

STABILITY TESTING



- A study of drug stability and of stability testing techniques is essential for the following main reason:
 - Patient safety
 - Drug activity
 - Legal requirement
- Stability testing is generally done to ensure that the deterioration does not exceed an acceptable level and the activity of the drug and safety of patient is ensured.




Causes of instability or decomposition of drugs

1. **Hydrolysis**

2. **Oxidation**

3. **Photolysis**

4. **Isomerisations**

○  The two most common causes of decomposition of drugs are hydrolysis and oxidation.



hydrolysis

- This problem is most important in systems containing water such as emulsions, suspensions, solutions etc.
- Also for drugs which are affected by traces of moisture in the form of water vapour from atmosphere.
- The main classes of drugs that undergo hydrolysis are the esters, amides and lactams.
- Hydrolysis is usually catalysed by hydrogen ion or hydroxyl ions and also by other acidic or basic species



Protection against hydrolysis

- Hydrolytic reactions in solid drug products such as tablets, capsule powders and granules may be prevented by avoiding their contact with moisture at the time of manufacturing, packaging in suitable moisture resistant container.
- pH adjustment in liquid preparation



- Partial or complete replacement of water with non-aqueous solvents such as alcohol, glycerine and propylene glycol.
- Hydrolysis of certain drugs such as benzocaine and procaine can be decreased by the addition of specific complexing agents like caffeine to the drug solution.
- Refrigeration of drugs and drug solutions also retards hydrolytic reactions.



- Hydrolysis of susceptible drugs such as penicillin and its derivatives can be prevented by formulating them in the form of dry powder for reconstitution (dry syrups or dry powder injections) or dispersible tablets instead of a liquid dosage form such as solution or suspension.



oxidation

- Instabilities in a number of pharmaceutical preparations are due to oxidation degradation of the active ingredients of these preparations when exposed to atmospheric oxygen.
- Oxidation involves either the addition of oxygen or removal of hydrogen.
- Oxidation and reduction reactions generally occur simultaneously.
- Oxidation is the loss of electrons while reduction is the gain of electrons.



- Autoxidation is a most common form of oxidative degradation that occurs in many of pharmaceutical preparations and free radical chain process.
- In an autoxidation degradation, only small amount of oxygen is required for initiating the reaction and thereafter oxygen concentration is relatively unimportant.
- The free radicals produced during the initial reaction are highly reactive and further catalyses the reaction to produce additional free radicals and causing a chain reaction



Protection against oxidation

- By using anti-oxidation agent.
- Replacement of air from the container of the drug preparation.
- Protection from light and storage at low temperature can also minimize oxidation reaction in certain preparation.



Photolysis

- Many pharmaceutical compounds including ascorbic acid, riboflavin undergo degradation when exposed to light.
- Exposure to light may produce oxidation-reduction, ring rearrangement or modification and polymerisation.
- A photochemical reaction may be accompanied by a thermal reaction.



- Use of amber colored container or by storing the product in dark.
- Packaging in cartons also act as a physical barrier to light.



Isomerisation

- Isomerisation is the process of conversion of a drug into its optical or geometric isomers.
- Since different isomers of a drug have different activities such as conversion from one form to another may be regarded as a form of degradation resulting in loss of therapeutic activity.



Accelerated stability analysis

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





Objectives of accelerated stability analysis

- To serve as a rapid means of selecting the best formulation from amongst a series of similar formulations of the product.
- To predict shelf life of product, which is the time period for which the product will remain satisfactory under normal or recommended storage conditions.
- To serve as a rapid means of quality control.



Common high stresses during stability testing

1. Temperature

-  Increase temperature increases degradation. Hence preparations are subjected to different elevated temperature.
-  At different time intervals, samples are withdrawn, extent and nature of degradation is determined.



2. Humidity

- High humidity conditions accelerates decomposition that results from hydrolysis.
- Products without containers are exposed to high humidity conditions, usually in humidity chambers and analyzed at regular interval.



3. Light

- Artificial light of varying intensity can be used to accelerate the effect of sunlight.
- The light source should however emit similar radiation as the sunlight.



Shelf life of drug

- Shelf life is the time period during which the dosage form is supposed to retain its original qualities.
- The predication of shelf life is based on applying the Arrhenius equation which gives the effect of temperature on rate constant k of chemical reaction.



Accelerated stability studies

- For accelerated stability studies, a storage condition of 40 ± 2 C.
- Relative humidity of $75 \pm 5\%$
- Has been recommended for all the 4 zones for drug substances and drug products intended to be stored at 25 or 30 C.
- The studies are usually carried out for 6 months.



- For drug substances and drug products intended to be stored in a refrigerator, the accelerated stability studies should be carried out at $25 \pm 2\text{C}$ and $60 \pm 5\%$ relative humidity.
- In general, the accelerated storage conditions must be at least 15 C above the expected actual storage temperature and appropriate relative humidity.

