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A DISCUSSION ON ROOM TEMPERATURE FOR STABILITY TESTING

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The United States Pharmacopeia (USP) defines room temperature as the temperature prevailing in a working area and controlled room temperature as the temperature between 15 and 30°C. It is usual to use data from long term stability testing conducted at about 25°C and short term stability testing at higher temperatures to support an expiration dating period with a storage condition of between 15 and 30°C. The Food and Drug Administration (FDA) seems to incline to interpret that the drug product should remain satisfactory for the entire expiration dating period at the highest temperature of the storage condition, which is 30°C in this case. Therefore long term stability testing at 30°C is required for the justification (1).

Several theories have been proposed to attempt to better define the storage condition centered around the so-called "room temperature" and to provide a reference temperature suitable for stability testing. Admittedly, this is not an easy task mainly because it is very difficult, if not impossible, to simulate the various conditions which the products are exposed to during their distribution.

In this discussion, we seek to unify the theories proposed so far.

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GENERAL THEORY

The condition that drug products are exposed to is undoubtly a complex one. To seek a "universal" reference temperature for stability testing is therefore resorted to an averaging process.

Let t_i be the time that a product is exposed to a storage temperature T_i. When such data are accumulated over a time period of t_o, in which there are n T_i's, the average rate constant (k) can be calculated using:

$$k = (\Sigma t_i k_i)/t_o \qquad \text{(Eq.1)}$$

where k_i is the rate constant at T_i.

When the Arrhenius equation is applicable:

$$k_i = A \exp(-E/RT_i) \qquad \text{(Eq.2)}$$

Subsitituting Eq.2 into Eq.1, we obtain:

$$k = [A\Sigma t_i \exp(-E/RT_i)]/t_o \qquad \text{(Eq.3)}$$

VIRTUAL TEMPERATURE

Haynes(2) chose the temperature to express this averaging process. Corresponding to k, there is a temperature which Haynes defined as the virtual temperature (T_v). The parameters k and T_v are related by:

$$k = A \exp(-E/RT_v) \qquad \text{(Eq.4)}$$

Combining Eqs.3 and 4 and solving for T_v lead to:

$$T_v = \frac{-E/R}{\ln\{[\Sigma t_i \exp(-E/RT_i)]/t_o\}} \qquad \text{(Eq.5)}$$

Haynes used monthly average temperature (T_i) and calculated the virtual temperature on an annual basis. Under that condition, t_i=1 month and t_o=12 months. Substituting these numbers into Eq.5 leads to the equation used by Haynes (2).

Haynes calculated annual virtual temperatures for representative cities in the United States as well as cities abroad. He concluded that 24°C would be a good reference temperature for dating purpose in the United States.

KINETIC RATIO

Extending the treatment of the virtual temperature, Scher (3) defined a kinetic ratio (α):

$$\alpha = k/k_r \qquad \text{(Eq.6)}$$

where k_r is the rate constant at a reference temperature (T_r). Using Eq.3 and $k_r = A \exp(-E/RT_r)$, we obtain:

$$\alpha = \frac{[\Sigma t_i \exp(-E/RT_i)]/t_o}{\exp(-E/RT_r)} \qquad \text{(Eq.7)}$$

When sufficient T-t data are gathered, the summation can take the form of an integration (3).

Using Eqs.5 and 7, we obtain:

$$\alpha = \exp[-(E/R)(1/T_v - 1/T_r)] \qquad \text{(Eq.8)}$$

It follows immediately from Eq.6 that:

$$t_{90} = t_{90,r}/\alpha \qquad \text{(Eq.9)}$$

where t_{90} and $t_{90,r}$ are the times required to reach 90% of the initial drug level at the virtual temperature and the reference temperature respectively. Note that t_{90} is conventionally accepted as the expiration dating period.

When $\alpha=1$, $t_{90}=t_{90,r}$. According to Eq.8 $\alpha=1$ only when $T_v=T_r$. When $\alpha<1$ ($T_v<T_r$), $t_{90,r}$ underestimates t_{90}. While when $\alpha>1$ ($T_v>T_r$), $t_{90,r}$ overestimates t_{90}. Ideally, if the stability test is performed at T_v, then t_{90} would be correctly derived. However, this is practically

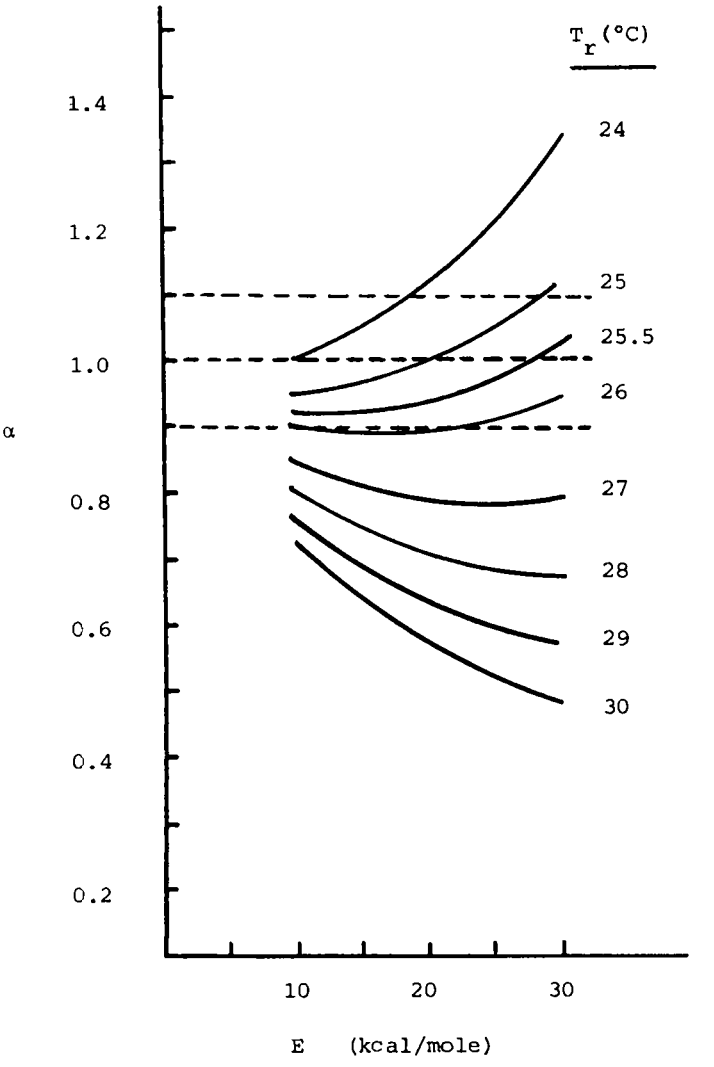

Figure 1

Relationship between annual α value and activation energy at various reference temperatures

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 α, then the estimation of t_{90}

from $t_{90,r}$ would have a maximum error of ±10%. This error is inevitable and is a price which must be paid for using a universal reference temperature.

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

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

REFERENCE THERMAL EXPOSURE

In March 1976, the Quality Control Section of the Pharmaceutical Manufacturing Association (PMA) formed a Committee for Stability and Expiration Dating to work on a uniform guideline for the stability studies, product storage and expiration dating. The proposed concepts are discussed in two reports (4,5).

TABLE I

The Virtual Temperatures for Exposure to the RTE for the Room Temperature and the RTE for the Controlled Room Temperature (Reference 4)

E (kcal/mole)	T_v (°C) RTE for RT	RTE for Controlled RT
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

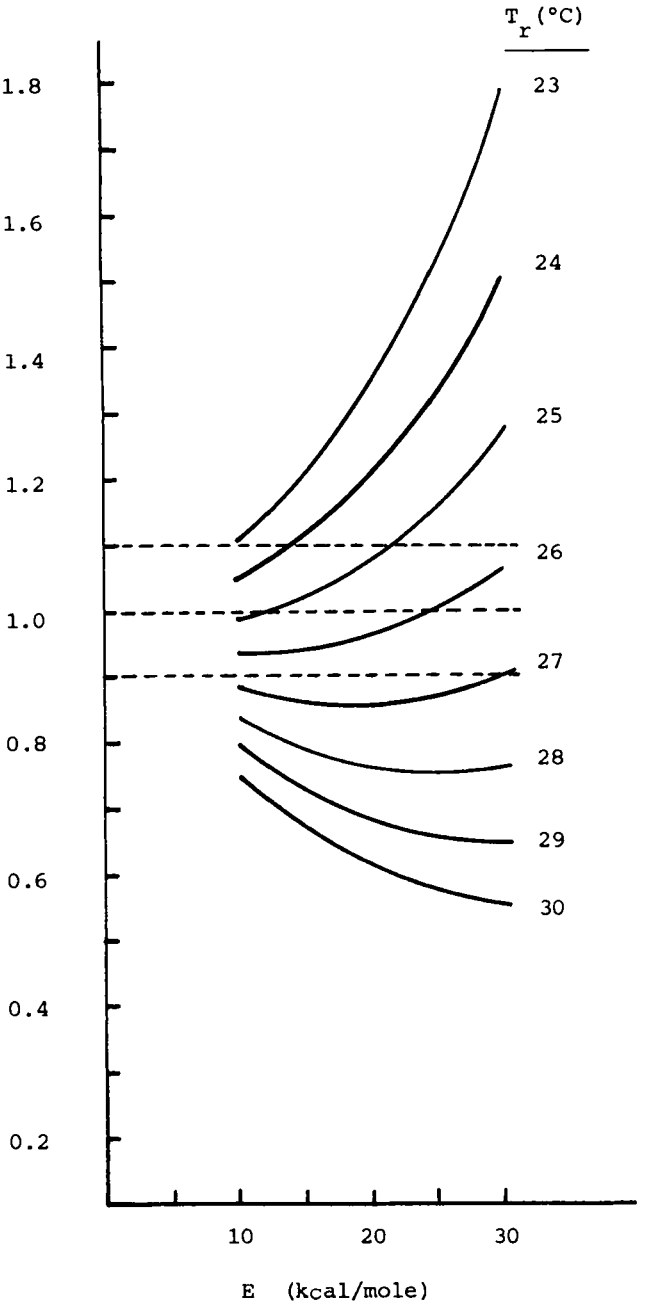

Figure 2

Relationship between annual α value and activation energy at various reference temperatures for the RTE for room temperature

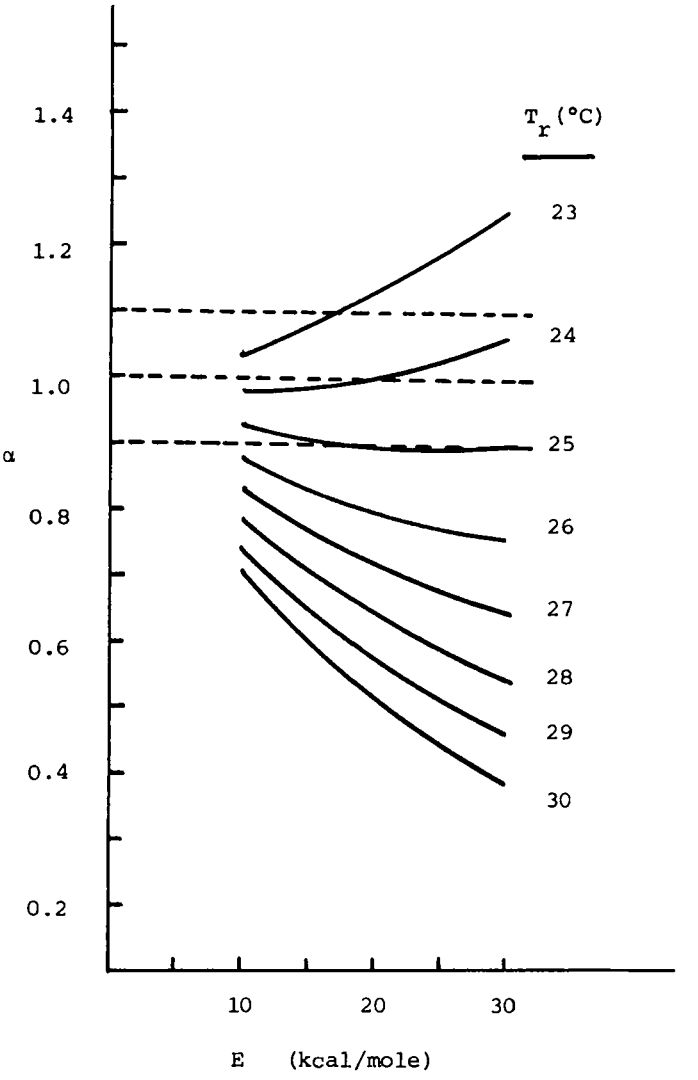

Figure 3

Relationship between annual α value and activation energy at various reference temperatures for the RTE for controlled room temperature

The Reference Thermal Exposure (RTE) is the concept pertinent to our discussion here. The RTE is a characteristic thermal condition in which the drug products are stored. This is simply the T_i-t_i relationship which we mentioned in the General Theory section.

(Appendix 1 shows that the concept of RTE is also an averaging process as discussed in General Theory section)

Using Eqs.5 and 7, the T_v and α corresponding to the RTE can be calculated. Table I shows the annual T_v's for the RTE for room temperature and the RTE for controlled room temperature presented in the PMA's report (5). Figures 2 and 3 show the relationship between α values and the activation energy for the RTE's at various reference temperatures. As can be seen from Figure 2, 26°C is a good choice as a reference for the RTE for room temperature. While 24°C is suitable for the RTE for controlled room temperature (Figure 3).

We have, essentially, returned to the conventionally recognized "room temperature" (25°C) or its vicinity after making a few turns along the way. The old rule is still a good rule.

TEMPERATURE TOLERANCE OF THE REFERENCE TEMPERATURE

Assuming that we have chosen 25°C as the reference temperature for conducting stability studies. Undoubtly, it is impossible to maintain a storage area absolutely isothermally at 25°C. Air conditioning, or heating if needed, is used to maintain the temperature as close as possible to 25°C. A question natually arises is how the temperature tolerance should be. The theoretical analysis on the effect of the temperature fluctuation in stability testing (6) can give insight for this question. Figure 4 shows the relationship between $C_{t_{90}}/C^{i}_{t_{90}}$ and a (see reference 6 for the definitions for these parameters) at various activation energy using a sine wave temperature-time relationship for a first order reaction. Since in all cases, the extent of drug degradation in the isothermal condition is underestimated, the t_{90} is

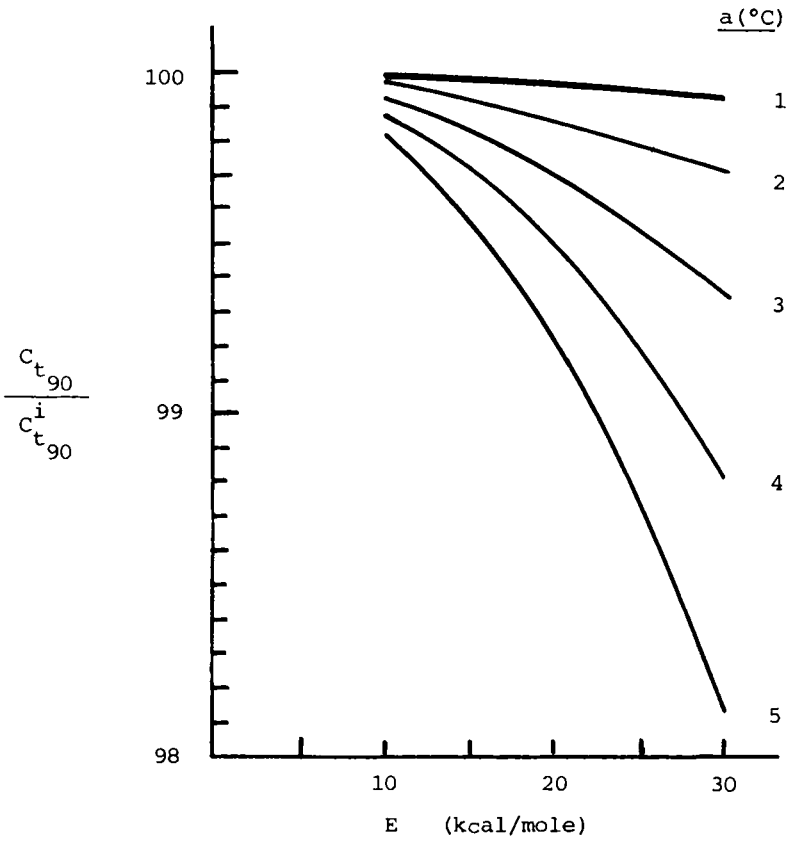

Figure 4

Comparison of drug levels under nonisothermal and isothermal conditions at t_{90} for the first order reaction. The nonisothermal condition used is $T(t)=T_o+a \sin(2\pi t/t_c)$, where $T_o=25°C, t_c=1$ hour.

underestimated as well. For example, when $C_{t_{90}}/C^{i}_{t_{90}}=0.99$, the t_{90} is underestimated by about 9%. This is equivalent to about 1 month for $t_{90}=12$ months and so on. With this consideration, it is considered that the maximal allowable temperature tolerance is $\pm 3°C$ when the reference temperature is 25°C.

REFERENCES

1. R.M. Patel, Stability and the FDA Guidelines - Proposed Guideline for StabilityStudies for Human Drugs and Biologicals, 13th Annual

Industrial Pharmacy Management Conference, Madison, Wisconsin, October 1980.

2. J.D. Haynes, J. Pharm. Sci.,60, 927(1971)

3. M. Scher, J. Pharm. Sci., 69, 325(1980)

4. Report of the PMA Quality Control Section Committee on Stability and Expiration Dating, Second edition, March 13, 1978.

5. Report of the PMA Quality Control Section Committee on Stability and Expiration Dating, March 1980.

6. Wu-huang Yang, Theoretical Analysis of the Effect of the Temperature Fluctuation in an Isothermal stability study, Drug Development and Industrial Pharmacy, Submitted

APPENDIX 1

Eqs.1.1, 1.2 and 1.3 can be used to calculate the drug levels at $t=jt_o$ $(j=1,2,...)$ and can be readily derived from the definition of k (Eq.3) and the appropriate rate equations.

Zero Order $$C_j = C_o - jA\Sigma t_i \exp(-E/RT_i) \quad \text{(Eq.1.1)}$$

First Order $$\ln C_j = \ln C_o - jA\Sigma t_i \exp(-E/RT_i) \quad \text{(Eq.1.2)}$$

Second Order $$1/C_j = 1/C_o + jA\Sigma t_i \exp(-E/RT_i) \quad \text{(Eq.1.3)}$$

A different data treatment is used in the PMA's reports (4,5). The drug degradation is treated as if products were sequentially stored at conditions with different T_i's. For a zero order reaction, the degradation incurred at each temperature is:

$$C_i - C_{i-1} = -k_i t_i \qquad i=1,2,...,n \quad \text{(Eq.1.4)}$$

where C_{i-1} and C_i are the initial and final concentration when the storage temperature is T_i. The total degradation under the annual RTE condition is simply the summation of Eqs.1.4:

$$\Sigma(C_i - C_{i-1}) = -\Sigma k_i t_i \quad \text{(Eq.1.5)}$$

Since $\Sigma(C_i - C_{i-1}) = C_n - C_o$, Eq.1.5 becomes:

$$C_n = C_o - A\Sigma t_i \exp(-E/RT_i) \quad \text{(Eq.1.6)}$$

Since PMA's RTE is an annual condition, C_n in Eq.1.6 is the same as C_1 in Eq.1.1. Therefore the concept of RTE is equivalent to the averaging process discussed in the General Theory.