IMPORTANCE OF ACCELERATED STABILITY STUDY

Accelerated stability testing

- All medicinal products decompose with time. Paradoxically, when this decomposition is being assessed the skilled formulator becomes a victim of his own expertise, as a good formulation will take a long time to decompose.
- Instability in modern formulations is often detectable only after considerable storage periods under normal conditions.
- To assess the stability of a formulated product it is usual to expose it to "high stress", i.e. condition of temperature, humidity and light intensity that cause break down.
- High stress conditions enhance the deterioration of the product and so reduce the time required for testing.
- **Thus these are the studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme**.
- This enables more data to be gathered in shorter time, which in turn will allow unsatisfactory formulation to be eliminated early in a study and will also reduce the time for a successful product to reach a market.
- It must be emphasized that extrapolation to normal storage condition must be made with care, the formulator must be sure that such extrapolation are valid.
- The results of accelerated testing studies are not always predictive of physical changes.

Significant change occurs due to accelerated testing

- **Significant change** at the accelerated conditions is defined as:
- A 5% potency loss from the initial assay value of a batch.
- Any specified degradants exceeding its specified limit.
- The product exceeding its pH limits.
- Dissolution exceeding the specified limits for 12 capsules or tablets.
- Physical Changes under Accelerated conditions of Temperature & Humidity

1. Under Light, both Primary and Secondary packaging affected, and fading of container color, and the print is fading.
2. Effervescent Tablet : Gain of moisture, loss of integrity
3. Capsule: Color fading in Blister and Sticking in a Glass bottle.
4. Powder : Spread within strip pockets
5. Suppositories : Softening
6. Change in Viscosity of a Gel, Jelly, Cream & Ointment
7. Lozenges : melting

8. Emulsions : Phase separation

Objective

1. Main aim of accelerated stability study to predict the stability profile of a drug product that prediction of self life of the product before launching into market.
2. The rapid detection of deterioration different initial formulations of the same product. This is of use in selecting the best formulation from a series of possible choices
3. Prediction of shelf life, which is the time a product will remain satisfactory when stored under expected or directed storage condition.
4. The provision of rapid mean of quality control, which ensures that no unexpected change has occurred in the stored product.

- Good formulation will invariably break down more slowly than poor ones. When the perceived optimal formulation is decided, attempts can be made to predict its likely stability at proposed storage conditions. These may be at 25^0C for ambient room temperature (or 300^0C for use in hot climates), or 0-40^0C for a refrigerator.
- The amount of decomposition that is acceptable in fixing an expiry date depends on the particular drug. This will be small if therapeutic index is low or if the decomposition products are toxic.

Stability Profiles: Accelerated stability study

Storage Condition	Testing Condition
Controlled room temperature 20-25^0C	40^0C and 75% RH for 6 months
Refrigerated condition 2-8^0C	25^0C and 60% RH for 6 months
Freezer condition -2^0 to -10^0C	5^0C for 6 months

Prediction of shelf life from accelerated stability data

Based on the principle of chemical kinetics demonstrated by

- **Garret and Carper method**
- **Free and Blythe method**

Shelf Life Determination Based on Arrhenius Plot (Garret and Carper method)

- The mathematical prediction of shelf life is based on the application of the arrhenious equation, which indicates the effect of temperature on the rate constant, k, of a chemical reaction of thermodynamic temperature, 1/T, is a straight line.

- If the slope of this line is determined from the results of temperature by extrapolation, the k value obtained. And this k value is substituted in appropriate order of reaction allows the amount of decomposition after a given time. Preliminary experiments are there for necessary to determine this order.
- **K=Ae-Ea/RT**

  Log K=Log A - Ea/2.303*RT

Where, K= rate constant

R= gas constant =1.987 cal/mole

T = absolute temperature

A = frequency factor

Ea = energy of activation

T10% = (2.303/K)*(log100/90)

T90% = (2.303/K)*(log100/10)

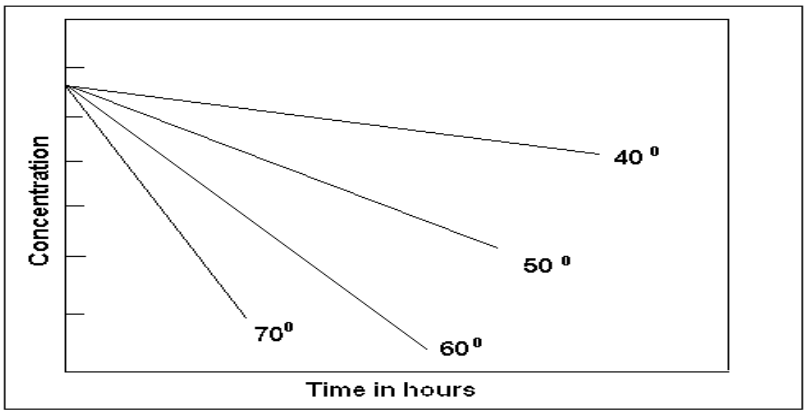
Garret and Carper method)

1. Keep several samples of the drug product at atleast three temperatures, such as **40°C, 50 °C and 60 °C.**

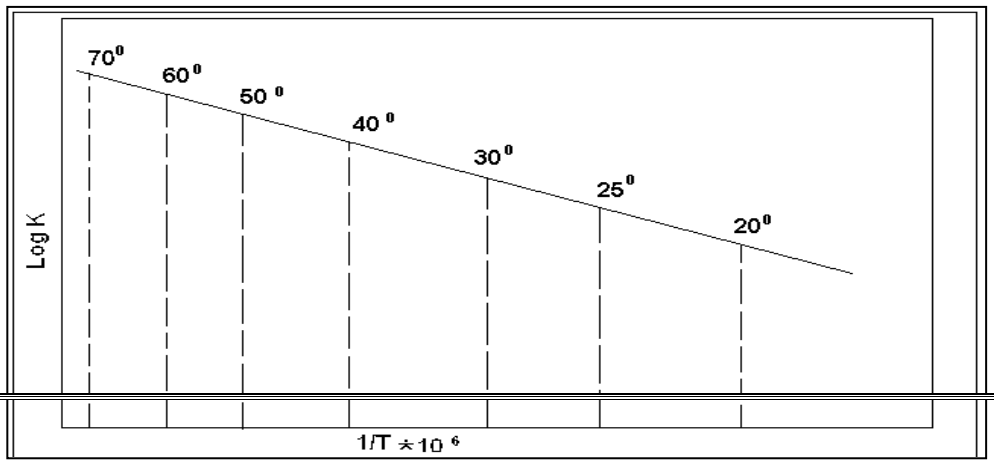
2. Determine the **drug content at all three storage points** by taking a number of samples and take the mean drug content. We do this for a few weeks.

3. At each temperature we plot a graph between **time and log percent drug remaining**. If the decomposition is **first order** this gives a straight line. If it is **zero order, percent drug remaining versus time** will give a straight line.

4. Next we take the **log K or log of reaction constant on Y axis and 1/T x 10-3 on X axis** and draw a best fit line. This line is the Arrhenius Plot, **extrapolate** this line to get **k at 25 °C** and from this we calculate the shelf-life.



Arrhenius plot for predicting drug stability at room temp.



- If the reaction is following zero-order

Expiration date at 25 ^{o}C = Initial potency – minimum potency / reaction rate at 25 °C

tx =Yo - Yx/ Ko

- If the reaction is following first order

Expiration date at 25 ^{o}C (tx) = Log initial potency – log minimum potency/reaction rate at 25

tx =log Yo – log Yx / K1

Where Yo = initial potency

Yx = final potency

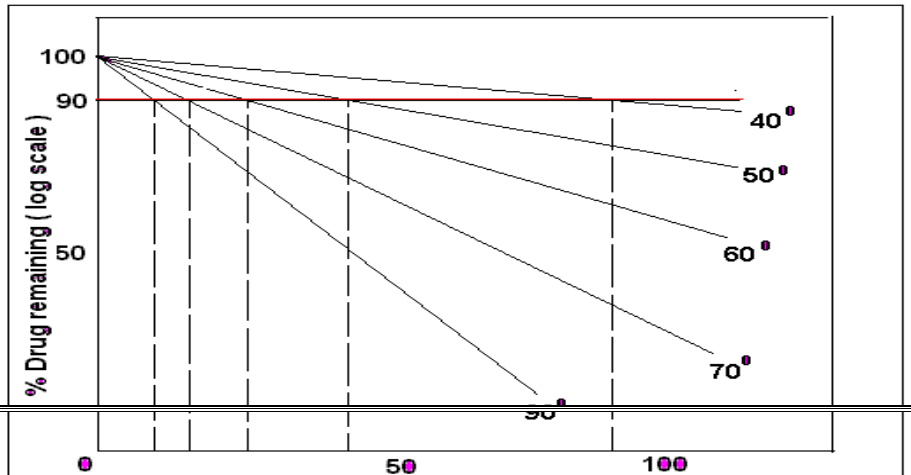
Ko = zero order constant

K1 = first order constant

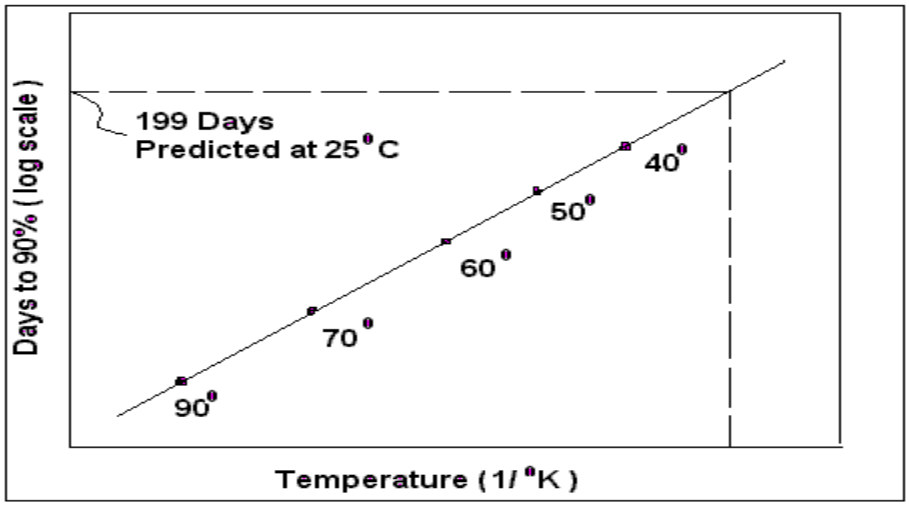
- **Limitation of arrhenious relationship for stability prediction:**
  - There are varieties of situation in which arrhenious equation can be erroneous or invalid.
  - Higher temperature may evaporate solvents thus producing unequal moisture concentration at different temperature.
  - At higher temperature stability for drugs sensitive to the presence of moisture and oxygen.
  - For dispersive systems viscosity decrease as a temperature increases and physical characteristic may alter and resulting in potentially large errors in predicting of stability.
  - In spite of these difficulties the application of accelerated testing to pharmaceutical product is often useful, and predicted shelf lives are sufficiently accurate.

SHELF LIFE DETERMINATION Based on t_{90} values (Free and Blythe /method)

In this method the fraction life period is plotted against a reciprocal temp. and the time in days required for drug to decompose to some fraction of its original potency at room temp. this approach clearly illustrate in below fig.



the log% of drug remaining is plotted against time and days and the time for the loss line at several temp. to reach 90% of the theoretical potency is noted by the doted line. Shelf life and expiration date are estimated in this way.



The log time to 90% is then plotted against 1/T and the time for 10% loss of potency at room temp. can be obtain from the resulting straight line by extrapolation to 25^0C

Limitation of accelerated stability studies

- ✓ Accelerated stability studies are valid only when the breakdown depends on temperature.
- ✓ Accelerated stability studies are valid only the energy of activation is about 10 to 30 kcal / mol. In solution phase most reaction has heat of activation in the range of 10 to 30 k.cal / mole. if energy of activation is less than 10 kcal / mol its rate would be fast at room temperature .in such cases elevated temperature has little influence on the decomposition .if energy of activation is higher than 30 kcal / mol very high temperature are required to enhance the degradation . Reaction at such high temperature may not have any relevance, because they do not reflect ambient storage condition.
- ✓ The result obtained for one set of condition for a preparation cannot be applied to other preparation of same drug.
- ✓ Stability prediction at elevated temperature is of little use when degradation is due to diffusion, microbial contamination, and photo-chemical reaction.
- ✓ Stability studies are meaningless when the product looses its physical integrity at higher temperature like coagulation of suspending agent, denaturation of proteins.
- ✓ Prediction will become erroneous when the order changes at elevated temperatures, as in case of suspension (zero order) which at higher temperature get converted to solution which follow 1^{st} order.

SHELF LIFE DETERMINATION BASED ON REAL TIME TESTING

Another method which involves real time testing and statistical analysis, followed for determining shelf life.

1. Keep three batches for stability study at least for 1 year at one fixed temperature.

2. Test them at 0, 1, 3, 6, 9, and 12 months for drug content. At each testing time test a number of samples, so that you have a mean and a standard deviation value of the result.

3. Now plot the graph of % drug content on Y axis and time on X axis along with confidence intervals. Where the lower 95% confidence curve intersects minimum potency, there you fix the shelf life.

As an example we can see the data and figure given in Tablets, Volume 3, by Hebet A Lieberman and Leon Lachmann.

Vitamin Tablets Stability Confidence Intervals at 40^{o}C

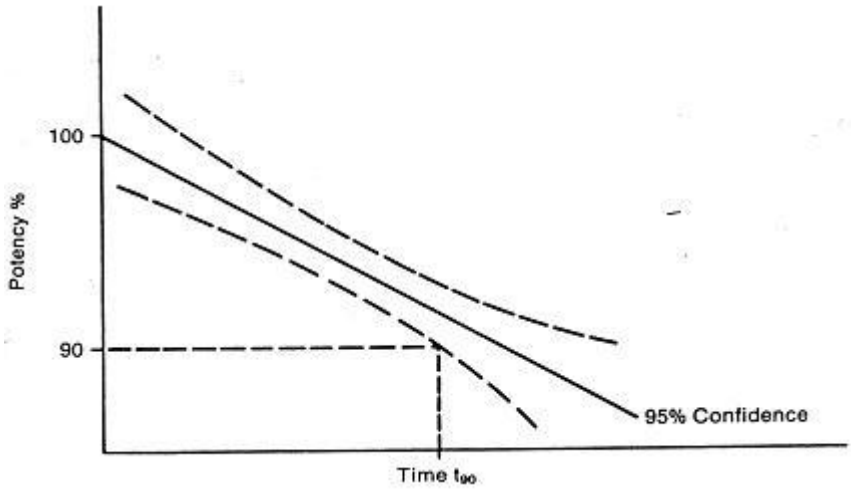


Fig: Plot of In potency against time showing 95% confidence limit line

Table: Vitamin Tablets Stability Confidence Intervals at 40^{o}C

Time (Months)	Results (mg/tablet)	Lower limit	Upper Limit
0	100.0	95.2	104.9
1	91.2	88.7	93.8
3	83.1	79.3	87.3
6	75.8	69.8	82.5
9	69.1	61.2	78.2
12	63.0	53.6	74.0

Where estimate of the standard error of regression(s)

$$\sqrt{\frac{\sum \left(y_i - \hat{y}_i \right)^2}{n - 2}}$$

y1 = predicted value at t1

n = sample size

Sy = standard error of the line

α = 0.1 two-sided

0.05 One-sided

This method also helps formulation scientists in fixing the amount of ***overages*** to be added to vitamin products.

Q_{10} method for Shelf life estimation.

Q_{10} approach taken by Simonelli & Dresback
Q_{10} is the factor by which the rate constant increases for a 10^0C temp. increase.
It is the ratio of two different reaction rate constants.
Commonly used Q values OF 2, 3 & 4 relate to the energy of activation of reaction for temperature for room temperature (25°C)

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$

$$\frac{K_2}{K_1} = \exp\left[\frac{-E_a}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)\right]$$

$$Q_{10} = \exp\left[\frac{-E_a}{R}\left(\frac{1}{(T+10)} - \frac{1}{T}\right)\right]$$

For an Arbitrary temp. change ΔT

$$Q_{\Delta} = \exp\left[\frac{-E_a}{R}\left(\frac{\Delta T}{(T+\Delta T)(T)}\right)\right]$$

$$Q_{\Delta} = \frac{K_{(T+10)}}{K_T} = Q_{10}^{(\Delta T/10)}$$

As is evident from this relationship, an increase in ΔT will decrease the shelf life and a decrease in ΔT will increase shelf life.

$$Q_{10} = \exp\left[\frac{-E_a}{R}\left(\frac{1}{(T+10)} - \frac{1}{T}\right)\right]$$

Scientists has found out that Activation energy (E_a) of all chemical decomposition reaction usually fall in the range 12 to 24 Kcal/mol.

With a typical value of 19 to 20 Kcal/mol.

Ea (K cal/mol.)	Q_{10} (30^0 to 20^0C)
12.2	2.0
19.4	3.0
24.5	4.0

Q_{10} = 4 provides the higher estimate for the increase in rate with increasing temp., where as
Q_{10} = 2 provides the lower estimate for the decrease in rate with decreasing temp.
Q_{10} = 4 will estimate the maximum likely decrease in shelf life with increasing temp. and
Q_{10} = 2 will provide the most conservative estimate of the increase in shelf life with decreasing temp.
The value Q_{10} = 3 gives our most likely estimate.

$\Delta T = T_2 - T_1$,
$T_2 = T_1 + \Delta T$

$$t_{90}(T) = \frac{a}{K_T}$$

$$t_{90}(T_1) = \frac{a}{K_{T_1}}$$

$$t_{90}(T_2) = \frac{a}{K_{(T_1+\Delta T)}}$$

$$t_{90}(T_2) = \frac{a}{K_{T_1} * Q_{10}^{(\Delta T/10)}}$$

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

Where,

t_{90} (T_2) is the estimated shelf life,
t_{90} (T_1) is the given shelf life at given temp., and
ΔT is the difference in the temp. T_1 and T_2

Note : the estimate of $t_{90}(T_2)$ is independent of the reaction order.

Example:

An antibiotic solution has a shelf life of 48 hrs. in the refrigerator (5^0C). What is its estimated shelf life at room temp.(25^0C)?using a Q_{10} value of 3.

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

$$= \frac{48}{3^{((25-5)/10)}}$$

$$= \frac{48}{3^2}$$

$$= 5.33 \text{ hrs.}$$

Importance of Q_{10} method in shelf life estimation

It solves many problems like one t_{90} (T_1) is the given shelf life at given temp., to determine the shelf life at another temp. t_{90} (T_2).

Some specific examples are.

- The expiration date is given for room temp. What is the expected extension of the shelf life in a refrigerator?
- The expiration date is given for refrigeration condition. How long the product may be left at room temp.?
- The expiration date is given for room temp. And it is desired to heat the product, what percent decomposition can be expected at higher temp.?
- The expiration date is given for refrigeration condition; the product is stored for a period of time at room temp. And is then returned to the refrigerator. What will be the corrected expiration date?

Overages

The excess quantity of drug that must be added to the preparation to maintain at least 100% of labeled amount during the expected self life of drug can be easily calculated and added to the preparation at the time of manufacture.

The international pharmaceutical federation has recommended that overage be limited to a maximum of 30% over the labeled potency of an ingredient. While adding over-age safety and toxicity should also be considered.

By convention overage to the of 10 % of excess dose of drug is added to the product at the time of manufacture. This is to ensure that the product contain 100 % labeled amount during the shelf life period. In other word at the end of one shelf period the concentration of drug of about 100 %. The same product will now take one more shelf life period in order to decrease the drug content to 90 % of labeled amount. Thus product will now take twice the shelf life as an expiry date.

Stress testing

- Stress testing to elucidate the intrinsic stability of the drug substance is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.
- The testing typically includes the effects of temperature (in 10oC increments (e.g. 50oC to 60oC) above that accelerated testing), humidity (e.g. 75%relative humidity or greater) where appropriate oxidation and photolysis on the drug substance.
- Stress testing of the drug product is undertaken to assess the effect of severe condition of the products. Such studies include photo stability testing and specific testing of the certain products.

Common high stresses or challenges

♦ Temperature challenge

An increase in temperature causes an increase in the rate of chemical reactions. The products are therefore stored at temperature higher than room temperature. Sample is removed at various time intervals and the extent of decomposition is determined by analysis. Sensitive analytical methods are used in all stability tests of this nature, as small change can be detected after very short storage periods.

The effects caused by high temperature should not confuse with those that arise from the effect of low humidity. Such confusion is possible because the relative humidity inside the high temperature in storage cabinet is lower than that of room temperature. This low humidity causes loss of moisture, which leads to apparent increase in the concentration of ingredients. If these concentration changes are not allowed for in subsequent analyses decomposition may be unsuspected.

LIMITATION:

Ø The arrhenious equation involve only one rate constant and therefore applies to a simple(single step) decomposition mechanism. It cannot be used for complex reactions (consecutive, parallel etc.) or heterogeneous process involving the phase boundaries.

Ø The higher temperature may reduce the moisture content of the product, thus slowing the hydrolysis, gelatin may soften or melt, and tablet coating may split.

Ø The effects of temperature on photochemical and microbiological destruction are not predictable.

♦ Humidity challenge

Storage of the product in atmosphere in high humidity will accelerate decomposition that result from hydrolysis. Marked acceleration will be obtained if the 'naked product' (i.e. not enclosed in a container) is subjected to these tests, which usually indicate the minimum humidity tolerated by the product without undue decomposition, and therefore useful in determining the degree of protection that should be afforded by a container.

- **Light challenge**

The source of artificial light used to accelerate the effect of sunlight or skylight. Day light fluorescent lamp provides a satisfactory source, and banks of such lamps may be used to accelerate the effect of light. To reduce the heating effect of this lamp, glass plates used. Otherwise it is difficult to separate the accelerated decomposition cause by light from that caused by increase temperature.

Objective	Use
To select adequate (from the view of stability) formulation and container closure system.	Development of product
To determine shelf life and storage condition	Development of the product and of the registration dossier
To verify no changes have been introduce in the formulation or manufacturing that can adversely affect the stability of the product	Quality assurance in general, including quality control

References

1. Aulton M. E, "Pharmaceutics the science of dosage form design", "Kinetics and stability testing".
2. Carstensen, J.T., "Stability and Dating of Solid Dosage Forms" *Pharmaceutics of Solids and Solid Dosage Forms*, Wiley-Interscience, 182-185, 1977
3. ICH Q1E Evaluation of stability data
4. Haynes, J.D., "Worldwide Virtual Temperatures for Product Stability Testing," *J. Pharm. Sci*., Vol. 60, No. 6, 927 (June 1971).
5. the theory and practice of industrial pharmacy leon lachman, Herbert liberman joseph kanig third edition.

QUESTIONS:

1. How is accelerated storage stability carried out? (University 2006)
2. outline of accelerated stability study as per ICH guidelines.(lm 04,07)
3. How is accelerated stability carried out? What are current perspectives in stability testing from view point of regulatory agencies (university 2004, 2007?)

4. Elaborate on the stability testing frequency of pharmaceuticals
5. Explain “shelf life determination based on arrehenius equation”
6. what is Q10 method & its importance in shelf life estimation(LM 06)
7. Define stress testing .why stress testing should be carried out?
8. How accelerated stability test differ from stress testing? (lm 05)
9. explain method of predicting shelf life & overages ?(LM 05)