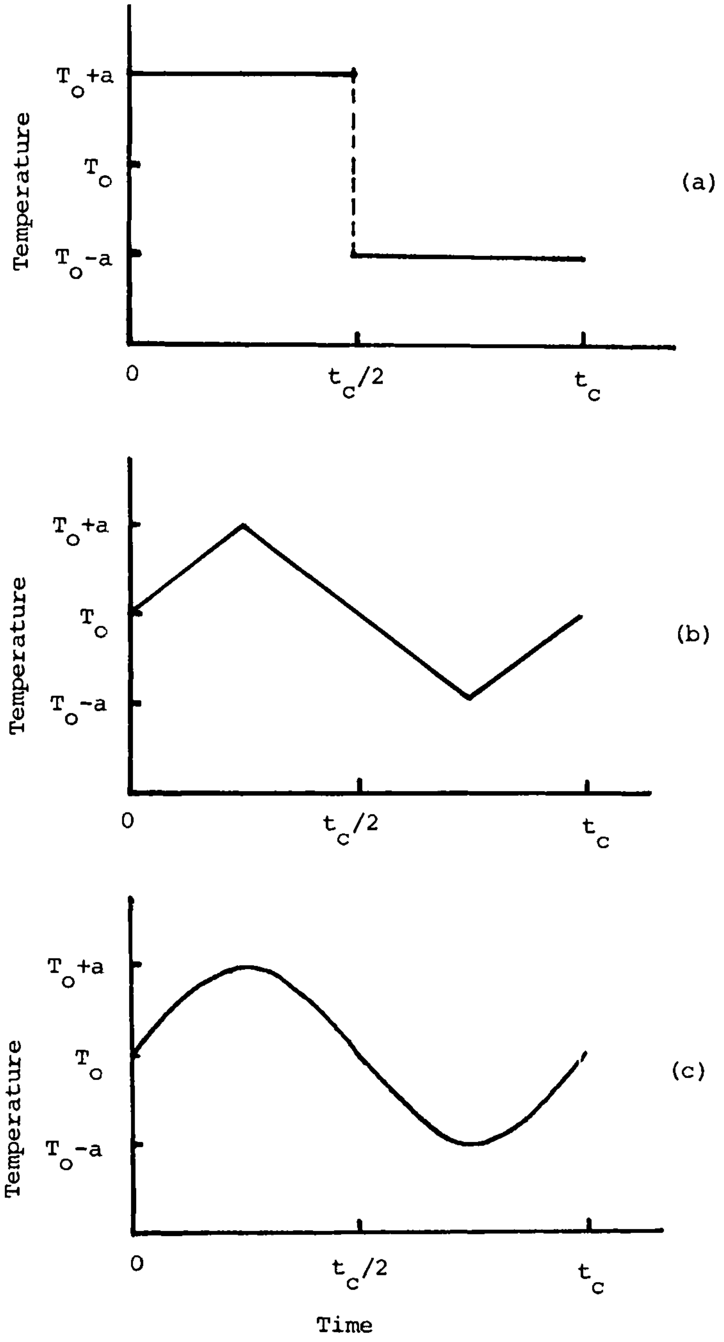

Figure 1

Temperature-time functions for the nonisothermal conditions. a: Eq.28; b: Eq.33; c: Eq.31.

kcal/mole. However, it should be emphasized that the discussions to be presented are by no means restricted by these ranges.

Since all equations in Table I are expressed in terms of I_c/t_c, it is convenient to use this ratio in the following discussions. The following conclusions are obtained.

(1) The ratio of I_c/t_c is always greater than 1. Thus, according to Eqs.12, 19, and 24, the ratio of A_n/A_n^i is always smaller than 1. This means that A_n is always smaller than A_n^i at any time.

(2) For a given set of a, t_c and E values, the value of I_c/t_c increases as the nominal temperature (T_o) decreases.

(3) For a given set of a, t_c and T_o values, the ratio of I_c/t_c increases with the activation energy (E).

(4) For a given set of t_c, T_o and E values, the value of I_c/t_c increases with the value of a.

(5) For a given set of a, T_o and E values, the value of I_c/t_c remains the same regardless the value of t_c (see Appendix 2 for a formal proof).

(6) For a given system under a given storage condition, the value of I_c/t_c is greatest for T(t) defined by Eq.28 (Table II), followed by Eq.31 and Eq.33.

According to Eqs.12, 19 and 24 (Table I), a larger I_c/t_c value dictates a smaller value for A_n/A_n^i which means that the drug level is more underestimated.

The T(t) function represented by Fig.1-a (Eq.28) is probably rare or even nonexistent in the real world. It, however, serves

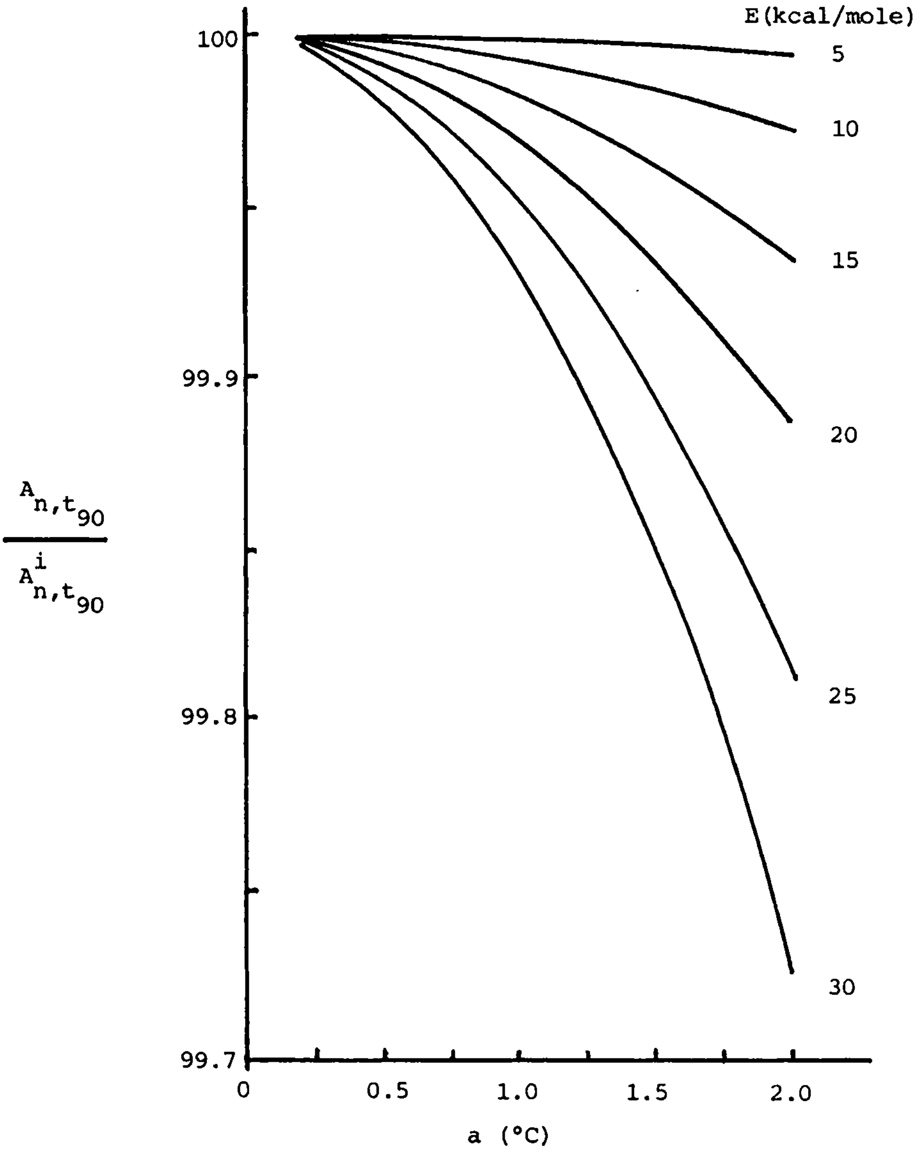

Figure 2

Comparison of drug levels under nonisothermal and isothermal condition at t_{90} for a first order degradation. T(t): Eq.31; T_o=30°C; t_c=1 hour.

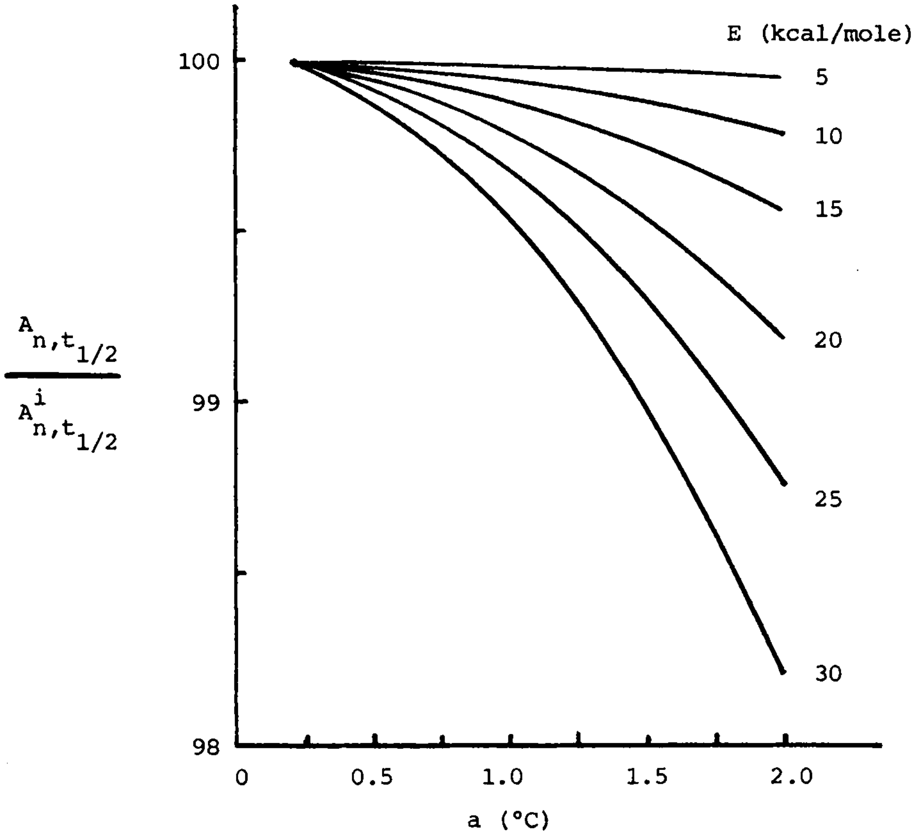

Figure 3

Comparison of drug levels under nonisothermal and isothermal condition at $t_{1/2}$ for a first order degradation. T(t):Eq.31; T_o=30°C; t_c=1 hour.

as an excellent example to illustrate that the relationship of $A_n=A^i_n$ dictated by intuition is wrong even under such a condition. The T(t) functions represented by Figs. 1-b and 1-c are probably very good simulations of the temperature-time relationship in an oven after examining a great number of temperature records of ovens.

It is desirable to have numerical values of A_n/A^i_n in order to appreciate the extent of underestimation.

Fig. 2 shows the relationship among $A_{n,t_{90}}/A^{i}_{n,t_{90}}$, a and E at T_o=30°C and t_c=1 hour for a first order degradation and the T(t) function expressed by Eq.32 . It is noted that for pharmaceutical systems the deviation from the isothermal value is no more than 0.3%. For a typical oven with a ±1°C tolerance, the deviation is not more than 0.1% from its isothermal value.

The relationship among $A_{n,t_{1/2}}/A^{i}_{n,t_{1/2}}$, a and E shown in Fig. 3 indicates that the deviation can be quite large if an improper thermoregulator is used for studying fast reactions. Fortunately, intuition usually directs a scientist to use the most accurate thermoregulator available to him for these fast reactions. It is shown in Fig. 3 that for a thermoregulator with a temperature tolerance of ±0.2°C, the deviations are so small that they can be completely neglected. Commercially available thermoregulators with such a temperature tolerance or much better specification are plentiful. However, a thermoregulator with specification better than 0.2°C may not be necessary according to this analysis except for extremely fast reactions.

APPENDIX 1

For a reaction with a mth kinetic order (m≠1), the rate equation is :

$$-dA/dt = k_o A^m \qquad \text{(Eq.1.1)}$$

Integrating Eq.1.1 from $A=A_o$ at t=0 to $A=A_1$ at $t=t_c$, we obtain:

$$1/A_1^{m-1} = 1/A_o^{m-1} + (m - 1)k_o I_c \qquad \text{(Eq.1.2)}$$

where I_c is defined in Eq.4.

In general, after n temperature cycles:

$$1/A_n^{m-1} = 1/A_o^{m-1} + n(m - 1)k_o I_c \qquad \text{(Eq.1.3)}$$

The counterpart of Eq.1.3 for an isothermal condition is:

$$1/A_n^{i,m-1} = 1/A_o^{m-1} + n(m - 1)k_o t_c \qquad \text{(Eq.1.4)}$$

The ratio of A_n/A_n^i can be derived by dividing Eq.1.3 by Eq.1.4 and noting that $t=nt_c$ (Eq.10):

$$\frac{A_n}{A_n^i} = \left[\frac{1/A_o^{m-1} + (m - 1)k_o t}{1/A_o^{m-1} + (m - 1)k_o t(I_c/t_c)}\right]^{1/(m-1)} \qquad \text{(Eq.1.5)}$$

Note that substituting m=0 for the zero order into Eq.1.5 leads to Eq.19 in Table I. Similarly substituting m=2 for the second order into Eq.1.5 results in Eq.24 in Table I.

The ratio of the drug level at the end of hth t_x (which is defined as the time period needed to reach x% of the initial level) for the nonisothermal condition to that for the isothermal condition can be derived in the following manner.

The t_x for Eq.1.1 is:

$$t_x = [(1/x)^{m-1} - 1]/[(m-1)k_o A_o^{m-1}] \qquad \text{(Eq.1.6)}$$

Thus t_x for Eq.1.1 is not constant, but a function of the initial drug level. In general the drug level at the onset of the hth t_x is:

$$A_{o,ht_x} = x^{h-1} A_o \qquad \text{(Eq.1.7)}$$

The totoal time elapsed after h t_x's is:

$$t = \sum_1^h t_{x,j} \qquad \text{(Eq.1.8)}$$

where $t_{x,j}$ represents the jth t_x.

Substituting Eqs.1.6 and 1.7 into Eq.1.8, we obtain after rearrangement:

$$t = \frac{(1/x)^{m-1} - 1}{(m - 1)k_o A_o^{m-1}} \sum_{1}^{h-1} [(1/x)^{m-1}]^j \qquad \text{(Eq.1.9)}$$

Simplifying Eq.1.9 leads to:

$$t = [(1/x)^{h(m-1)} - 1]/[(m-1)k_o A_o^{m-1}] \qquad \text{(Eq.1.10)}$$

Substituting Eq.1.10 into Eq.1.5, we obtain:

$$\frac{A_{n,ht_x}}{A^{i}_{n,ht_x}} = \left[\frac{(1/x)^{h(m-1)}}{1 + [(1/x)^{m-1} - 1](I_c/t_c)}\right]^{1/(m-1)} \qquad \text{(Eq.1.11)}$$

Note that using x=1/2 and m=0 for the zero order reaction in Eq.1.11 leads to Eq.21 in Table I. Using h=1 in Eq.21, Eq.20 can be obtained. Eqs.26 and 25 for the second order reaction can be derived in a similar manner.

APPENDIX 2

When a different cycle time is involved, for example:

$$t'_c = k't_c \qquad \text{(Eq.2.1)}$$

where k' is a proportionality constant.

The ratio of I'_c/t'_c is expressed as:

$$I'_c/t'_c = \{\int_0^{t'_c} \exp[(E/R)(1/T_o - 1/T'(t))]dt\}/t'_c \qquad \text{(Eq.2.2)}$$

where T'(t) is the nonisothermal condition expressed in terms of t'_c. Let us use Eq.31 as an example. Thus:

$$T'(t) = T_o + a \sin(2\pi t/t'_c) \qquad \text{(Eq.2.3)}$$

Substituting Eqs.2.1 and 2.3 to Eq.2.2, we obtain:

$$\frac{I'_c}{t'_c} = \frac{\int_0^{k't_c} \exp\{(E/R)[1/T_o - 1/(T_o + a \sin(2\pi t/k't_c))]\}dt}{k't_c} \qquad \text{(Eq.2.4)}$$

Introducing a new variable u=t/k'. Eq.2.4 can be converted to:

$$\frac{I'_c}{t'_c} = \frac{\int_0^{t_c} \exp\{(E/R)[1/T_o - 1/(T_o + a\sin(2\pi u/t_c))]\}du}{t_c} \qquad \text{(Eq.2.5)}$$

Since u is a dummy variable, the numerator on the right hand side of Eq.2.5 is equal to I_c defined in Eq.4. Therefore:

$$I'_c/t'_c = I_c/t_c \qquad \text{(Eq.2.6)}$$

Thus for a given set of a, T_o and E values, the ratio of I_c/t_c remains constant regardless of the value of t_c.