STABILITY AND SHELF LIFE

INTRODUCTION

- Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation.
- Scientific and commercial success of a pharmaceutical product can only be ensured with the understanding of the drug development process and the myriad tasks and milestones that are vital to a comprehensive development plan.
- The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products

INTRODUCTION

- Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications
- In other words, it is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging.
- Stability testing thus evaluates the effect of environmental factors on the quality of the a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labeling instructions.
- The data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation

INTRODUCTION

- Stability testing is termed as a complex process because of involvement of a variety of factors influencing the stability of a pharmaceutical product.
- These factors include stability of the active ingredient(s); interaction between active ingredients and excipients, manufacturing process followed, type of dosage form, container/closure system used for packaging and light, heat and moisture conditions encountered during shipment, storage and handling
- In addition, degradation reactions like oxidation, reduction, hydrolysis or racemization, which can play vital role in stability of a pharmaceutical product, also depend on such conditions like concentration of reactants, pH, radiation, catalysts etc., as well as the raw materials used and the length of time between manufacture and usage of the product.

INTRODUCTION

- A pharmaceutical product may undergo change in appearance, consistency, content uniformity, clarity (solution), moisture contents, particle size and shape, pH, package integrity thereby affecting its stability.
- Such physical changes may be because of impact, vibration, abrasion, and temperature fluctuations such as freezing, thawing or shearing etc.
- The chemical reactions like solvolysis, oxidation, reduction, racemization etc. that occur in the pharmaceutical products may lead to the formation of degradation product, loss of potency of active pharmaceutical ingredient (API), loss of excipient activity like antimicrobial preservative action and antioxidants etc.
- Stability of a pharmaceutical product can also be affected because of microbiological changes like growth of microorganisms in non sterile products and changes in preservative efficacy

STABILITY TESTING METHODS

- Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product development.
- In early stages, accelerated stability testing (at relatively high temperatures and/or humidity) is used in order to determine the type of degradation products which may be found after long-term storage. Testing under less rigorous conditions i.e. those recommended for long-term shelf storage, at slightly elevated temperatures is used to determine a product's shelf life and expiration dates.
- The major aim of pharmaceutical stability testing is to provide reasonable assurance that the products will remain at an acceptable level of fitness/quality throughout the period during which they are in market place available for supply to the patients and will be fit for their consumption until the patient uses the last unit of the product

STABILITY TESTING METHODS

REAL TIME STABILITY TESTING

- Real-time stability testing is normally performed for longer duration of the test period in order to allow significant product degradation under recommended storage conditions.
- The period of the test depends upon the stability of the product which should be long enough to indicate clearly that no measurable degradation occurs and must permit one to distinguish degradation from inter-assay variation
- During the testing, data is collected at an appropriate frequency such that a trend analysis is able to distinguish instability from day-to-day ambiguity.
- The reliability of data interpretation can be increased by including a single batch of reference material for which stability characteristics have already been established.
- Stability of the reference material also includes the stability of reagents as well as consistency of the performance of the instrument to be used throughout the period of stability testing

STABILITY TESTING METHODS

Accelerated stability testing

- In accelerated stability testing, a product is stressed at several high (warmer than ambient) temperatures and the amount of heat input required to cause product failure is determined.
- This is done to subject the product to a condition that accelerates degradation.
- This information is then projected to predict shelf life or used to compare the relative stability of alternative formulations.
- This usually provides an early indication of the product shelf life and thus shortening the development schedule.
- In addition to temperature, stress conditions applied during accelerated stability testing are moisture, light, agitation, gravity, pH and package

STABILITY TESTING METHODS

Accelerated stability testing

- In accelerated stability testing the samples are subjected to stress, refrigerated after stressing, and then assayed simultaneously.
- Because the duration of the analysis is short, the likelihood of instability in the measurement system is reduced in comparison to the real-time stability testing.
- Further, in accelerated stability testing, comparison of the unstressed product with stressed material is made within the same assay and the stressed sample recovery is expressed as percent of unstressed sample recovery.
- For statistical reasons, the treatment in accelerated stability projections is recommended to be conducted at four different stress temperatures.
- However, for thermolabile and proteinaceous components, relatively accurate stability projections are obtained when denaturing stress temperatures are avoided

STABILITY TESTING METHODS

Accelerated stability testing

- The concept of accelerated stability testing is based upon the Arrhenius equation

$$\ln K = \ln A + \frac{\Delta E}{RT}$$

K = degradation rate/s,

A = frequency factor/s, (Specifically relates to molecular collision, deals with the frequency of molecules that collide in the correct orientation and with enough energy to initiate a reaction.

It is a factor that is determined experimentally, as it varies with different reactions)

ΔE = activation energy (kJ/mol),

R = universal gas constant (0.00831kJ/mol),

T=absolute temperature (K)

This equation describe the relationship between storage temperatures and degradation rate.

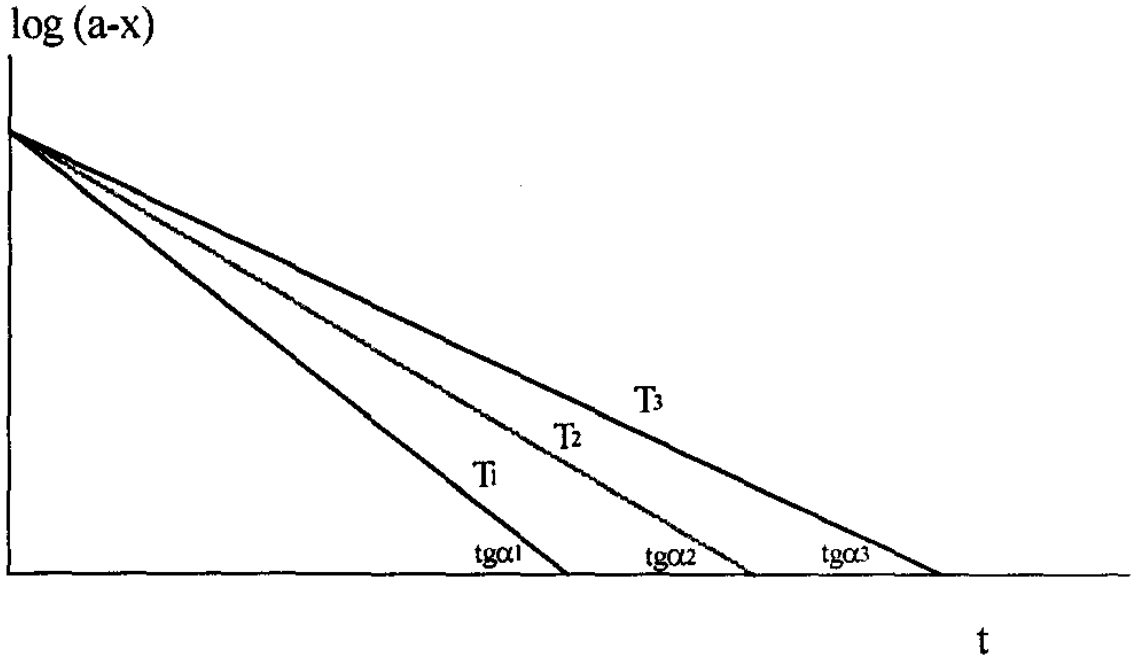
Using Arrhenius equation, projection of stability from the degradation rates observed at high temperatures for some degradation processes can be determined.

- When the activation energy is known, the degradation rate at low temperatures may be projected from those observed at "stress" temperatures
- The stress tests used in the current International Conference on Harmonization (ICH) guideline (e.g., 40% for products to be stored at controlled room temperature) were developed from a model that assumes energy of activation of about 83 kJ per mole

STABILITY TESTING METHODS

- It explains the effect of temperature on rate of a reaction. According to Arrhenius, for every 10^{o} rise in temperature, the speed of reaction increases about 2-3 times
- **Estimation of k value**
- The reaction is conducted at several temperatures.
- Concentration of reactants is determined (log(a-x).
- Appropriate graphs are drawn for the kinetic data.
- Data is processed for all the orders.
- The order of the reaction is identified.
- From the slopes of the lines, k values are calculated for all temperatures.

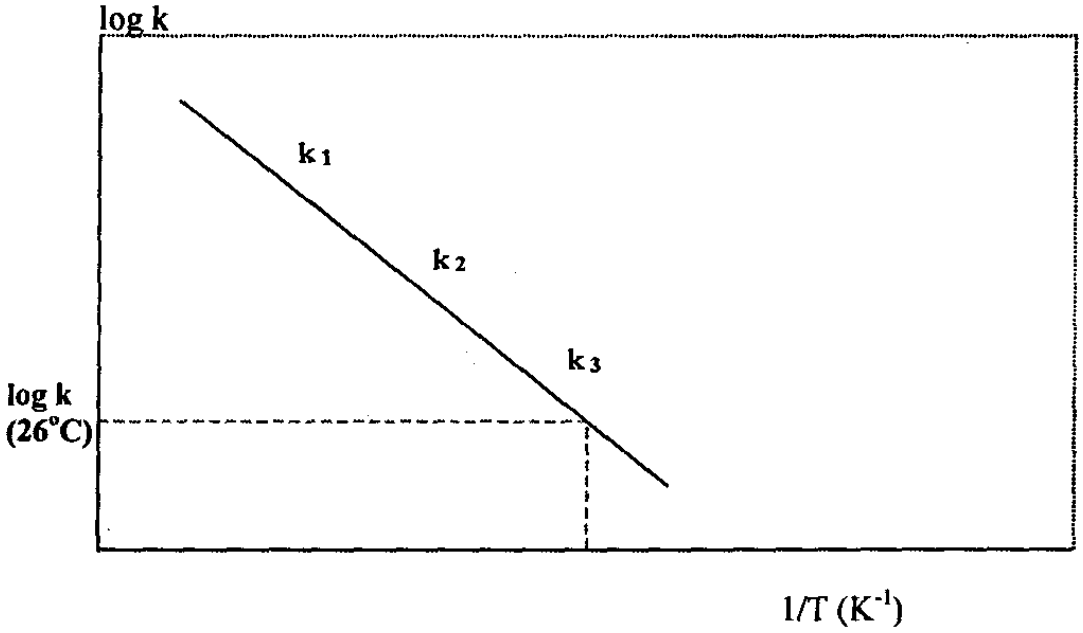
STABILITY TESTING METHODS



$$tg\ \alpha = - k / 2{,}303$$

$$K = - 2{,}303\ tg\ \alpha$$

STABILITY TESTING METHODS



By using Arrhenius relationship, Log k values are plotted against reciprocal of absolute temperature

Extrapolate the straight line to room temperature (k25) and read the log k value on y-axis

STABILITY TESTING METHODS

- With substitution of the k26 value in the equation, the shelf life of the product is calculated:

$$t90=\frac{2,303}{k}log\frac{100}{90}$$

- Shelf life is defined as the time necessary for the drug to decay to 90% of its original concentration.

STABILITY TESTING METHODS

Retained sample stability testing

- This is a usual practice for every marketed product for which stability data are required. In this study, stability samples, for retained storage for at least one batch a year are selected.
- If the number of batches marketed exceeds 50, stability samples from two batches are recommended to be taken. At the time of first introduction of the product in the market, the stability samples of every batch may be taken, which may be decreased to only 2% to 5% of marketed batches at a later stage.
- In this study, the stability samples are tested at predetermined intervals i.e. if a product has shelf life of 5 years, it is conventional to test samples at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months.
- This conventional method of obtaining stability data on retained storage samples is known as constant interval method

STABILITY TESTING METHODS

Retained sample stability testing

- Stability testing by evaluation of market samples is a modified method which involves taking samples already in the market place and evaluating stability attributes.
- This type of testing is inherently more realistic since it challenges the product not just in the idealized retained sample storage conditions, but also in the actual marketplace

STABILITY TESTING METHODS

- **Cyclic temperature stress testing**
- This is not a routine testing method for marketed products. In this method, cyclic temperature stress tests are designed on knowledge of the product so as to mimic likely conditions in market place storage.
- The period of cycle mostly considered is 24 hours since the diurnal rhythm on earth is 24 hours, which the marketed pharmaceuticals are most likely to experience during storage.
- The minimum and maximum temperatures for the cyclic stress testing is recommended to be selected on a product by- product basis and considering factors like recommended storage temperatures for the product and specific chemical and physical degradation properties of the products. It is also recommended that the test should normally have 20 cycles

EXPIRATION DATE/SHELF LIFE

- An expiration date is defined as the time up to which the product will remain stable when stored under recommended storage conditions. Thus, an expiration date is the date beyond which it is predicted that the product may no longer retain fitness for use.
- If the product is not stored in accordance with the manufacturer's instructions, then the product may be expected to degrade more rapidly.
- Shelf life is the time during which the product, if stored appropriately as per the manufacturer's instructions, will retain fitness for use (>90% of label claim of potency).
- The expiration date is also defined as the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications, if stored under defined conditions and after which it should not be used

EXPIRATION DATE/SHELF LIFE

- **Estimation of Shelf Life**
- The shelf life is determined from the data obtained from the long term storage studies. The data is first linearized and test for goodness of fit is applied. The linearized data is then analyzed to see that the slope and the intercepts are matching.
- For determination of significance of difference in case of slope or intercept, statistical tests like t-test should be applied. The data is available in the form of only five data points i.e. 0, 3, 6, 9 and 12 months, either pooled from the three batches or from the three individual batches if they are not fit for pooling. In case data is not fit for pooling, stability estimates are to be made on the worst batch. The shelf life/expiry date is determined from the regression line of this five point data based on calculation of 95% one-sided confidence limit.

EXPIRATION DATE/SHELF LIFE

- **Estimation of Shelf Life**
- For reading the expiry date, 90% drug concentration is considered as the lowest specification limit and the point where the extension line cuts the 95% confidence limit line is taken as an expiry date.
- For new drugs, it is a general practice to grant only two-year expiry initially, which is based on satisfactory one year long-term and 6 months accelerated stability data.
- The expiry date for third and later years is allowed only on production of real-time data for the subsequent years

EXPIRATION DATE/SHELF LIFE

- **Estimation of Shelf Life**
- Most pharmaceutical products are characterized by only one shelf life. However, in some cases a product may have two e.g. a freeze-dried (lyophilized) protein product may have only 1 shelf life, say 2 years, for the product stored in the dry condition and a 2nd shelf life, say 2 days, for the product when it has been reconstituted with the appropriate vehicle and is ready for injection.

PROTOCOL FOR STABILITY TESTING

- The protocol for stability testing is a pre-requisite for starting stability testing and is necessarily a written document that describes the key components of a regulated and well-controlled stability study.
- Because the testing condition is based on inherent stability of the compound, the type of dosage form and the proposed container-closure system, the protocol depends on the type of drug substance or the product.
- In addition, the protocol can depend on whether the drug is new or is already in the market
- The protocol should also reflect the regions where the product is proposed to be marketed e.g. if the product is planned to be used in climatic zones I-III, IVa and IVb, the stability program must include all these zones

PROTOCOL FOR STABILITY TESTING

- A well designed stability protocol should contain the following information:
- **1. BATCHES**
- Stability studies at developmental stages are generally carried out on a single batch while studies intended for registration of new product or unstable established product are done on first three production batches, while for stable and well-established batches, even two are allowed.
- If the initial data is not on a fullscale production batch, first three batches of drug product manufactured post-approval should be placed on long-term studies using the same protocol as in approved drug application.
- Data on laboratory scale batches obtained during development of pharmaceuticals are not accepted as primary stability data but constitute supportive information.
- In general, the selection of batches should constitute a random sample from the population of pilot or production batches

PROTOCOL FOR STABILITY TESTING

- **Containers and closures**
- The testing is done on the product in immediate containers and closures proposed for marketing.
- The packaging materials include aluminum strip packs, blister packs, Alu-Alu packs, HDPE bottles etc. This may also include secondary packs, but not shippers.
- Products in all different types of containers/closures, whether meant for distribution or for physician and promotional samples, are to be tested separately.
- However, for bulk containers, testing in prototype containers is allowed, if it simulates the actual packaging

PROTOCOL FOR STABILITY TESTING

- **Orientation of storage of containers**
- Samples of the solutions, dispersed systems and semi solid drug products for stability studies must be kept upright and positioned either inverted or on the side to allow for full interaction of the product with the container-closure.
- This orientation helps to determine whether the contact between the drug product or solvent and the closure results in the extraction of chemical substances from the closure components or adsorption of product components in to the container-closure.

PROTOCOL FOR STABILITY TESTING

Sampling time points

- Frequency of testing should be such that it is sufficient to establish the stability profile of the new drug substance. For products with a proposed shelf life of at least 12 months, the testing frequency at the long-term storage condition should be every 3 months over the first year, every 6 months over the second year and annually thereafter throughout the proposed shelf life expiration date. In the case of accelerated storage conditions, a minimum of three time points, including the initial and end points, for example, 0, 3, and 6 months is recommended.
- When testing at the intermediate storage condition is necessary as a result of significant change at the accelerated storage condition, a minimum of four test points, including the initial and final time points, is recommended, for example, 0, 6, 9 and 12 months

PROTOCOL FOR STABILITY TESTING

Sampling Plan

- Sampling plan for stability testing involves, planning for the number of samples to be charged to the stability chambers and sampling out of the charged batch so as to cover the entire study.
- The first step should be the development of the sampling time points followed by the number of samples needed to be drawn at each pull point for complete evaluation of all test parameters and finally adding up to get the total number of samples. For example there would be a requirement of about 100 tablets per pull out in a long term or accelerated stability studies including 10 each for assay, hardness and moisture determination, 6 each for dissolution and disintegration and 50 for friability.
- This multiplied by the total number of pull outs will give the total number of tablets required for a study. This is followed by the development of a sampling plan, which includes the selection of the containers representing the batch as a whole but in an unbiased manner. A stratification plan has been suggested whereby from a random starting point every *nth* container is taken from the filling or packaging line (*n* is chosen such that the sample is spread over the whole batch)

PROTOCOL FOR STABILITY TESTING

Test parameters

- The stability test protocol should define the test parameters that would be used for evaluation of the stability samples. The tests that monitor the quality, purity, potency, and identity which could be expected to change upon storage are chosen as stability tests.
- Therefore appearance, assay, degradation products, microbiological testing, dissolution, and moisture are standard tests performed on stability test samples.
- Microbiological tests include sterility, preservative efficacy and microbial count as applicable e.g. for liquid injectable preparations.
- The batches used for stability study must meet all the testing requirements including heavy metals, residue on ignition, residual solvents etc. Some of these are required at the time of product release but not required to be repeated during stability testing

STABILITY TEST EQUIPMENT

- The equipment used for stability testing is called stability chamber. These are specialized environmental chambers that can simulate the storage condition and enable evaluation of product stability based on real-time, accelerated and long-term protocols.
- They are available in both walk-in and reach-in styles. Smaller chambers are preferred for accelerated testing, as the retention time of products is much less in these cabinets, while the walk-in chambers are preferred for long-term testing.

STABILITY TEST EQUIPMENT

- Such chambers or rooms are engineered and qualified to ensure uniform exposure of the set conditions to all the samples in the chamber. These chambers are expected to be dependable and rugged because of the requirement of uninterrupted use for years.
- They are fitted with appropriate recording, safety and alarm devices. In addition, photostability chambers are also available and utilized both with and without temperature and humidity control.
- Two types of light sources are usually employed in photostability chambers, one is the combination of cool white and near UV fluorescent tubes, while second are the artificial daylight lamps, e.g., xenon or metal halide.
- The visible light intensity is estimated using a lux meter. The calculation is made on how many hours of exposure is needed