ScienTek Software, Inc.

Mean Kinetic Temperature - A Short History

By Mike W.H. Yang, Ph.D., Director of Software Development, ScienTek Software, Inc.
Edited and Typeset in LaTeX by Daniel Yang
www.StabilitySystemii.com - iStability® MKT (Calculate Mean Kinetic Temperature)

Contents

$$T_k = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{e^{-\frac{\Delta H}{RT_1}} + e^{-\frac{\Delta H}{RT_2}} + \cdots + e^{-\frac{\Delta H}{RT_n}}}{n}\right)}$$

1 Introduction

The United States Pharmacopeia (USP) defines Mean Kinetic Temperature (MKT) as the "single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, MKT may be considered as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variation." [1].

This statement is a condensation of numerous proposals, developments, and discussions from decades of efforts.

This short article will present a short history leading to the MKT concept.

2 A Discussion on Normal Storage Temperature

Table 1 lists the definitions given in the USP XX related to the various storage conditions. A normal storage temperature is the temperature (or more likely a temperature range) specified on the label of the drug product.

An expiration dating period is usually understood to have been determined under this normal storage temperature.

The definitions for room temperature and *controlled* room temperature in Table 1 are broad and therefore ambiguous. They have been subjected to different interpretations. For example, when a product is specified to be stored between 15° and 30°C (*controlled* room temperature), the formulator may mean that he has stability data to show that the drug product should remain satisfactory at, say, 25°C for the specified expiration dating period. He may have some short term stability data at, say, 30°C to cover him for the temperatures between 25° and 30°C. His rationale is that the product will probably be subjected to a temperature such as 30°C for only a short period of time during its shelf life. Yet, the regulatory agency may incline to interpret that the drug product should remain satisfactory for the entire period at the highest temperature of the range, which in this case is 30°C [2]. Therefore long term stability testing data at 30°C would be required to justify the expiration dating period set for $15-30$°C.

There have been several theories proposed attempting to better define the term of room temperature and subsequently providing a reference temperature for stability studies of drug products. This is not an easy task mainly because it is very difficult, if not impossible, to simulate the various conditions which the drug products are subjected to during their distribution. In the following sections, we will discuss these theories.

Table 1: USP's Definitions on Storage Conditions

Description	Definition
Cold	Any temperature not exceeding 8°C (i) Refrigerator: temperature maintained between 2 and 8°C thermostatically (ii) Freezer: temperature maintained between −20° and −10°C thermostatically
Cool	Any temperature between 8° and 15°C
Room Temperature	The temperature prevailing in a working area
Controlled Room Temperature	Temperature maintained between 15° and 30°C thermostatically
Warm	Any temperature between 30° and 40°C
Excessive Heat	Any temperature above 40°C

3 Virtual Temperature

Haynes [3] developed the concept of *Virtual Temperature*, which is characteristic for a specific geographical location.

Assume that the monthly average temperature is T_i. Corresponding to this is an average rate constant k_i for that month. These two terms are related by the Arrhenius Equation:

$$k_i = Ae^{-\frac{E}{RT_i}} \tag{1}$$

The yearly average rate constant is:

$$k = \frac{\sum k_i}{12} = \frac{A\sum e^{-\frac{E}{RT_i}}}{12} \tag{2}$$

Corresponding to this yearly average rate constant is a temperature which is defined as the Virtual Temperature (T_v). Again, k and T_v are related by the Arrhenius Equation,

$$k = Ae^{-\frac{E}{RT_v}} \tag{3}$$

Combining EQ(2) and (3), we obtain:

$$T_v = \frac{-\frac{E}{R}}{\ln\left(\frac{\sum e^{-\frac{E}{RT_i}}}{12}\right)} \tag{4}$$

The T_v calculated is the *annual* average temperature. It is apparent that T_v's also can be calculated in such a way to reflect seasonal characteristics.

Using an E value of 14 kcal/mole and temperature data secured from the weather bureau, Haynes calculated the annual virtual temperatures for some representative cities around the world (Table 2). Also included in Table 2 are the virtual temperatures calculated based on six consecutive hottest months to reflect seasonal characteristics and the restricted annual temperatures calculated by truncating any monthly average temperature below 17°C to 17°C to account for the heating needed.

The annual virtual temperatures are somewhat insensitive to the change of the activation energy (E). For example, the annual virtual temperature for 20 kcal/mole for most cities differ from the values in Table 2 by less than 0.3°C and by less than 0.5°C for 30 kcal/mole.

The drug level remaining at the end of the *first* year can be calculated using the annual temperature:

$$\begin{aligned} \textit{zero-order}\text{: } & C - C_o = -A\sum e^{-\frac{E}{RT_i}} \\ \textit{first-order}\text{: } & \ln\left(\frac{C}{C_o}\right) = -A\sum e^{-\frac{E}{RT_i}} \\ \textit{second-order}\text{: } & \frac{1}{C_o} - \frac{1}{C} = -A\sum e^{-\frac{E}{RT_i}} \end{aligned} \tag{5}$$

Table 2: Virtual Temperatures

City	Restricted Annual Average Temperature	Virtual Temperature (°C)	
		Annual Basis	*Six Consecutive Hottest Months*
Atlanta	19.9	20.4	23.1
Boston	18.1	18.2	19.3
Chicago	18.5	18.7	20.2
Cleveland	18.4	18.6	20.0
Detroit	18.2	18.3	19.5
Galviston	22.0	22.7	26.4
Los Angeles	18.9	19.0	20.8
New Orleans	21.9	22.7	26.2
New York	18.6	18.7	20.3
Philadelphia	19.1	19.4	21.5
Portland	17.4	17.4	17.9
St. Louis	19.8	20.3	23.0
San Francisco	17.0	17.0	17.0
Tampa	22.5	23.1	26.3
Washington	19.3	19.7	21.9
Sidney	18.8	18.9	20.6
Brussels	17.1	17.1	17.2
London	17.0	17.0	17.0
Havana	25.1	25.2	27.0
Munich	17.0	17.0	17.0
Bombay	27.1	27.1	28.0
Tokyo	19.2	19.5	21.6
San Juan	25.6	25.6	26.5

From Ref. [3].

4 Kinetic Ratio

With the same mathematical analysis used by Haynes and an additional reference temperature, Scher [4] defined a parameter called the *Kinetic Ratio* (α):

$$\alpha = \frac{k}{k_r} \tag{6}$$

where k_r is the rate constant at a reference temperature T_r. The parameter k is an average rate constant and can be similarly defined by EQ(2). Instead of using monthly average temperature, temperature recordings with six hour intervals in a warehouse were used. Thus EQ(2) becomes:

$$k = \frac{A\int_0^{12} e^{-\frac{E}{RT}}\,dt}{12} \tag{7}$$

where T is a function of time t (in unit of month in EQ(7)). The integral can be numerically integrated. Again, this kinetic ratio can also be calculated to reflect the seasonal characteristics.

Therefore, on an annual basis, the kinetic ratio can be calculated using:

$$\alpha = \frac{\dfrac{\int_0^{12} e^{-\frac{E}{RT}}\,dt}{12}}{e^{-\frac{E}{RT_r}}} \tag{8}$$

Table 3 lists the values of annual and quarterly kinetic ratios for different activation energy as well as different reference temperatures.

The following equation relating the shelf life to the kinetic ratio is a useful way to use the information listed in Table 3:

$$t_{90} = \frac{t_{90,r}}{\alpha} \tag{9}$$

where t_{90} is the shelf life when the product is subjected to the nonisothermal condition in the warehouse and $t_{90,r}$ is the shelf life of the product when stored at the reference temperature *isothermally*. The value of t_{90} is defined as the time period when the drug quantity decreases to 90% of the initial quantity. It is a concept that is similar to half life ($t_{\frac{1}{2}}$). EQ(9) can be derived from EQ(6).

When the value of α is 1, we have a perfect match between t_{90} and $t_{90,r}$. For the definitions given by EQ(6) and EQ(3), it is obvious that the value of α is 1 only when T_r is the same as T_v. When the value of α is less than 1, $t_{90,r}$ underestimates t_{90}. However, when the value of α is greater than 1, $t_{90,r}$ overestimates t_{90}. Ideally, if the stability study is performed at T_v, then t_{90} would be correctly determined. However, this is practically impossible since every pharmaceutical system has its own T_v. Therefore for the purpose of expiration dating, a reference temperature is sought to provide α values as close as possible to 1 for all possible E values (10 to 30 kcal/mole for pharmaceutical systems). If we accept a range of 0.9 to 1.1 for the value of α, then the estimation of t_{90} from $t_{90,r}$ would have a maximum error of $\pm 10\%$. This error is inevitable and is a price which must be paid for using an universal reference temperature.

Figure 1 (p. 8) is a graph showing the relationship between annual α values and E at various reference temperatures in the Dallas warehouse where Scher obtained his temperature data. As can be observed for the value of E in the range of 10 to 30 kcal/mole, 25.5°C would be a good reference temperature to perform long term stability studies if drug products are to be stored in the Dallas warehouse or a similar condition.

It is immediately apparent from Figure 1 that the use of 30°C for the expiration dating purpose is a very conservative approach.

Table 3: Annual and Quarterly Kinetic Ratios

Activation Energy (kcal/mole)	α_y		α_1		α_2		α_3		α_4	
	24°	30°	24°	30°	24°	30°	24°	30°	24°	30°
9.94	1.009	0.722	0.708	0.507	0.998	0.715	1.404	1.006	0.927	0.664
19.87	1.112	0.571	0.507	0.261	1.027	0.528	1.999	1.027	0.915	0.470
29.81	1.324	0.488	0.167	0.135	1.088	0.401	2.886	1.063	0.955	0.352

From Ref. [3]. α is the annual kinetic ratio. α_1 is the kinetic ratio for the first quarter (winter) and so on.

5 Reference Thermal Exposure (RTE)

In March 1976, the Quality Control Section of the Pharmaceutical Manufacturing Association (PMA) formed a Committee on Stability and Expiration Dating to work on a uniform guideline for stability studies, product storage, and expiration dating. Representatives from twenty-eight companies participated in the committee.

The first detailed report was issued by the committee in March 1978 [5]. While the scope of the report is wide and deep, a consensus was not reached. This is not unusual for any standardization process. Two years later in March 1980, a simplified report with minor changes was issued without any endorsement from the PMA [6].

Table 4: Reference Thermal Exposure for Room Temperature of a Dallas Warehouse

Temperature (°C)	**Number of hours per year**
≤ 20	4074
21	300
22	300
23	300
24	300
25	340
26	359
27	369
28	369
29	369
30	369
31	359
32	349
33	230
34	150
35	80
36	60
37	50
38	20
39	10
40	3

From Ref. [6].

One of the concepts proposed in these reports is pertinent to our discussion here. This is the *Reference Thermal Exposure* (RTE), which is a characteristic thermal condition for a particular warehouse in which drug products are to be stored. The RTE for room temperature of a Dallas warehouse is illustrated in Table 4 [6]. The RTE for *controlled* room temperature of the same warehouse is shown in Table 5 and is constructed simply by truncating the time periods from $29 - 40$°C to 28°C, taking into consideration that air conditioning is applied when the temperature is above 28°C.

Table 5: Reference Thermal Exposure for *Controlled* Room Temperature of a Dallas Warehouse

Temperature (°C)	**Number of hours per year**
≤ 20	4074
21	300
22	300
23	300
24	300
25	340
26	359
27	369
28	2418

From Ref [6].

To illustrate the data analysis using the concept of RTE, we will first discuss in a general way and subsequently show that the RTE is merely an extension of the concept of the virtual temperature.

The RTE specifies the time period t_i of a product exposed to an environment with a temperature T_i. For example, for the RTE shown in Table 4, the products can be considered as if they were exposed to, say, 20°C for 4074 hours on an annual basis and then at 21°C for 300 hours and so on. Using zero-order kinetics, the drug remaining after exposure to T_1 for a time period of t_1 can be calculated using:

$$C_1 - C_o = -k_1 t_1 \tag{10}$$

where k_1 is the rate constant at T_1.

Subsequently, the drug products are exposed to T_2 for a period of t_2 and again the drug remaining is calculated by:

$$C_2 - C_1 = -k_2 t_2 \tag{11}$$

Similarly,

$$\begin{array}{ccccc} C_3 & - & C_2 & = & -k_3 t_3 \\ \vdots & & \vdots & & \vdots \\ C_n & - & C_{n-1} & = & -k_n t_n \end{array} \tag{12}$$

Summing EQ(10) through EQ(12), we obtain:

$$C_n - C_o = -\sum k_i t_i \tag{13}$$

Since $k_i = Ae^{-\frac{E}{RT_i}}$, EQ(13) can be converted to:

$$C_n - C_o = -A\sum t_i e^{-\frac{E}{RT_i}} \tag{14}$$

Note the similarity between EQ(5) and EQ(14). Under the conditions used for the virtual temperature, T_i in EQ(14) becomes the monthly average temperature and t_i is one month and therefore EQ(14) becomes EQ(5).

The left hand side of EQ(14) is $\ln(\frac{C_n}{C_o})$ for first-order kinetics and $\frac{1}{C_o} - \frac{1}{C_n}$ for second-order kinetics.

For a particular RTE and a drug product, the right hand side of EQ(14) is a constant. Let it be defined as:

$$b = -A \sum t_i e^{-\frac{E}{RT_i}} \tag{15}$$

Following the derivation for EQ(14), the drug level at the end of the second year under this RTE is:

$$C_{2n} - C_n = b \tag{16}$$

Combining EQ(14) and EQ(16), we obtain:

$$C_{2n} = C_o + 2b \tag{17}$$

In general, after j years exposure to the RTE, the drug level remaining is:

$$C_{jn} = C_o + jb \tag{18}$$

For other kinetic orders, EQ(18) becomes:

$$\textit{first-order}: \ \ln C_{jn} = \ln C_o + jb \tag{19}$$

$$\textit{second-order}: \ \frac{1}{C_{jn}} = \frac{1}{C_o} - jb \tag{20}$$

In the PMA's report, C_{jn}'s are then used in conjunction with an appropriate rate equation to project a shelf life.

Perhaps, it would be helpful to illustrate this general analysis using an example. We will use the example presented in the PMA's report [6].

A first-order kinetics is used. The parameters needed to calculate the values of b, namely A and E are determined with isothermal kinetic studies using the Arrhenius Equation. These values are $A = 1.11459 \times 10^{12}$ week^{-1} and $E = 20.242$ kcal/mole.

Using the RTE described in Table 4, the value of b calculated according to EQ(15) is -0.089958. Using EQ(19) for the first-order kinetics, $j = 1$ for the first year and $C_o = 1$, we obtain:

$$C_n = C_o e^b = 0.91397 \tag{21}$$

Similarly,

$$C_{2n} = C_o e^{2b} = 0.83534 \tag{22}$$

And so on.

Table 6 shows the drug levels at various times after exposure of products to the RTE for room temperature (Table 4) and *controlled* room temperature (Table 5). These data are then used to calculate the expiration dating period with the conventional method. An example of such a computation using STABILITY SYSTEM (`http://www.stabilitysystem.com`) is shown in Figure 4a (p. 11) and 4b (p. 12).

It is interesting to calculate the virtual temperature and the kinetic ratio for the RTE's listed in Table 4 and Table 5. For these calculations, we must use:

$$T_v = \frac{-\frac{E}{R}}{\ln\left(\frac{\sum t_i e^{-\frac{E}{RT_i}}}{t_o}\right)} \tag{23}$$

$$\alpha = \frac{\frac{\sum t_i e^{-\frac{E}{RT_i}}}{t_o}}{e^{-\frac{E}{RT_r}}} \tag{24}$$

where t_o is the total time under consideration. Since the rate constant is expressed in terms of week, $t_o = 52$ weeks if we wish to calculate T_v and α on an annual basis. All t_i's should also be converted from hours to weeks. Table 7 lists the T_v's calculated for the RTE described in Table 4 and Table 5. Listed in Table 7 are also some kinetic ratios based on several reference temperatures. It is observed that if we choose 25.6°C as the reference temperature to conduct the stability studies for this system, we will be able to predict precisely the expiration dating period in the real world. Similarly, the reference temperature of choice would be 24°C when dealing with the RTE for *controlled* room temperature.

However, we are *not* interested in only one situation. Shown in Table 8 are the virtual temperatures calculated for the RTE for room temperature and *controlled* room temperature at various E values. Figure 2 (p. 9) and Figure 3 (p. 10) are graphs similar to Figure 1, but are for the nonisothermal conditions listed in Table 4 and Table 5. It can be observed that for the product exposed to the RTE for room temperature, long term stability studies conducted at 26°C should be enough. On the other hand, for the RTE for *controlled* room temperature, a reference temperature at 24°C can be chosen for long term stability studies.

The above analyses are not without defects. The virtual temperatures calculated by Haynes are based on the weather data, which do not necessarily reflect the temperatures in an enclosed area such as a warehouse. The concept of the RTE represents a big step toward expressing the real world. However, the RTE as proposed is theoretically useful only for the whole year. This is a weakness recognized in the PMA's report [5]. To be more useful, the RTE based on the seasonal or monthly temperature data is preferred. The mathematical analysis presented in the section can be readily extended for such purpose.

Table 6: Drug Levels at Various Times after Exposure of Product to RTE for Room Temperature and *Controlled* Room Temperature

Age (week)	Drug Level	
	Room Temperature RTE	*Controlled Room Temperature RTE*
0	1.00000	1.00000
52	0.91397	0.92783
104	0.83534	0.86087
156	0.76348	0.79874
208	0.69779	0.74110
260	0.63776	0.68761

Table 7: The Virtual Temperatures and Kinetic Ratios for a System whose $A = 1.11459 \times 10^{12}$ week^{-1} and $E = 20.242$ kcal/mole with Exposure to RTE for Room Temperature and *Controlled* Room Temperature

RTE	T_v (°C)	Kinetic Ratio		
		$T_r = 24$°C	25°C	26°C
For Room Temperature (Table 4)	25.6	1.201	1.070	0.955
For *Controlled* Room Temperature (Table 5)	24.0	1.000	0.891	0.795

Table 8: The Virtual Temperatures for Exposure to the RTE for Room Temperature and *Controlled* Room Temperature

Activation Energy (kcal/mole)	Virtual Temperature (°C)	
	RTE for Room Temperature	*RTE for Controlled Room Temperature*
10	24.8	23.6
15	25.2	23.8
20	25.6	24.0
25	26.0	24.2
30	26.4	24.3

6 Mean Kinetic Temperature

The official USP Mean Kinetic Temperature is [1]:

$$T_k = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{e^{-\frac{\Delta H}{RT_1}} + e^{-\frac{\Delta H}{RT_2}} + \cdots + e^{-\frac{\Delta H}{RT_n}}}{n}\right)} \qquad (25)$$

Besides the minor difference in symbols used, the Mean Kinetic Temperature is essentially the Virtual Temperature in EQ(4). The ΔH in EQ(25) is E in EQ(4).

With the advancement in the digital temperature recording, the temperature readings can be taken more frequently. With the advancement in the computer technologies, the computation of Mean Kinetic Temperature can also be easily performed.

ScienTek Software, Inc. has a software program available called iStability® MKT (formerly STABILITY SYSTEM II), which is used by companies worldwide to calculate Mean Kinetic Temperature.

iStability® MKT is a general purpose application and is not tied to any commercially-available temperature monitoring system. Feel free to visit our website for more information: `http://www.StabilitySystemii.com`

Figure 1: Relationship between annual α value and the activation energy at various reference temperatures (From Ref. [7])

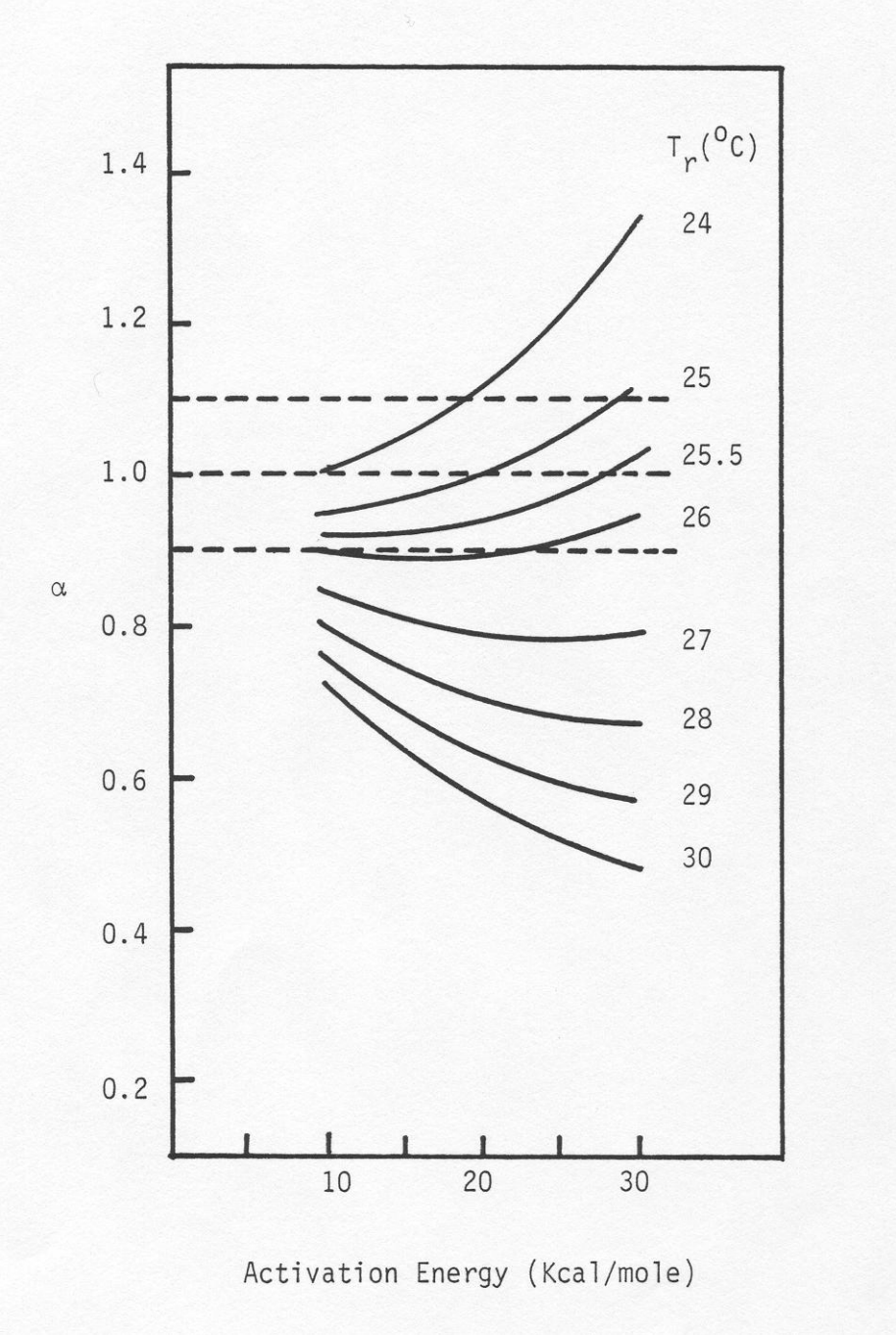

Figure 2: Relationship between annual α value and the activation energy at various reference temperatures for the RTE for room temperature (From Ref. [7])

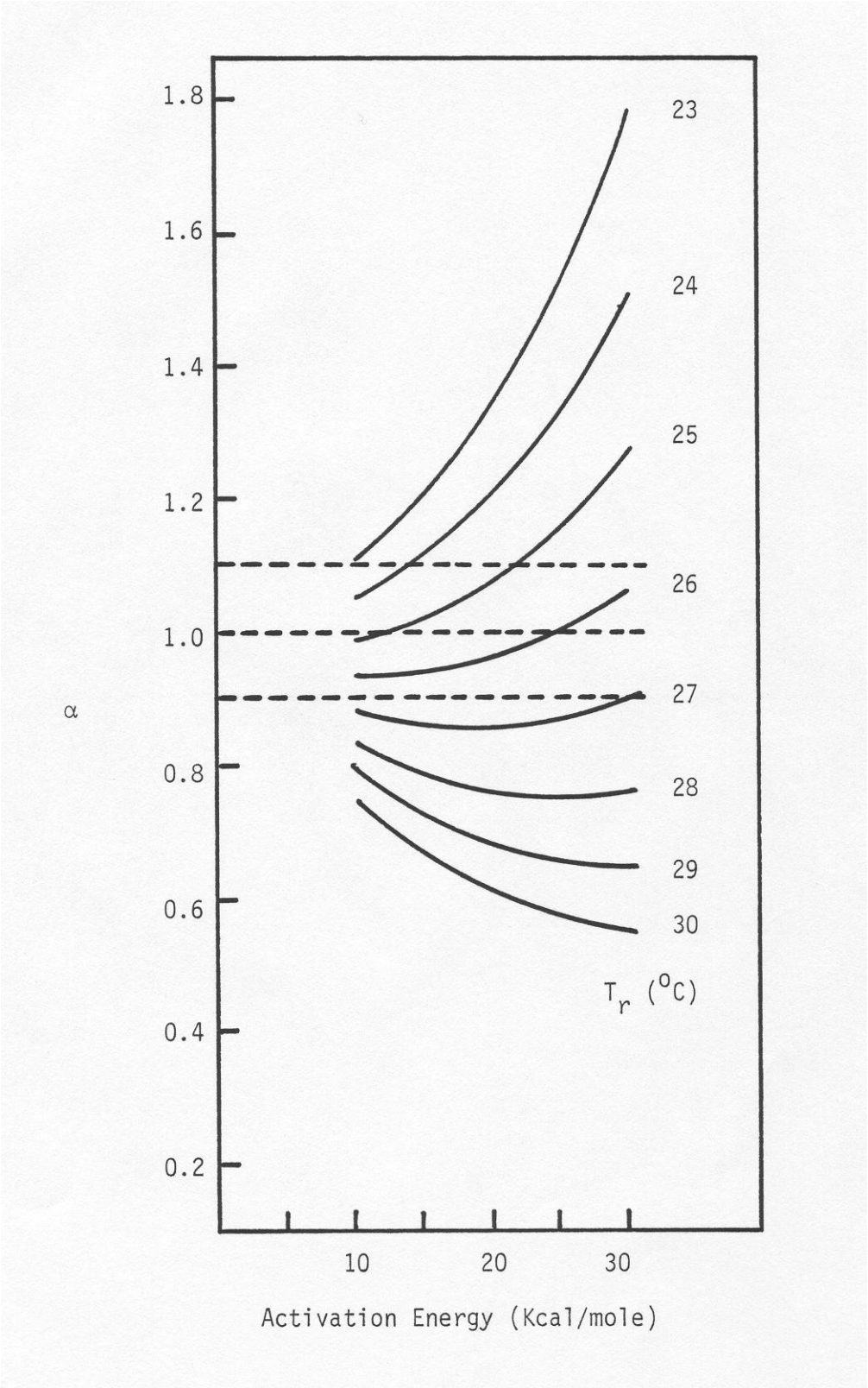

Figure 3: Relationship between annual α value and the activation energy at various reference temperatures for the RTE for *controlled* room temperature (From Ref. [7])

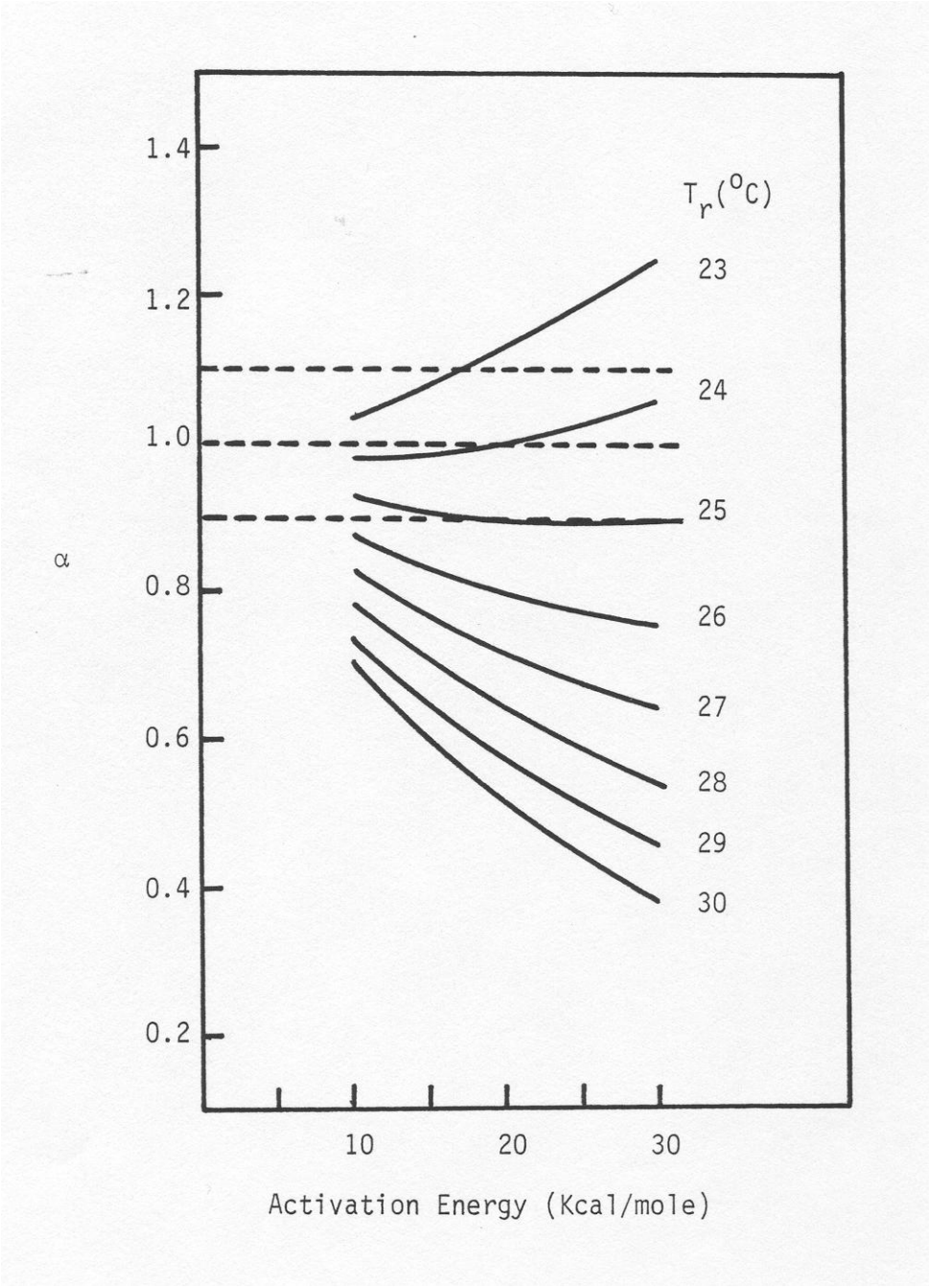

Figure 4a: Computation of expiry dating periods for room temperature RTE using the STABILITY SYSTEM software package

```
STABILITY SYSTEM by ScienTek Software, Inc.                          | Jul 17, 2006| 09:06:42
Licensed to XYZ Pharmaceuticals, Tustin, California.
Expiry Dating Calculation                                                          Page 1
================================================================================================

File name: Table6_RT_RTE     Test: DRUG


_____________________________
AGE(week)        VALUE
_____________________________
0                1
52               0.91397
104              0.83534
156              0.76348
208              0.69779
260              0.63776



STABILITY SYSTEM by ScienTek Software, Inc.                          | Jul 17, 2006| 09:06:42
Licensed to XYZ Pharmaceuticals, Tustin, California.
Expiry Dating Calculation                                                          Page 2
================================================================================================

File name: Table6_RT_RTE     Test: DRUG

LEAST SQUARES REGRESSION ANALYSIS

  Number of data =  6
  R square =  0.995716121391207
  R = - 0.997855761816911
  Kinetic order =  0
  y = 0.988885238095238 - 5.96138147566719E-03 x (in months)

      Theory: 1
  Lower spec: 0.9
  Upper spec: 1.1

  At 95% confidence level: (t critical value = 2.13226879866518 )

  Intercept is not significantly different from the theoretical (t statistic= 1.54755676752328 )

  Slope is significantly different from zero (t statistic= 30.4915279098728 )

  Expiry dating = 14.91 months based on regression line.
  Expiry dating = 13.02 months based on confidence limit.
  No adjustment of intercept is made since intercept is not
      significantly different from theoretical.


ANALYSIS OF VARIANCE (ANOVA) TABLE

  Source    DF    Sum of squares       Mean squares         F value             Significance
  ____________________________________________________________________________________________
  model     1     9.15571222857146E-02 9.15571222857146E-02 929.733274278549    0
  error     4     3.93907047617548E-04 9.84767619043869E-05
  ____________________________________________________________________________________________
  total     5     9.19510293333321E-02

  Parameter       Estimate             Standard error       t for Ho: Parameter=0
  ____________________________________________________________________________________________
  intercept        .988885238095238     7.18213518108931E-03 137.68680387679
  slope           -5.96138147566719E-03 1.9550943768013E-04  30.4915279098728
```

Figure 4b: Computation of expiry dating periods for *controlled* room temperature RTE using the STABILITY SYSTEM software package

```
STABILITY SYSTEM by ScienTek Software, Inc.                          | Jul 17, 2006| 09:06:40
Licensed to XYZ Pharmaceuticals, Tustin, California.
Expiry Dating Calculation                                                          Page 1
================================================================================================

File name: Table6_CRT_RTE     Test: DRUG


_____________________________
AGE(week)        VALUE
_____________________________
0                1
52               0.92783
104              0.86087
156              0.79874
208              0.74110
260              0.68761



STABILITY SYSTEM by ScienTek Software, Inc.                          | Jul 17, 2006| 09:06:40
Licensed to XYZ Pharmaceuticals, Tustin, California.
Expiry Dating Calculation                                                          Page 2
================================================================================================

File name: Table6_CRT_RTE     Test: DRUG

LEAST SQUARES REGRESSION ANALYSIS

  Number of data =  6
  R square =  0.997022831771891
  R = - 0.998510306292274
  Kinetic order =  0
  y = 0.992044285714286 - 5.1434929356358E-03 x (in months)

      Theory: 1
  Lower spec: 0.9
  Upper spec: 1.1

  At 95% confidence level: (t critical value = 2.13226879866518 )

  Intercept is not significantly different from the theoretical (t statistic= 1.54104755736379 )

  Slope is significantly different from zero (t statistic= 36.599980982043 )

  Expiry dating = 17.9 months based on regression line.
  Expiry dating = 16.44 months based on confidence limit.
  No adjustment of intercept is made since intercept is not
      significantly different from theoretical.


ANALYSIS OF VARIANCE (ANOVA) TABLE

  Source    DF    Sum of squares       Mean squares         F value             Significance
  ____________________________________________________________________________________________
  model     1     6.81576490414282E-02 6.81576490414282E-02 1339.55860788591    0
  error     4     2.03522708570381E-04 5.08806771425951E-05
  ____________________________________________________________________________________________
  total     5     6.83611717499986E-02

  Parameter       Estimate             Standard error       t for Ho: Parameter=0
  ____________________________________________________________________________________________
  intercept        .992044285714286     5.1625365146572E-03  192.162182852892
  slope           -5.1434929356358E-03  1.40532666892895E-04 36.599980982043
```

7 References

1. USP 27, pp. 2578-2579.
2. R. M. Patel, *Stability and the FDA Guidelines, Proposed Guidelines for Stability Studies for Human Drugs and Biologicals*, 15th Annual Industrial Pharmacy Management Conference, Madison, Wisconsin, October 13, 1980.
3. J. D. Haynes, *J. Pharm. Sci.*, **60**: 927 (1971).
4. M. Scher, *J. Pharm. Sci.*, **69**: 325 (1980).
5. *Report of the PMA Quality Control Section, Committee on Stability and Expiration Dating*, March 13, 1978.
6. *Report of the PMA Quality Control Section, Committee on Stability and Expiration Dating*, March 1980.
7. Yang, *Drug Development and Industrial Pharmacy*, **9**: 849 (1983).