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PROJECTION OF TENTATIVE EXPIRY DATE FROM ONE-POINT ACCELERATED STABILITY TESTING II. OVERAGE CONSIDERATION

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ABSTRACT

A previous publication (1) analyzed a statement originated from the Food and Drug Administration (FDA) that a drug product which is stable for three months at 37-40°and 75% or higher relative humidity can be given a tentative expiry period of two years from the date of manufacture. Conditions which can be uesd to make a successful projection using such a proposal have been established. These conditions are applicable only to pharmaceutical systems which do not contain an overage. The theoretical discussion is extended in this communication to analyze the effect of the overage on the proposed projection of the expiry period. The analysis shows that the inclusion of the overage lowers the threshold activation energy needed to satisfy the FDA's proposal.

An expiry period is currently required on the labeling of a drug product. Due to the stability characteristics of most drug entities, establishing an expiry date through stability testing under normal storage conditions is usually a time-consuming process. A tentative expiry period projected from accelerated stability testing is currently an accepted practice as stated specifically in the Current Good Manufacturing Practice (2). In this regard, it has been proposed that satisfactory results from three-month stability testing of a drug product at 37-40° and 75% or higher relative humidity can be employed to project a tentative expiry period of two years from the date of manufacture (3,4). This proposal has been analyzed and its validity and limitations were established(1). However, no overage of the active ingredient was considered in reference 1. Since an overage is at times included, it becomes desirable to consider the effect of adding an overage on the projection based on the proposed one-point stability test. This communication presents such a theoretical analysis.

The calculation procedure has been described (1). The present communication takes into account of the overage when the expiry period at the normal storage condition (25°) is calculated. It is worthy to emphasize that the expiry period is defined as the time required for the drug level of a product to reach 90% of the label strength.

Figure 1 shows the relationship between the threshold activation energy required to satisfy the proposal and the drug

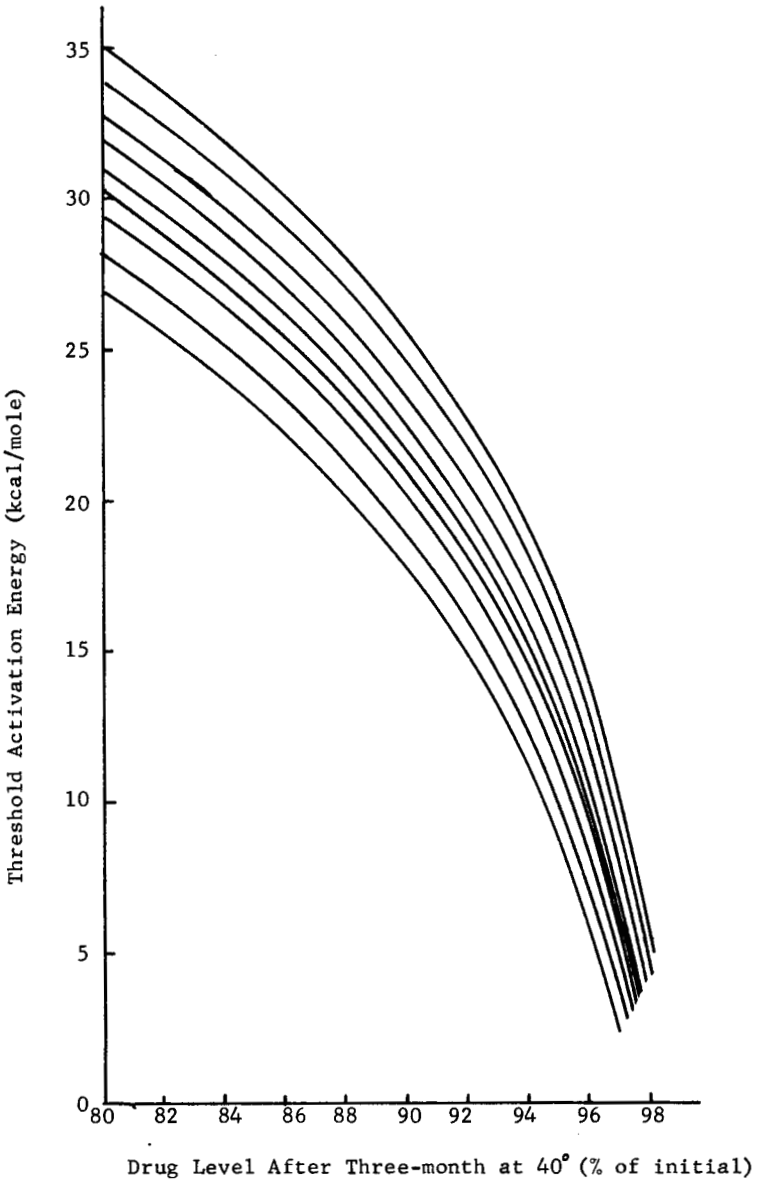

Figure 1

The relationship between the threshold activation energy required to satisfy FDA's proposal and the drug level remaining after three-month stability testing at different overage levels. A first order degradation is used in the calculation. The overages are, from top to bottom, 0,1,2,3,4,5,6,8 and 10%.

level remaining after a three-month stability test at 40° with different overage levels. Overages ranging from 0-10% are shown in Figure 1 since the USP usually allows a maximum of 10% overage of an active ingredient. As anticipated, the threshold activation energy is lowered with an increasing overage for a given drug level remaining at the end of three-month testing at 40°. Stated in another way, for a given degradation activation energy, the drug level (expressed as % of initial) remaining at the end of three-month testing at 40° to satisfy the FDA's proposal is lowered with an increasing overage.

Curves similar to those shown in Figure 4 of reference 1 can also be constructed for an appropriate overage and can be used to aid in screening prototypes in the development stage as alluded in the same reference.

REFERENCES

1. Wu-huang Yang and S.B. Roy, Drug Devel. and Ind. Pharm., 6, 591 (1980)

2. Code of Federal Regulations, Title 21, Section 211.166.

3. J.S. Davis, "The Dating Game," Presented at the Proprietary Association's Twelfth Manufacturing Controls Seminar, New Jersey, October 1978.

4. J.S. Davis, "A Discussion of the FDA Stability Guidelines," Presented at APhA Academy of Pharmaceutical Sciences, St. Louis meeting, March 1981.