Statistical Evaluation of Accelerated Stability Data Obtained at a Single Temperature. II. Estimation of Shelf-Life from Remaining Drug Content

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Accelerated stability data obtained at a single temperature (40 °C) is statistically evaluated and the utility of the actual value of remaining drug content observed in the test for estimation of shelf-life is discussed. The distribution of the time required for 10% degradation at 25 °C, $t_{90(25)}$, is calculated from the observed drug content, taking the experimental errors into consideration. The probability that the $t_{90(25)}$ is longer than a specified shelf-life, which is calculated from the distribution, is represented as a function of the observed drug content. The probability was found to depend on the experimental errors in the assay and temperature control as well as in the activation energy of degradation (E_a). The relationship between the observed drug content and the shelf-life assured with a certain probability is shown graphically, so that one can reasonably predict the expected shelf-life as a function of E_a if the accuracy and precision of the assay and temperature control are known.

Keywords drug stability; accelerated stability test; shelf-life; experimental error; statistical evaluation; distribution; shelf-life estimate

In a previous paper,[1] accelerated stability data obtained at a single temperature was statistically evaluated, and the utility of such data for assessment of stability was discussed, focussing on the chemical stability of solution-state dosage forms. The probability that the drug content of a product is observed to be within the lower specification limit in the accelerated test was interpreted graphically, and the effect of experimental errors on this probability was also addressed. It was shown that the probability depends on experimental errors in the assay and temperature control as well as the true degradation rate and activation energy (E_a). Without knowing the values of the E_a and the accuracy and precision of the assay and temperature control, the observation that the drug content remains within the lower specification limit can provide only limited information on the shelf-life of the drug. The previous paper discussed the utility of the observations when the drug content meets the specification. The utility of the actual value of remaining drug content observed in the accelerated test for the assessment of stability was not evaluated.

The present paper describes a method for estimating the time required for 10% degradation at 25 °C, $t_{90(25)}$, from the value of remaining drug content observed in an accelerated test at a single temperature, *i.e.* 40 °C. The $t_{90(25)}$ is a main determinant of the product shelf-life. The relationship between the $t_{90(25)}$ and the observed value of remaining drug content is interpreted graphically, and the effect of experimental errors in the assay and temperature control on the value of remaining drug content necessary to assure the shelf-life is discussed.

Theoretical

The probability that a certain value of remaining drug content, x, is observed at time t in the accelerated test carried out at 40 °C, $P(x)$, can be related to the time required for 10% degradation at 25 °C, $t_{90(25)}$, by Eq. 1, as shown in the previous paper.[1]

$$P(x)=\frac{1}{\sqrt{2\pi}\sigma}\exp\left[-\frac{(100-C/t_{90(25)}-x)^2}{2\sigma^2}\right] \quad (1)$$

where σ is the standard deviation of the drug content assay, and C is a constant represented by Eq. 2 when the reaction is assumed to follow zero order kinetics:

$$C=10\left\{\exp\left[-\frac{E_a}{R}\left(\frac{1}{313}-\frac{1}{298}\right)\right]\right\}\cdot t \quad (2)$$

In Eq. 2, E_a represents the activation energy and R is the gas constant. When a certain value of drug content, D, is observed at 40 °C, the distribution of $t_{90(25)}$ can be represented by Eq. 3.

$$P(t_{90(25)})=\frac{1}{\sqrt{2\pi}\sigma}\left\{\exp\left[-\frac{(100-C/t_{90(25)}-D)^2}{2\sigma^2}\right]\right\}\frac{C}{{t_{90(25)}}^2} \quad (3)$$

Some examples of the distribution of $t_{90(25)}$ are shown in Fig. 1, for the case where the percent remaining is observed to be 80, 85, 90 or 95% after 6 months ($t=6$) of storage at 40 °C. The standard deviation of the assay is assumed to be 2% and the E_a is 20 kcal/mol. Integration of Eq. 3, in the range where $t_{90(25)}$ is smaller than a certain period, gives the probability that the period cannot be assured as the shelf-life. The value of $t_{90(25)}$ at which the area under the curve reaches 5% of the total corresponds to the shelf-life assured with 0.95 of probability. Computing programs for the calculation were written in BASIC and compiled on a PC-9801 VX (NEC, Tokyo).

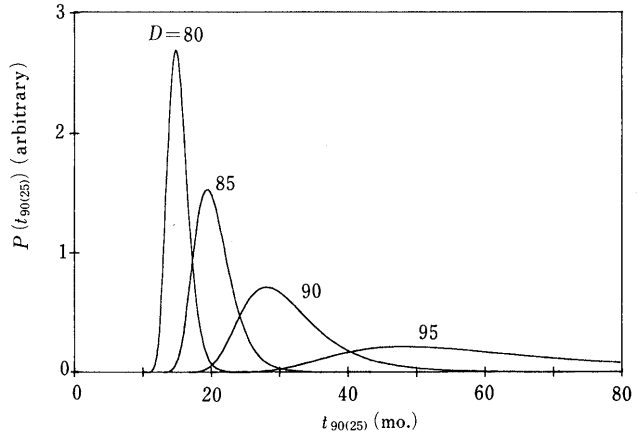

Fig. 1. Distribution of $t_{90(25)}$ Expected When Various Percent Remaining Was Observed

Assay standard deviation: 2%. E_a: 20 kcal/mol. D: percent remaining after 6 months of storage at 40 °C.

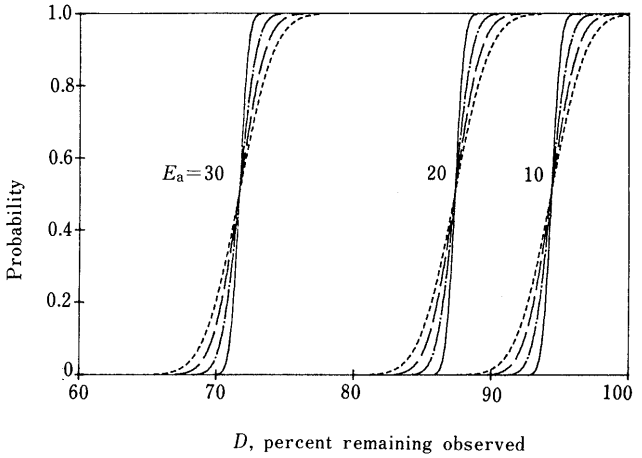

Fig. 2. Effect of Assay Errors on Probability ($t_{90(25)}$>2 Years) as a Function of Percent Remaining Observed, D

Assay standard deviation: ——, 0.5; — — —, 1; — —, 1.5; ------, 2%. Numbers represent the E_a (kcal/mol).

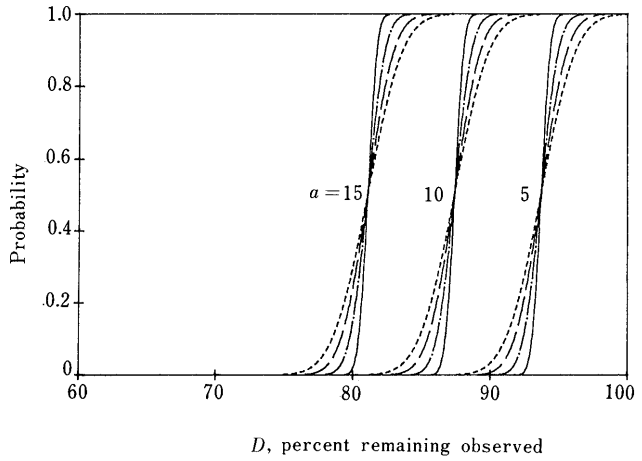

Fig. 3. Effect of Assay Errors on Probability (the Time Required for Various Percent (a) of Degradation>2 Years) as a Function of Percent Remaining Observed, D

Assay standard deviation: ——, 0.5; — — —, 1; — —, 1.5; ------, 2%. E_a: 20 kcal/mol.

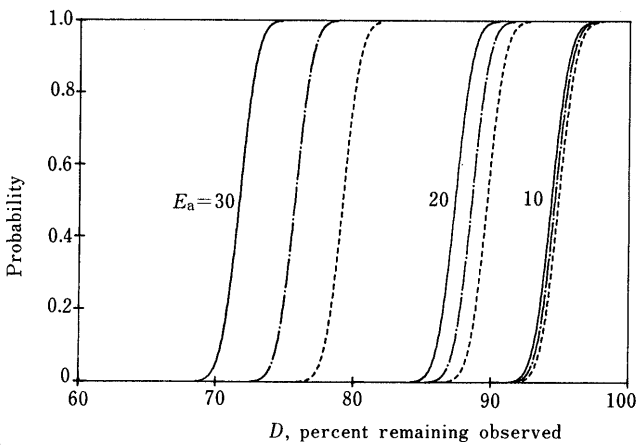

Fig. 4. Effect of Temperature Errors on Probability ($t_{90(25)}$>2 Years) as a Function of Percent Remaining Observed, D

Temperature: ——, 40; — — —, 39; ------, 38 °C. Assay standard deviation: 1%. Numbers represent the E_a.

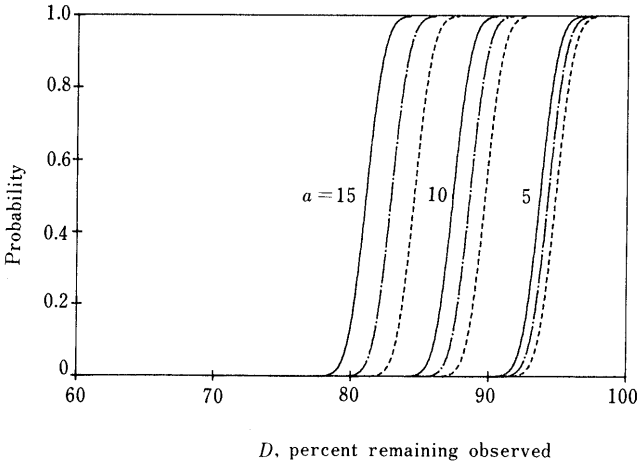

Fig. 5. Effect of Temperature Control Errors on the Probability (the Time Required for Various Percent (a) of Degradation>2 Years)

Temperature: ——, 40; — — —, 39; ------, 38 °C. E_a: 20 kcal/mol. Assay standard deviation: 1%.

Results and Discussion

The data for remaining drug content observed in the accelerated stability tests should be useful in some way as an aid in the estimation of $t_{90(25)}$. The smallest value of $t_{90(25)}$ which is estimated from the remaining drug content data may correspond to the shelf-life to be assured, if the lower specification limit of the drug content is 90%. Assuming that a certain percent remaining was observed at the 6th month at 40 °C, the probability that the $t_{90(25)}$ is longer than a specified shelf-life depends on the E_a and the standard deviation of the assay errors as represented by Eq. 3.

For the following discussion, the shelf-life is assumed to be 2 years. Figure 2 shows the probability that $t_{90(25)}$ is expected to be longer than 2 years plotted against the observed percent remaining when E_a is 30, 20 or 10 kcal/mol. The probability descreases with decreasing E_a. For example, when the percent remaining was observed to be 90%, the probability that $t_{90(25)}$ is longer than 2 years is very small when E_a is 10 kcal/mol, while 2 years of shelf-life can be assured with high probability when E_a is 30 kcal/mol. Figure 3 shows the probability that the time required for 15%, 10% or 5% degradation is expected to be longer than 2 years when E_a is 20 kcal/mol. As shown in Figs. 2 and 3, the probability depends largely on the assay errors.

Temperature control errors also affect the probability that $t_{90(25)}$ is longer than a specified period. Figure 4 shows the probability that the $t_{90(25)}$ is longer than 2 years plotted against the percent remaining observed at temperatures lower than 40 °C (38 and 39 °C) when the standard deviation of the assay is 1%. Figure 5 shows the probability that the time required for 15, 10 or 5% degradation is longer than 2 years under the same temperature conditions when E_a is 20 kcal/mol. Figures 4 and 5 show that even 1 °C difference makes a big difference in the probability.

Figures 6 and 7 show the relationship between the observed percent remaining and the $t_{90(25)}$ to be assured with 0.95 of probability. The percent remaining required to assure the shelf-life depends on the experimental errors. Figures 6 and 7 show the effect of assay errors and temperature control errors, respectively. The shelf-life to be assured from the observed percent remaining decreases

TABLE I. Percent Remaining after 6 Months of Storage at 40 °C to Assure 1, 2 or 3 Years of Shelf-Life ($p>0.95$)

E_a (kcal/mol)	Shelf-life (year) 1 S.D.[a] 0.5	1	1.5	2	2 S.D.[a] 0.5	1	1.5	2	3 S.D.[a] 0.5	1	1.5	2
10	89.6	90.4	91.2	92.1	95.2	96.0	96.9	97.7	97.1	97.9	98.7	99.5
20	75.6	76.4	77.2	78.0	88.2	89.0	89.9	90.7	92.4	93.2	94.1	94.9
30	44.1	44.9	45.8	46.6	72.5	73.3	74.1	74.9	81.9	82.8	83.6	84.4

a) S.D.: assay standard deviation.

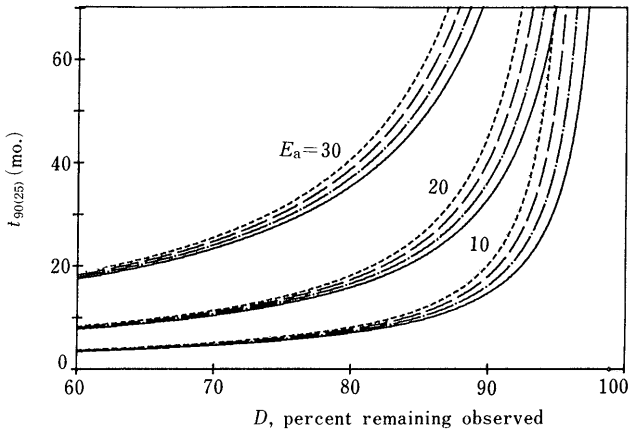

Fig. 6. Effect of Assay Errors on Shelf-Life Assured as a Function of Percent Remaining Observed, D ($p>0.95$)

Assay standard deviation: ------, 0.5; ——, 1; ——, 1.5; ——, 2%. Numbers represent the E_a.

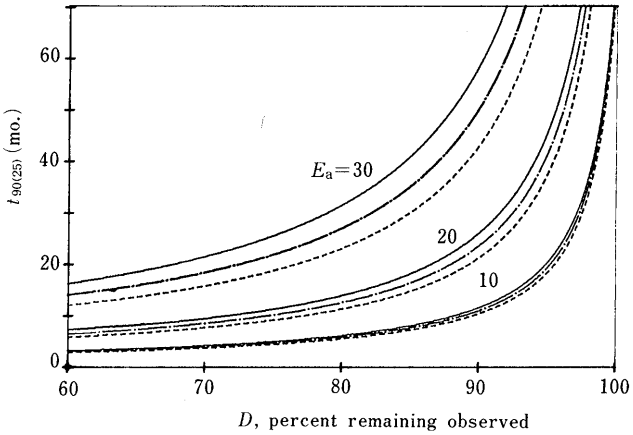

Fig. 7. Effect of Temperature Errors on Shelf-Life Assured as a Function of Percent Remaining Observed, D ($p>0.95$)

Temperature: ——, 40; ——, 39; ------, 38 °C. Numbers represent the E_a.

markedly with an increase in the errors. Table I shows the lower limits of drug content which should be observed after 6 months at 40 °C in order to assure 1, 2 or 3 years-shelf-life for several combinations of E_a and assay errors.

Conclusion

How can the value of remaining drug content observed in a single-temperature accelerated stability test be utilized in assessing stability? The distribution of $t_{90(25)}$ can be calculated by using Eq. 3 from the actual value of remaining drug content observed in the accelerated test. Integration of the distribution of $t_{90(25)}$ can provide the probability that the $t_{90(25)}$ is longer than a specified shelf-life. It is shown that the probability depends on E_a of the degradation and the experimental errors in the assay or temperature control (Figs. 2 to 5). The relationship between the observed value of remaining drug content and the $t_{90(25)}$ assured with a certain probability is shown graphically (Figs. 6 and 7). Therefore, if the accuracy and precision of the assay and temperature control are known, one can reasonably predict the expected shelf-life as a function of E_a, from the stability data at 40 °C. By using a conservative estimate for E_a, one can then predict the minimum shelf-life.

References

1) S. Yoshioka, Y. Aso and Y. Takeda, *Chem. Pharm. Bull.*, **38**, 1757 (1990).