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PROJECTION OF TENTATIVE EXPIRY DATE FROM ONE-POINT ACCELERATED STABILITY TESTING

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ABSTRACT

The Food and Drug Administration (FDA) is proposing that a satisfactory three-month stability testing of a drug product at 37 to 40°C and 75% or higher relative humidity can be employed to project a tentative expiry date of two years from the date of manufacture. This proposal is theoretically analyzed and its limitation is established. A successful projection of the expiry date according to FDA's proposal depends on the drug level at the end of the accelerated stability testing, the activation energy, and the temperature of the accelerated condition and the normal storage condition. The applicability of this method in assessing the stability characteristics of pharmaceutical formulations in the development process is discussed.

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INTRODUCTION

It is stated in the Current Good Manufacturing Practice (GMP) that the purpose of an expiry date for a pharmaceutical product is to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use. An expiry date is required for all drug products except some specific exemptions as determined by the Food and Drug Administration. It is required that the expiry date be established through a suitably designed stability testing program conducted under labeled storage conditions, however FDA also accepts, on the tentative basis, the expiry date projected from an accelerated stability testing. In this connection, FDA is proposing that a satisfactory three-month stability testing of a drug product at 37 to 40°C and 75% or higher relative humidity can be employed to project a tentative expiry date of two years from the date of manufacture (1). Essentially this represents the projection of a tentative expiry date from a one-point accelerated stability testing. This proposal has been subjected to a great deal of argument in the pharmaceutical industry. This paper analyzes the proposal critically on the theoretical basis and establishes its limitations. The applicability of this one-point accelerated stability test-

ing in the assessment of the stability characteristics of a drug product in the development stage is also discussed.

THEORETICAL

Assume that the degradation of the drug in the product follows the first-order kinetics, the integrated rate equation is,

$$\ln A = \ln A_0 - kt \qquad \text{(Eq. 1)}$$

where A_0 is the initial drug level in the product; A, the drug level remaining in the product after a period of time, t; and k, the rate constant.

Let's further assume that the degradation kinetics obeys the Arrhenius relationship, which is expressed as follows,

$$\ln \frac{k_2}{k_1} = \frac{E_a}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right) \qquad \text{(Eq. 2)}$$

where k_1 and k_2 are rate constants of the degradation at two different temperatures, T_1 and T_2 respectively; E_a, the activation energy of the degradation; and R, the gas constant.

A stability study for the product is performed at T_2 for a period of time, t, if the drug level at time t is determined, it is then possible to calculate the

expiry date at a different and lower temperature, T_1, using the following steps. (a) Calculate the rate constant k_2 at T_2 using Eq. 1. (b) If the activation energy is known, the rate constant k_1 at T_1 can be calculated from Eq. 2. (c) The rate constant k_1 can be used to calculate the expiry date at T_1 using Eq. 1 again. Note that, in this paper, the expiry date is defined as the time required for the drug level of a product to reach 90% of the initial level.

By performing a series of calculations as described above with different A values at time t at T_2 and different E_a values, a family of curves can be constructed when the expiry date at T_1 is plotted versus the activation energy as shown in Figure 1.

Similar curves can be constructed for the degradation with other kinetic orders using appropriate rate equations. A computer program capable of calculating a series of such values was prepared.

RESULTS AND DISCUSSION

The curves shown in Figure 1 represent the relationship between the expiry date at 25 °C and 75% RH and the activation energy of a first-order degradation at different drug levels remaining after three-month stability tesing at 40 °C and 75% RH.

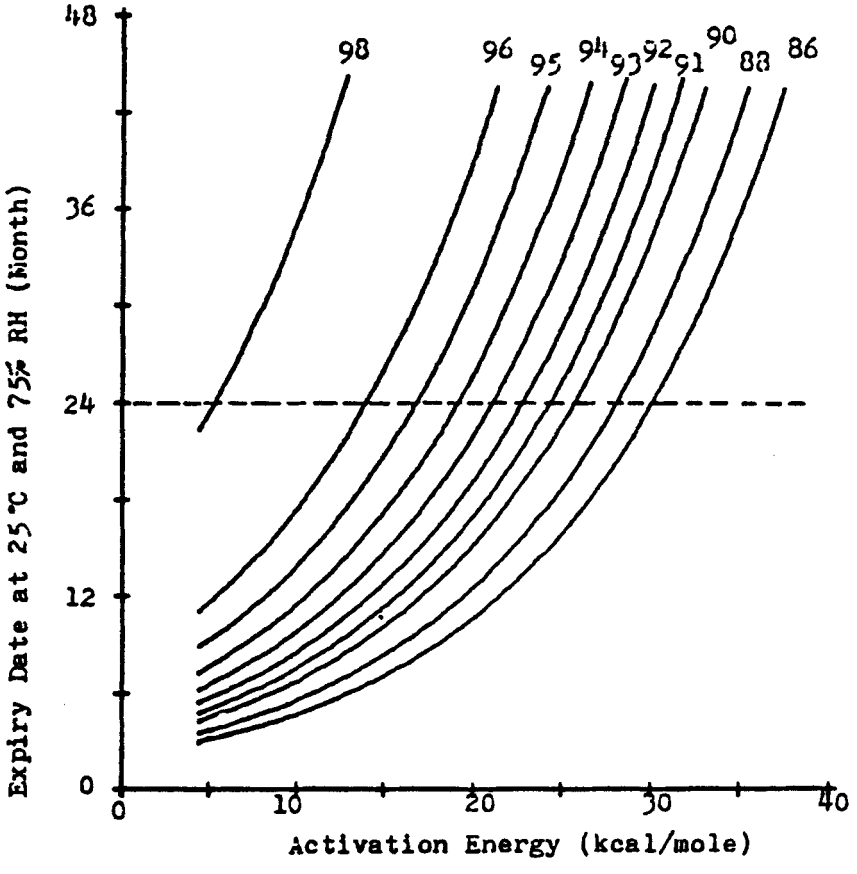

Figure 1

Relationship among the expiry date at 25°C and 75% RH, activation energy of the degradation, and the drug level remaining at the end of three-month stability testing at 40°C and 75% RH

The validity and the limitation of FDA's proposal can be explained by the following argument. Assume that after three-month stability testing at 40°C and 75% RH, the drug level remaining is 90% of the initial level

(and thus satisfactory), it can be calculated that the activation energy required to satisfy FDA's two-year (24 months) projection to 25°C and 75% RH is 25.8 kcal/mole. This threshold activation energy is actually the activation energy corresponding to the intersection of the curve and the 24-month horizontal line as shown in Figure 1. As can be seen, for this particular case, if the activation energy is equal to or greater than 25.8 kcal/mole, FDA's proposal is valid since the product has at least 24 months as the expiry date at 25°C and 75% RH. However, FDA's proposal becomes invalid if the activation energy is smaller than 25.8 kcal/mole. Table 1 presents the activation energy of the degradation reactions for the purpose of the comparison.

These threshold activation energy required to satisfy FDA's proposal are plotted versus the drug level remaining after three-month stability testing at 40°C and 75% RH in Figure 2. The following decision rule can be formulated for Figure 2 in determining whether or not one can make the projection as proposed by FDA. If the activation energy of the degradation is equal to or greater than the activation energy value read from Figure 2 for a particular A value at the end of the accelerated testing, FDA's proposal is valid; otherwise the proposal is not valid.

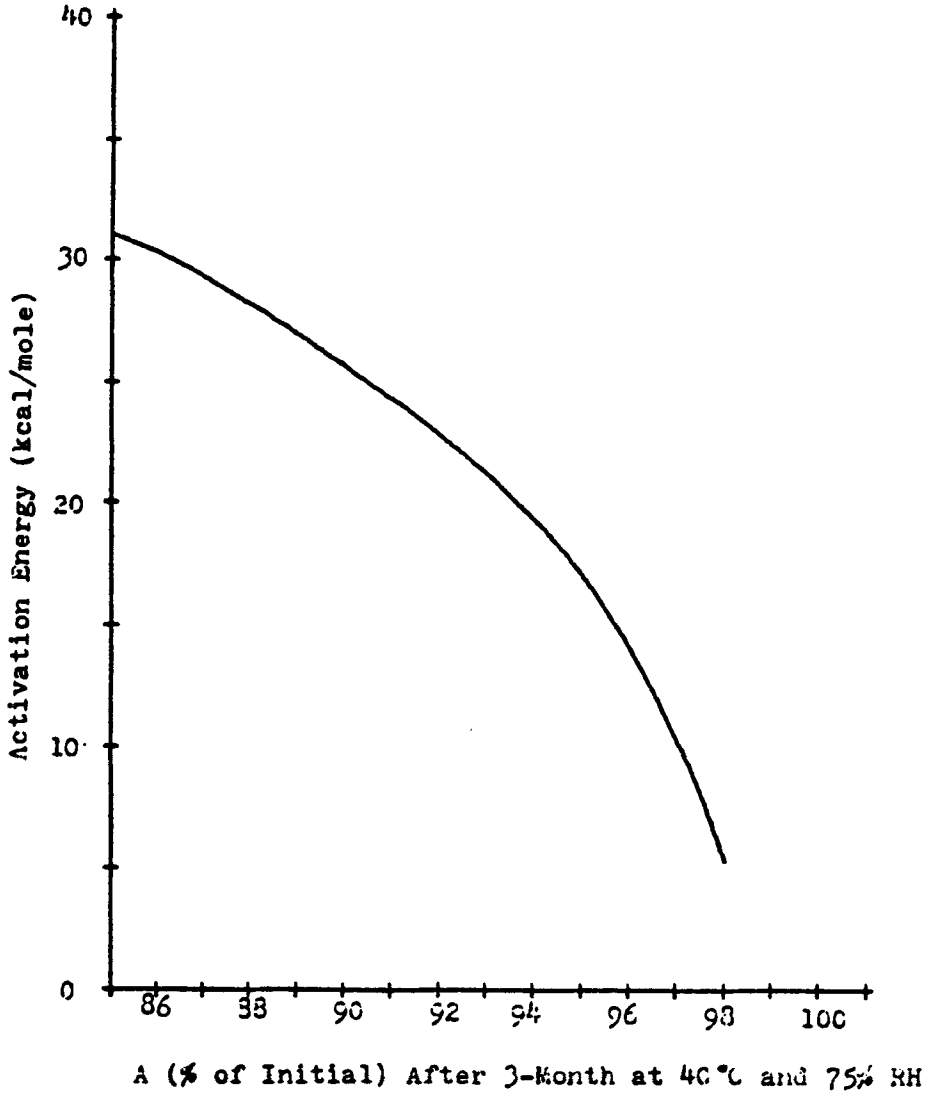

Figure 2

Threshold activation energy to satisfy FDA's proposal at various drug levels remaining at the end of three-month stability testing at 40 °C and 75% RH

TABLE 1

Activation Energy Of Some Degradation Reactions

Drug	Type of Reaction	Activation Energy kcal/mole
Ascorbic Acid	Oxidation	20 - 24 (2,3)
Acetaminophen	Hydrolysis	17 (4)
Penicillin G. Procaine	Hydrolysis	17.8 - 20.9 (5)
Atropine	Hydrolysis	17.2 (6)

Another factor which can affect the validity of the projection of a tentative expiry date is the choice of the temperature of either the accelerated condition or the normal storage condition, or both. Assume that the same product discussed previously is subjected to an accelerated stability testing at 40 °C and 75% RH, at the end of three-month period, the drug level remaining is 90% of the initial level. The curves in Figure 3 show the difference in the projected tentative expiry date at three different normal storage temperatures: 30 , 25 and 4 °C. As expected, for a particular activation energy the lower the normal storage temperature the longer the projected expiry date. For example, if the activation energy is 20 kcal/mole, the projected expiry date is 8.64 months at 30 °C, 15.1 months at 25 °C, and 194.3 months at 4 °C.

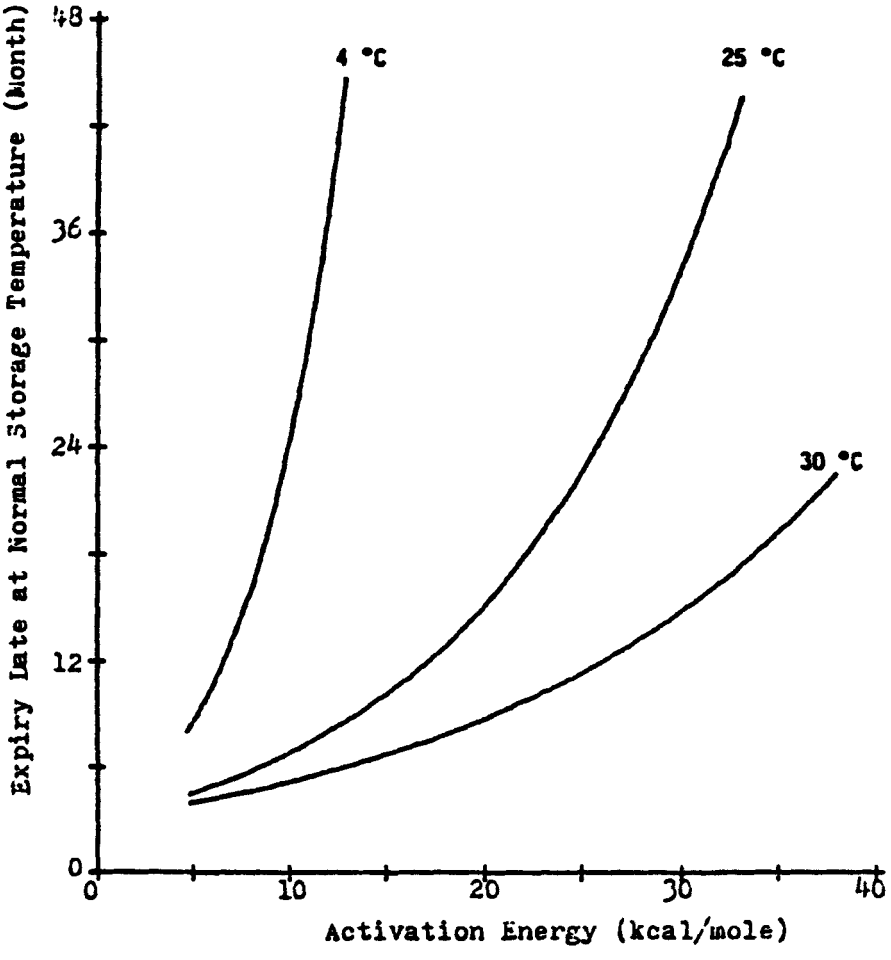

Figure 3

Relationship between the expiry date at different normal storage temperatures and the activation energy of the degradation when the drug level remaining is 90% of the initial level at the end of three-month stability testing at 40 °C and 75% RH

To satisfy FDA's proposal for 24-month projection of this particular product the threshold activation energy, as defined previously, is 39.3 kcal/mole at 30°C, 25.8 kcal/mole at 25°C, and 9.97 kcal/mole at 4°C. Therefore, according to the decision rule elaborated previously FDA's proposed projection is not valid when the normal storage temperature is either 30 or 25°C, and is acceptable when that temperature is 4°C. This decision is obviously dependent upon the drug level remaining at the end of the accelerated testing. For example, should that level be 95% of the initial level, then only the projection made to 30°C is not valid since in this case the threshold activation energy is 25.7 kcal/mole at 30°C, 16.8 kcal/mole at 25°C, and 6.5 kcal/mole at 4°C.

It is thus apparent that FDA's proposal should be employed with caution. Wherther or not the projection of a tentative expiry date can be made depends on the drug level at the end of the accelerated stability testing, the activation energy, and temperatures of the accelerated condition and the normal storage condition.

Curves similar to that shown in Figure 2 can be constructed for different projected expiry dates. These are shown in Figure 4 for 18, 24, 30, and 36 months. These curves are very useful in screening formulations

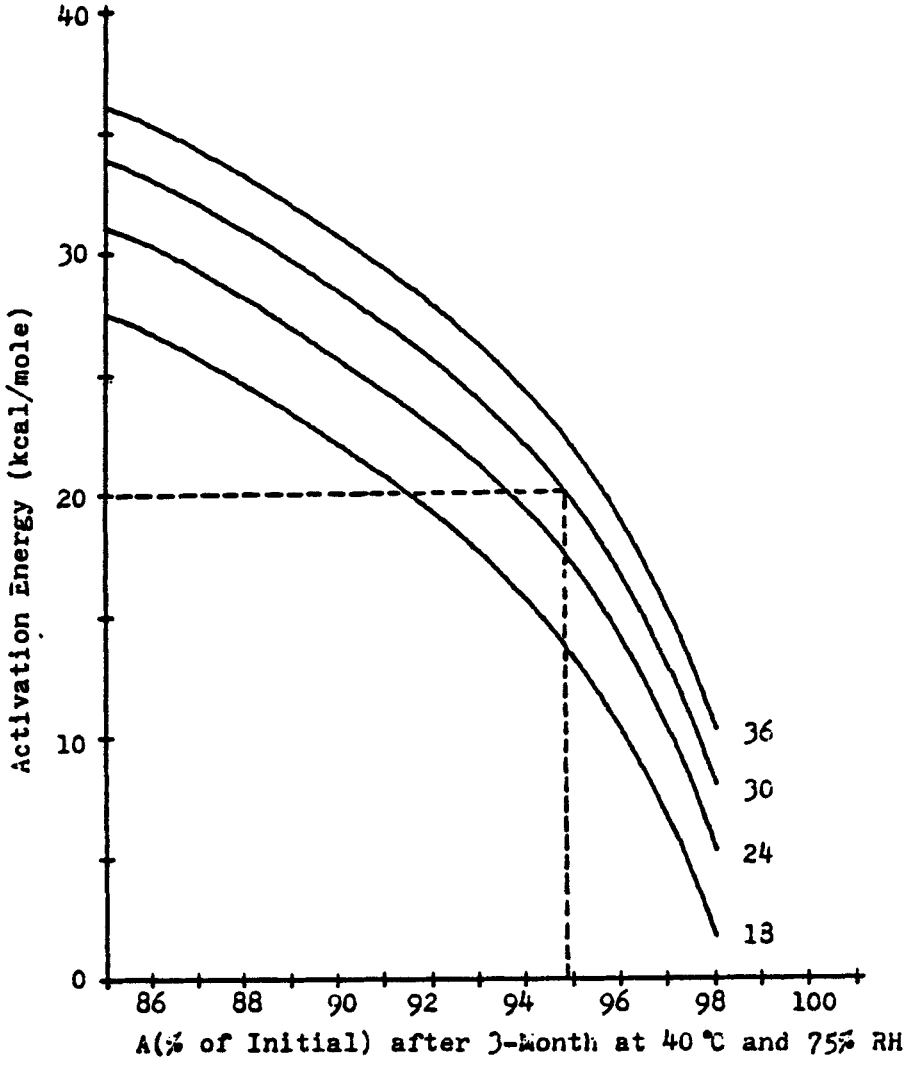

Figure 4

Threshold activation energy to satisfy different projected expiry dates at various drug levels remaining at the end of three-month stability testing at 40 °C and 75% RH

in the development stage. For example, a liquid formulation, buffered at pH 6, with a projected expiry date of 30 months at 25°C and 75% RH will be developed. One can prepare a few possible formulations which are then subjected to stability studies at 40°C and 75% RH for three months. If the activation energy of the degradation at pH 6 is known to be 20 kcal/mole, it can be seen immediately from Figure 4, for such system, that the formulation will have at least 30 months as the expiry date at 25°C and 75% RH provided that the drug level is at least 94.8% of the initial level at the end of the 3-month stability study at 40°C and 75% RH (as illustrated by the dash lines in Figure 4). Thus formulations which do not meet the requirement can be quickly eliminated at the early stage of the development process.

It should be emphasized that it is assumed that the Arrhenius relationship holds true in this theoretical discussion. For this assumption to be applicable all other conditions should be kept constant except the temperature in making the projection. Thus when a tentative expiry date is projected to 25°C from an accelerated stability testing at 40°C and 75% RH, it refers to the expiry date at 25°C and 75% RH. For drug products which are not sensitive to moisture, this projected tentative expiry date actually represents a worst situation. It is also noted that the assumption of the Arrhenius rela-

tionship in this paper means that only chemical degradation of the active ingredient is discussed, the physical stability characteristics of the drug products is assumed to be satisfactory under the accelerated conditions. For this reason, this discussion may be more applicable to the solution dosage form than to solid and semi-solid dosage forms.

The assumption of the Arrhenius relationship is probably a reasonable one. Evidences showing that the drug degradation in various delivery systems follows the Arrhenius relationship are numerous. In addition, the temperature range for the accelerated condition suggested in FDA's proposal (37-40°C) is quite moderate. These temperatures most likely do not induce a change in the degradation mechanism of the active ingredient which is one of the conditions that must be satisfied for the Arrhenius relationship to be applicable.

A nomographic chart which is also derived from Arrhenius relationahip was reported(7) to project the expiry date at normal storage condition, however, two accelerated conditions are required for this projection.

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