

6.2.6. Accelerated Stability Testing in Expiration

Dating of Pharmaceutical Dosage Forms

Accelerated stability analysis is designed to predict stability and shelf-life of formulations under normal or recommended storage conditions by carrying out the study under accelerated conditions of temperature, moisture, and light.

In accelerated stability testing, a product is stored at elevated stress conditions. Degradation at recommended storage conditions could be predicted based on the degradation at each stress condition and known relationships between the acceleration factor and the degradation rate. A product may be released based on the accelerated stability data, but the real-time testing should be done in parallel to confirm the shelf-life prediction.

Temperature is probably the most common acceleration factor used for chemicals, pharmaceuticals, and biological products since its relationship with the degradation rate is well characterised by the Arrhenius equation. This equation describes a relationship between temperature and the degradation rate:

$$\delta = A \exp \left(\frac{-E_a}{RT} \right)$$

This relationship can be used in accelerated stability studies when the following conditions are met:

- 1) A zero- or first-order kinetic reaction takes place at each elevated temperature, as well as at the recommended storage temperature.
- 2) The same model is used to fit the degradation patterns at each temperature.

Humidity and pH can be used along with temperature to accelerate degradation, but modelling of multi-factor degradation is very complex.

6.2.6.1. Objectives of Accelerated Stability Studies

Accelerated stability testing is generally undertaken with the following objectives:

- 1) To serve as a rapid means of selecting the best formulation from amongst a series of similar formulations of the product.
- 2) To predict the shelf-life of product.
- 3) To serve as a rapid means of quality control.

6.2.6.2. Expiration Dating

The expiration dating (or shelf-life) of a drug is the time interval for which a drug product is expected to remain within an approved shelf-life specification, provided that it is stored according to label storage conditions and is packed in the original container closure system. Expiry is the actual date placed on the container or label of a drug product designating the time after which it should not be used.

In general, this is answered through stability testing that monitors chemical and physical product attributes as a function of time, temperature, and other environmental factors:

- 1) Expiration date related to specific storage condition stated on the label should be derived on the data obtained from an appropriate stability-testing programme using a reliable stability-indicating assay method.
- 2) The stability programme should include:
 - i) Numbers and sizes of containers per sample time,
 - ii) Testing of drug product in the marketed container closure system at appropriate storage condition(s), and
 - iii) An adequate number of batches, usually at least three production batches, to be placed on long-term stability testing for a new product initially and one production batch per year thereafter.
- 3) Tentative expiration dates can be assigned based on data from accelerated stability studies. A rule of thumb for solid dosage forms allows a 2-year tentative expiration date at room temperature if the drug has retained 90% of its original potency after 90 days of storage at 40°C and 75% relative humidity.
- 4) Long-term stability studies should be conducted to confirm the predicted expiration date.

6.2.6.3. Accelerated Stability Study Profile

The profile of accelerated stability study is given in the table 6.2:

Table 6.2: Stability Profiles - Accelerated Stability Study

Storage Conditions	Testing Conditions
Controlled room temperature 20-25°C	40°C and 75% RH for 6 months
Refrigerated condition 2-8°C	25°C and 60% RH for 6 months
Freezer condition 2-10°C	5°C for 6 months

6.2.6.4. Prediction of Shelf-Life from Accelerated Stability Data

On the basis of chemical kinetics, shelf-life can be predicted from accelerated stability studies performed by the following methods:

- 1) **Shelf-Life Determination Based on Arrhenius Plot (Garret and Carper Method):** The shelf-life can be mathematically predicted by applying Arrhenius equation. On plotting the effect of temperature on rate constant (k) of a chemical reaction of thermodynamic temperature (1/T), a straight line is obtained.

The value of k is obtained, if the slope of this line is determined from the results of temperature by extrapolation. Further, the value of k is substituted in appropriate order of reaction allowing the amount of decomposition after a given time. Therefore, for the determination of this order some preliminary experiments are necessary:

$$K = Ae^{-E_a/RT}$$

$$\text{Log } K = \text{Log } A - E_a/2.303*RT$$

Where, K = Rate constant.

R = Gas constant (1.987 cal/mole).

T = Absolute temperature.

A = Frequency factor.

E_a = Energy of activation.

$$T_{10\%} = (2.303/K) * (\log 100/90).$$

$$T_{90\%} = (2.303/K) * (\log 100/10).$$

Methods

The steps involved in **Garret and Carper** method are:

- i) Samples of the drug product are kept at **40°C, 50°C, and 60°C**.
- ii) Drug content is determined at all the three storage points by taking a few samples and determining their mean drug content for a few weeks.
- iii) A graph between **time** and **log concentration** is plotted for each temperature (**figure 6.8**).
- iv) In the next step, a best fit line is drawn by taking $1/T \times 10^{-6}$ on x-axis and the **log K** or **log of reaction constant** on y-axis (**figure 6.9**). The line obtained is the **Arrhenius plot** which is extrapolated to get k at **25°C** for the calculation of shelf-life.

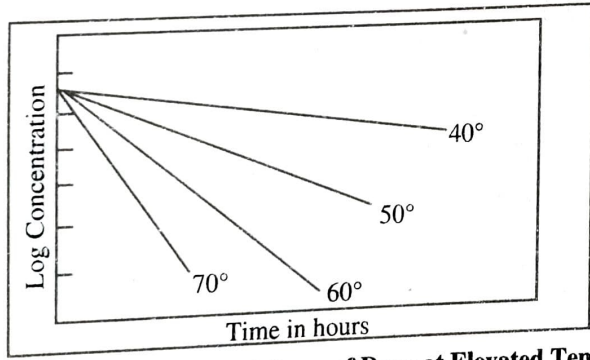


Figure 6.8: Accelerated Breakdown of Drug at Elevated Temperature

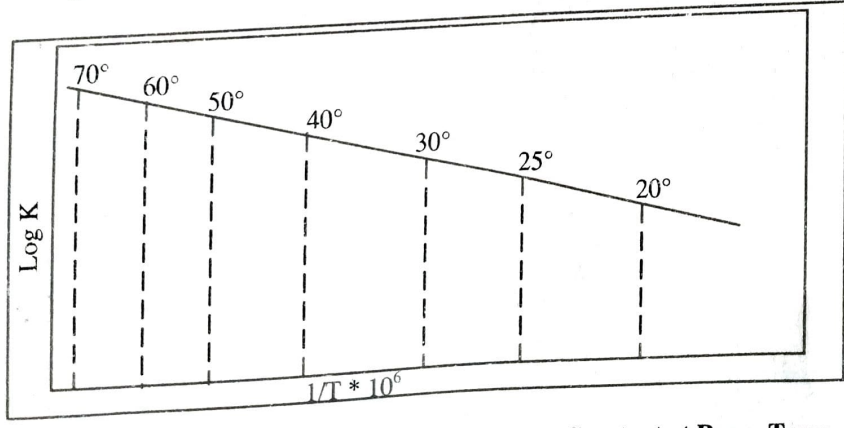


Figure 6.9: Arrhenius Plot for Predicting the Rate Constant at Room Temp

If the Reaction is Following Zero-Order: Expiration date at 25°C = Initial potency - minimum potency / reaction rate at 25°C

$$t_x = Y_0 - Y_x / K_0$$

If the Reaction is Following First-Order: Expiration date at 25°C (t_x) = Log initial potency - log minimum potency / reaction rate at 25°C.

$$t_x = \log Y_0 - \log Y_x / K_1$$

Where, Y_0 = Initial potency.

Y_x = Final potency.

K_0 = Zero-order constant.

K_1 = First-order constant.

Limitations of Arrhenius Relationship for Stability Prediction

In the following given conditions, the Arrhenius equation becomes invalid:

- At higher temperature, solvents may evaporate resulting in unequal moisture concentration at different temperatures.
- Parameters, such as moisture and oxygen decrease the stability of drugs at higher temperatures.
- Physical characteristics of dispersive systems may alter due to the increase in temperature. When the temperature increases, viscosity of the system decreases, resulting in potentially large errors during stability predictions.

Despite of these drawbacks, accelerated stability studies of pharmaceutical products are useful in predicting shelf-lives more accurately.

- Shelf-Life Determination Based on t_{90} Values (Free and Blythe Method):**
In this method, fractional life period is plotted against reciprocal temperature. At room temperature, some fraction of the drug decomposes in a few days.

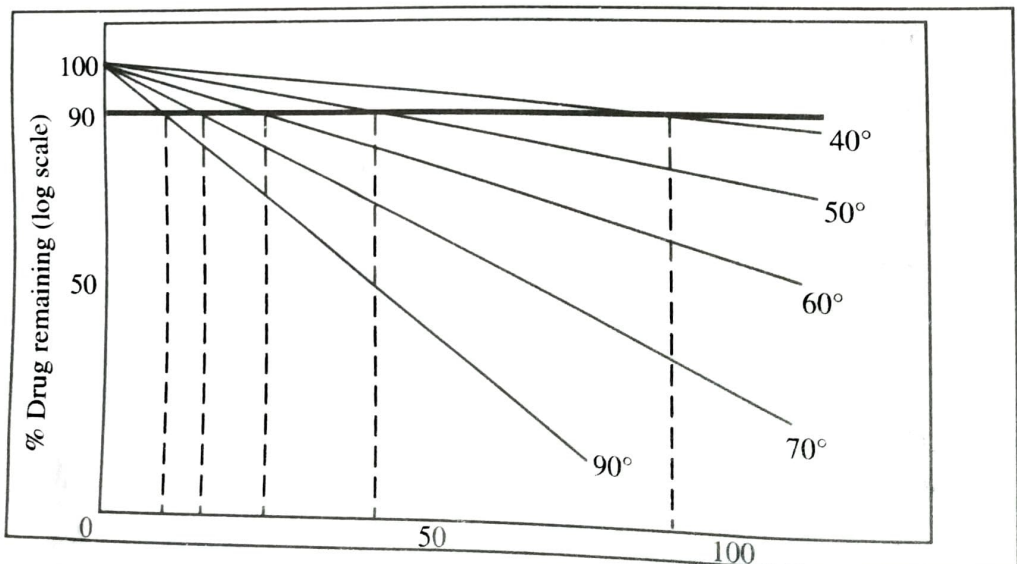


Figure 6.10: Time in Days for Required Drug Potency to Fall to 90% Original Value

The **log % of drug remaining** is plotted against **days and time** for loss line at several temperatures (**figure 6.10**). The theoretical potency when reaches to 90% is denoted by the dotted lines. In this way, the expiration date and shelf-life are calculated.

The **log time to 90%** is plotted against **1/T** (**figure 6.11**) and by extrapolating the straight line to 25°C, the time for 10% loss of potency can be determined.

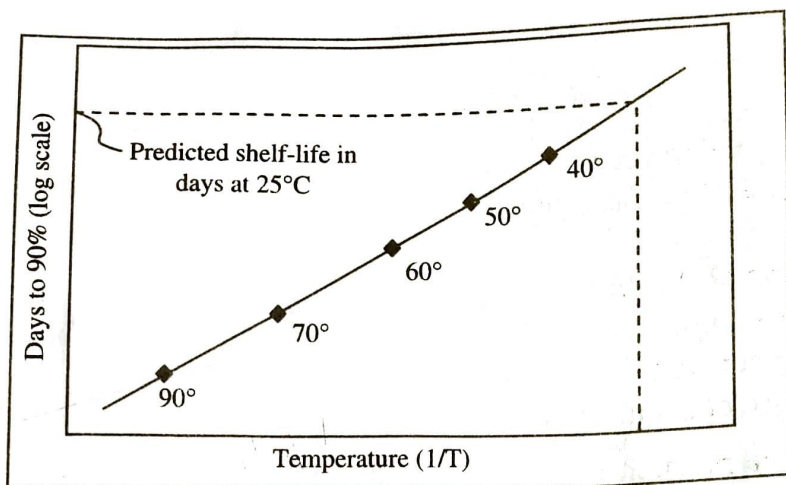


Figure 6.11: Plot of t_{90} against $1/T$ to find Predicted Shelf-Life at 25°C

6.2.6.5. Limitations of Accelerated Stability Studies

Limitations of accelerated stability studies are:

- 1) Accelerated stability studies are applicable only when temperature is responsible for the breakdown of pharmaceutical substances.
- 2) These studies are applicable when the activation energy is around 10-30kcal/mol. Most of the reactions in solution phase have the same value of activation energy. If the activation energy is less than 10kcal/mol, the reaction proceeds at room temperature.

In such a situation, increased temperature does not affect the decomposition reaction. If activation energy is higher than 30kcal/mol, decomposition reaction is enhanced by higher temperature.

- 3) Results obtained from one set of conditions for a preparation are not applicable to the other preparation of the same drug.
- 4) If degradation is influenced by microbial contamination, photo-chemical reaction, or diffusion, the elevated temperature has no role in stability prediction.
- 5) If product loses its physical integrity at higher temperature (like, denaturation of proteins, coagulation of suspending agents), stability studies do not have any importance.
- 6) At elevated temperatures, the order changes making the predictions invalid. **For example**, suspension following zero-order changes to the solution following first-order reaction at higher temperature.