Drug Stability

Introduction:

- Stability studies **ensuring the maintenance of drug/product quality, safety and efficacy throughout the shelf life.**
- Stability studies are considered **as pre-requisite for the acceptance and approval** of any pharmaceutical product.
- Stability testing is a **routine procedure** performed on drug substances and products.
- Stability studies are **employed at various stages of the product development.**

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Definition:

- **Stability of A Pharmaceutical Product:**
  "The capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications."
- **Stability of A Drug:**
  "The time from the date of manufacture and packaging of the formulation until its chemical or biological activity is NLT a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously."

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Objectives:

1. To determine maximum expiration date/ shelf life.
2. To provide better storage condition.
3. To determine the packaging components.
4. To gather information during preformulation stage to produce a stable product.

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Reasons Behind Stability Study:

1. There may be **chemical degradation of the active drug**, leading to substantial lowering of the quantity of the therapeutic agent in the dosage form.
2. Chemical degradation of the active drug may not be extensive, **a toxic product may be formed** in the decomposition process.
3. Instability of drug product can lead to a **decrease in its bioavailability** rather than loss of drug or formation of toxic degradation products.
4. There may substantial **changes in the physical appearance** of the dosage form.
5. While drug substance itself may retain its potency, **excipients** such as antimicrobial preservatives, solubilizers, emulsifying or suspending agents **may degrade, compromising the integrity of the product.**

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Advantages of Stability Studies:

1. The stability studies are **essential for well being of the patient** suffering from disease for which product is designed.
2. Stability studies **assure the identity, potency and purity of ingredients**, as well as those of formulated product.
3. Accelerated stability studies are performed **to find out the rate of degradation of the product** if stored for longer period under specific conditions.
4. Forced degradation study is carried out **to check the effect of stressed external conditions** on the drug product.
5. Stability study is to provide evidence **to establish shelf life for the drug and recommended storage conditions.**
6. Stability studies are used **to find out degradation pathway** (physical, chemical or microbiological).

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Expiry Date/Shelf Life:

1. **Definition:** "Drug can not be used after this date because the concentration of drug is decreased and become lower than therapeutic concentration. In addition, some products of drug degradation are toxic and harmful to patients."
2. The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use guidance document Q1A(R2) (ICH Q1A) defines shelf life as, "The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label."

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Expiry Date/Shelf Life: CONTD...

3. An expiration date, which **is expressed traditionally in terms of month and year, denotes the last day of the month.**
4. The expiration date should **appear on the immediate container and the outer retail package.**
5. However, when **single-dose containers** are packaged in **individual cartons**, the **expiration date may be placed on the individual carton** instead of the immediate product container.
6. If **a dry product** is to be reconstituted at the time of dispensing, **expiration dates are assigned to both dry mixture and the reconstituted product.**
7. **Tamper resistant packaging** is used where applicable.
8. Shelf life is typically **expressed in units of months, i.e. 24 months, 36 months, to a maximum of 60 months.**

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Expiry Date/Shelf Life: CONTD...

9. The phrase "shelf life" and "expiry date" is often interchangeably used in the industry, as both terms reflect the same concept: there is a period of time where a product is stable and safe for use, but is made limited based on thorough stability research.
10. Shelf life/expiry dates reflect the time where a product will work both safely and effectively.
11. This is why "shelf life testing" is also referred to as "stability testing".
12. The amount of time a product can stay stable under certain environmental conditions, equates to its shelf life.

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Expiry Date/Shelf Life: CONTD...

13. After the **opening of the drug container,** the expiry date will be shorter as a result of the **decreased concentration of drug during usage and the effects of external factors.**

Example:

1. **Eye drops:** can be used for one month after opening the droppers
2. **Syrups and suspension of antibiotics:** can be used for one week by storage in room temperature and for two weeks by storage in 4C°.
3. **Tablets and capsules:** remain stable in the package but after removal the expiry date will change
4. **Ampoules:** must be used immediately but the vials (multidose) are stable for 24 h for the presence of preservatives.

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Expiry Date/Shelf Life: CONTD...

- Shelf-life is also defined as the **time required for the concentration of the reactant to reduce to 90% of its initial** concentration.
- **Represented as t90 and the units of time /conc.**

$$t90 = \frac{(a-0.9a)}{ko} = \frac{0.1\,a}{ko}$$

Where , a = initial concentration .

ko = specific rate constant for zero order reaction.

The time from the date of manufacture and packaging of the formulation until its chemical or therapeutic activity is maintained to a predetermined level of labeled potency and, its physical characteristic have not changed appreciably or deleteriously.

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Factors Effecting Drug Stability:

➢ The primary factors effecting stability:

- pH, Temperature, Moisture, Humidity, Light, Storage Containers & Closures and Oxygen

➢ The major factors effecting drug stability are:

- Particle size (suspension and emulsion), pH, additives and molecular binding and diffusion of drugs and excipients .

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Effect of Temperature:

- **High temperature accelerates** oxidation, reduction and hydrolysis reaction which lead to drug degradation.

Effect of pH:

- **Acidic and alkaline pH** influences the rate of decomposition of most drugs. Many drugs are stable between pH 4 and 8.
- **Weekly acidic and basic drugs** show good solubility when they are ionized and they also **decompose faster when they are ionized.**
- So **if the pH of a drug solution has to be adjusted to improve solubility and the resultant pH leads to instability** then a way out of this tricky problem is **to introduce a water miscible solvent into the product.**

- **It will increase stability by:**
  - suppressing ionization
  - reducing the extreme pH required to achieve solubility
  - enhancing solubility and
  - reducing the water activity by reducing the polarity of the solvent.
- For example, 20% propylene glycol is placed in chlordiazepoxide injection for this purpose.
- Some buffers such as acetate, citrate, lactate, phosphate and ascorbate **buffers are utilized to prevent drastic change in pH.**
- As little as 1 pH unit change in pH can cause a change of ten fold in rate constant. So when we are formulating a drug into a solution we should carefully prepare a **pH–decomposition profile** and then formulate the solution at a pH which is acceptable physiologically and stability-wise also.

Effect of Moisture:

1. **Water catalyses chemical reactions** as oxidation, hydrolysis and reduction reaction.
2. Water **promotes microbial growth.**
3. Presence of moisture influences chemical stability, crystal structure, powder flow, compaction lubricity, dissolution rate, and polymer film permeability in solid dosage forms and lead to growth of microorganisms, change in thixotropy in semi-solid dosage forms.
4. Moreover, unit operations obviously depending on the amount and state of water present are also influenced by it.
5. Therefore, moisture **influences the properties of individual active ingredients and excipients**, and it is essential to characterize the effect of moisture on these individual components.

Effect of Light:

- Refer content under “Photolysis”.

Types of Stability:

- Therapeutical Stability
- Physical Stability
- Chemical Stability
- Microbiological Stability
- Toxicological Stability

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Types of Stability: CONTD...

- **Chemical**:
  Each active ingredient retains its chemical integrity and labeled potency within the specified limit.
- **Physical**:
  The physical stability properties includes appearance, palatability, uniformity, dissolution and suspendability are retained.
- **Microbiological**:
  Sterility or resistance to microbial growth is retained according to specified requirement.
- **Therapeutical**: Therapeutic activity remains unchanged .
- **Toxicological**: No significant increase in toxicity occurs.

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Degradation Types:

A. Physical Degradation

B. Chemical Degradation

1. **Oxidation**
2. **Decarboxylation**
3. **Photolysis**
4. **Racemization**
5. **Hydrolysis**

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Degradation Types: CONTD...

Physical Degradation:

- The physical stability properties includes appearance, palatability, uniformity, dissolution and suspendability are retained and maintained throughout the shelf life of the drug.
- It includes following :
  - Loss of water
  - Loss of volatile oil
  - Water absorbance
  - Polymorphism
  - Color change

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Degradation Types: CONTD...

Physical Degradation Includes Following:

- **Loss of volatile content:** Volatile compounds used such as alcohol ether, camphor oils, etc. Try to escape from the formulation leads to degradation of formulation.
  Example: Nitroglycerine from drugs evaporate.
  Prevention: Such products should be placed in well closed container. Temperature should be proper.
- **Loss of water:** Water loss from liquid preparation (o/w emulsion) leads to changes in stability. It causes crystallization of drug product which may lead to increase in potency, and decrease in weight.
  Example : Water evaporates from Na2SO4.BORAX.
  Prevention: Storing the pharmaceutical product in a well closed container.

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Degradation Types: CONTD...

- **Water absorbance:** Pharmaceutical formulations which are hygroscopic in nature absorb the water from its external environment leads to degradation.
  Example: Gelatin capsule, deliquescent salts like– CaCl3, Potassium Citrate.
  Prevention: Products should be placed in well-closed container and in dry place.
- **Polymorphism:** A stable crystal form is effected (it may loosen) leads to the formation of polymorph and cause instability in formulation. This may lead to alteration in solubility, dissolution of drug
- **Color change:** Loss or development of color may occur (due to change in PH, use of reducing agent, exposure to light).

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Degradation Types: CONTD...

Chemical Degradation:

- Chemical degradation of a dosage form occurs through several pathways like–
  1. **Hydrolysis**
  2. **Oxidation**
  3. **Decarboxylation**
  4. **Isomerization**
  5. **Racemization**
  6. **Epimerization**
  7. **Photolysis**
- Above reactions may lead to lowering of therapeutic agent in the dosage form, formation of toxic product, decreased bioavailability etc.

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Degradation Types: CONTD...

1. Hydrolysis:

1. Most important in systems containing water such as **emulsion, suspension, solutions, etc.**
2. Also for drugs which are affected by **moisture (water vapor)** from atmosphere.
3. It is usually **catalyzed by hydrogen ion(acid) or hydroxyl ion(base).**
4. **In this active drug is decomposed with solvent.**
5. Usually solvent is water some time reaction may involve pharmaceutical cosolvents such as ethyl alcohol or polyethylene glycol.
6. Main classes of drugs that undergo hydrolysis are the **esters, amide, alkali, acids.**

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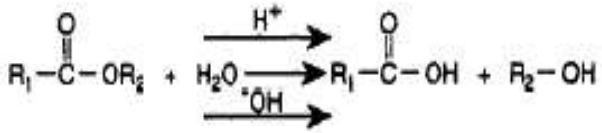
- **Ester hydrolysis:**

Involve acyl – acid cleavage.

Example: Aspirin, Atropine, Physostigmine, Procaine.

R .COOR (ester) + H2O → RCOOH (acid) + HOR(alcohol)



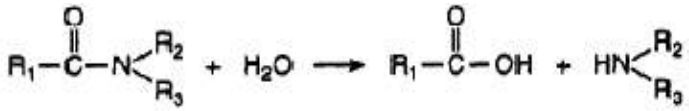
- **Amide hydrolysis:**

It is more stable than ester, susceptible to specific and general acid base hydrolysis.

It involves cleavage of amide linkage to give an amine instead of alcohol as in case of esters.

Example: Chloramphenicol , Barbiturates.

RCONHR(amide) + H2O → RCOOH + NH2R(AMINE)



Protection Against Hydrolysis:

1. **Avoiding contact with moisture** at time of manufacture.
2. Packaging in suitable **moisture resistant packs** such as strip packs and storage in controlled humidity and temperature.
3. In liquid dosage form since, hydrolysis is acid or base catalyzed, an **optimum pH for max stability** should be selected and the formulation should be stabilized at this pH by inclusion of **proper buffering agents.**
4. Hydrolysis of certain drugs such as benzocaine and procaine can be decreased by the **addition of specific complexing agent** like caffeine to the drug solutions .
5. Hydrolysis susceptible drugs such as penicillin and derivatives can be prevented by formulating them in the **dry powder form for reconstitution or dispersible tablets** instead of a liquid dosage form such as solutions or suspensions.

2. Oxidation:

1. Oxidation is controlled by environment i.e., light, trace elements, oxygen and oxidizing agent.
2. Occurs when exposed to atmospheric oxygen.
3. Either the **addition of oxygen or removal of hydrogen.**
4. **Oxidation is the loss of electrons while reduction is the gain of electrons.**

- **Autoxidation:**

1. The reaction between the compounds and molecular oxygen is required for initiating the chain reaction is called ***autoxidation.***
2. **Free radicals produced** during initial reaction are highly reactive and **further catalyze the reaction** produced additional free radicals and **causing a chain reaction.**
3. **Heavy metals** such as copper, iron, cobalt, and nickel have been known to **catalyze the oxidative degradation.** Heat and light further influence the kinetics of oxidative degradation processes.

Auto-oxidation of Ascorbic Acid:

1. The ascorbate ion is the predominant species at typical biological pH values. It is a mild reducing agent and antioxidant.
2. It is oxidized with loss of one electron to form a radical cation and then with loss of a second electron to form dehydroascorbic acid.
3. It typically reacts with oxidants of the reactive oxygen species, such as the hydroxyl radical. Such radicals are damaging to animals and plants at the molecular level due to their possible interaction with nucleic acids, proteins, and lipids.
4. Sometimes these radicals initiate chain reactions. Ascorbate can terminate these chain radical reactions by electron transfer.

5. Ascorbic acid is special because it can transfer a single electron, owing to the resonance-stabilized nature of its own radical ion, called semidehydroascorbate. The net reaction is:

$$RO^{\bullet} + C_6H_7O\ 6 \rightarrow RO\ + C_6H_7O^{\bullet}6 \rightarrow ROH + C_6H_6O_6$$

6. The oxidized forms of ascorbate are relatively unreactive and do not cause cellular damage.
7. However, being a good electron donor, excess ascorbate in the presence of free metal ions can not only promote but also initiate free radical reactions.
8. On exposure to oxygen, ascorbic acid will undergo further oxidative decomposition to various products including diketogulonic acid, xylonic acid, threonic acid and oxalic acid.

- **Steps Involved Oxidation Reaction:**

➢ **Initiation:** Formation of free radicals is taken place.

R--H → R' + [H'}

➢ **Propogation:** here the free radical is regenerated and react with more oxygen.

R' + O2 → R'—O2

R'O2 + RH → ROOH + R'

➢ **Hydroperoxide Decomposition:**

ROOH → RO' + OH'

➢ **Termination:** free radicals react with each other resulting in inactive products.

R'--O2 + X → Inactive product

RO2 + RO2 → Inactive product

- **Example Of Drugs Decomposed By Oxidation Pathways**

• Archis oil, clove oil, ethyl oleate, Heparin, Ascorbic acid, Morphine, Vitamin A, Vitamin B12, etc.

Protection Against Oxidation:

A. Use of Antioxidants:

Antioxidants are Mainly of 3 types :

1. **The first group probably inhibits the oxidation by reacting with free radicals.**

   Example: Tocopheral, Butylated Hydroxyl Anisole (BHA), Butylated Hydroxyl Toluene's (BHT). Concentration 0.001–0.1%.

2. **The second group comprising the reducing agents,** have a lower redox potential than the drug or other substance that they should protect and are therefore more readily oxidized.

   Example: Ascorbic Acid And Iso-ascorbic Acid, Potassium Or Sodium Salts Of Metabisulfite.

3. The third group, little antioxidant effect themselves but **enhance the action of true antioxidant.**

   Example: Citric acid, tartaric acid, disodium edetate and lecithin.

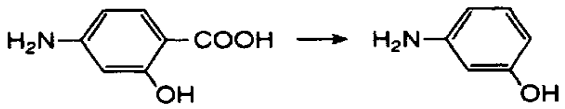
B. Use of Chelating Agent:

When heavy metals catalyze oxidation.

Example: EDTA, citric acid, tartaric acid form complexes.

3. Decarboxylation:

1. Decarboxylation is a chemical reaction that **removes a carboxyl group and releases carbon dioxide(CO_2).**
2. Drug substances having a **carboxylic acid group** are sometimes susceptible to decarboxylation.
3. **Example:** 4-Aminosalicylic acid.



4-aminosalicylic acid

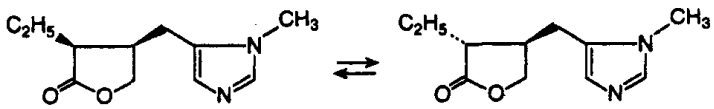
4. Isomerization:

- Isomerization is the process by which **one molecule is transformed into another molecule which has exactly the same atoms, but the atoms are rearranged.**

  e.g. A-B-C → B-A-C

Examples:

1. **Pilocarpine** undergoes epimerization by base catalysis.
2. **Tetracyclines** such as rolitetracycline and ergotamine exhibit epimerization by acid catalysis.



pilocarpine isopilocarpine

Degradation Types: CONTD...

- **Optical Isomers:** (also called **enantiomers**) **differ in only one characteristic--their interaction with plane polarized light.**
- One of the optical isomers rotates the light in one direction, the other rotates the light in the opposite direction but by the same amount.
- In every other way, such as boiling point, density, refractive index, viscosity, etc., the two optical isomers are identical.

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Degradation Types: CONTD...

- **Geometric Isomers:** have the **same structural formulas but differ in the arrangement of groups at a single atom, at double bonds, or in rings.**
- *Cis*- and *trans*-platin are examples of geometric isomers based on the different arrangement of groups at a single atom.
- *Cis*- and *trans*-2-butene differ in the arrangement of the methyl groups about the double bonds.

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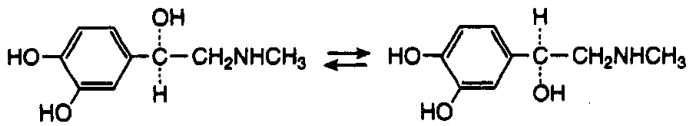
Degradation Types: CONTD...

5. Racemization:

1. Racemization refers to **partial conversion of one enantiomer into another.**
2. **Epinephrine** is oxidized and undergoes racemization under strongly acidic conditions.



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Degradation Types: CONTD...

6. Epimerization:

1. In stereochemistry, **epimer** refers to one of a pair of stereoisomers.
2. **The two isomers differ in configuration at only one stereogenic center.**
3. All other stereocenters in the molecules, if any, are the same in each.
4. Epimerization can be spontaneous (generally a slow process), or catalyzed by enzymes.
5. **Examples:** Doxorubicin and epirubicin are two epimers that are used as drugs.

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7. Photolysis:

1. Exposure to light cause substantial degradation of drug molecule.
2. When molecules are exposed to electromagnetic radiation they absorb light (photons) at characteristic wavelength which cause increase in energy which can:
   A. Cause decomposition
   B. Retained or transferred
   C. Be converted to heat
   D. Result in light emission at a new wavelength (fluorescence , phosphorescence)
3. Natural sun light lies in wavelength range (290-780nm) of which only higher energy (UV) range (290-320) cause photo degradation of drugs.

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- **Example of phototoxic drugs:**
  Furosemide, Acetazolamide, Cynocobalamine.
- **Example:**
  - Sodium Nitroprusside in aqueous solution (which is administered by IV infusion for management of acute hypertension).
  - If protected from light it is stable to at least 1yr.
  - If exposed to normal room light it has a shelf life of 4 hrs.
- **Protection:**
  1. Use of amber colored bottles.
  2. Storing the product in dark, packaging in cartons also act as physical barrier to light.
  3. Coating of tablets with polymer films.

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ICH Guidelines for Stability Testing:

- **Stability of 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 therapeutic and toxicological specification.
- These stability data involves selected parameters that taken together from the stability profile.
- Pharmaceutical products are expected to meet their specification for identifying purity, quality and strength throughout their defined storage period at specific storage condition.

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International Conference on Harmonization (ICH):

- **ICH** stands for **International Conference on Harmonization** of Technical Requirements for Registration of Pharmaceuticals for Human use.

Objectives of ICH:

- Harmonization of registration applications within the three regions of the EU, Japan and the United States.
- ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

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ICH Guidelines: CONTD...

ICH Guidelines:

- **Quality Guidelines "Q"** (chemical and pharmaceutical QA)
- **Safety Guidelines "S"** (in vitro and in vivo pre-clinical studies)
  - covering Carcinogenicity Testing, Genotoxicity Testing, Toxicokinetics and Pharmacokinetics etc.
- **Efficacy Guidelines "E"** (clinical studies in human subject)
  - Covering clinical safety, Dose Response Studies, Good Clinical Practices, Clinical evaluation etc.
- **Multidisciplinary Guidelines "M"**
  - Covering Medical Terminology, Electronic Standards for Transmission of Regulatory Information etc.
  - Important for Stability
  - » Guideline **M4**: The Common Technical Document (CTD)

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ICH Guidelines: CONTD...

ICH Guidelines for Stability Studies:

- **$Q_1A(R_2)$:** Stability Testing of New Drug Substances and Products.
- **Q_1B:** Stability Testing: Photostability Testing of New Drug Substances and Products.
- **Q_1C:** Stability Testing for New Dosage Forms.
- **Q_1D:** Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products.
- **Q_1E:** Evaluation of Stability Data.
- **Q_1F:** Stability Data Package for Registration Applications in Climatic Zones III and IV.

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ICH Guidelines: CONTD...

Principle of Guidelines:

1. **Purpose of stability testing** is to provide evidence how quality varies with time under influence of :
   - temperature
   - humidity
   - light
2. **Establish re-test period for drug substances**

   Retest Period: the period after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification, and thus suitable for use in manufacturing.

   A retest period should be proposed on the basis of stability results and may be extended to five years (e.g., Ethambutol, or Isoniazid).

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ICH Guidelines: CONTD...

3. **Establish shelf life for drug products.**

   Shelf life: (expiry date/expiration dating period): the period of time during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product.
   The shelf-life is used to establish the expiry date of each batch.
4. Recommends storage conditions.
5. Gives test conditions based on analysis of effects of climatic conditions in the three regions of the EU, Japan, USA.
6. Gives mean kinetic temperature which is derived from climatic data.
7. Divided world into four climatic zone I-IV.
   - this guideline addresses climatic zones I and II
8. And the stability information generated in one of the three regions is mutually acceptable to the other two provided:
   1. Information is consistent with this guideline,
   2. Labelling is in accord with national/ regional requirements.

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ICH Guidelines: CONTD...

Type, Size, Number of Batches:

- **ICH/ WHO Guidelines:**
- At least 3 primary batches of drug product, should be of the same formulation, packaged in same container as proposed for marketing
- 2 out of 3 batches should be pilot scale batches.
- Stability to be performed on each strength, container size.

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ICH Guidelines: CONTD...

Long Term Stability Studies:

- Study is performed at 25^0C/60% **or** 30^0C/ 65%.
- Ideally 12 months data is to be generated but 6 months data is also acceptable in circumstances for submission of registration dossier, continued till end of shelf life.
- For parenterals stability has to carried out at 2-8^0 C for drugs to be stored in freezer testing should be done at -20^0 C

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ICH Guidelines: CONTD...

Climatic Zones / Storage Conditions:

CLIMATIC ZONE	DEFINITION	STORAGE CONDITIONS
I	TEMPERATE CLIMATE	21°C/45 % R.H
II	SUBTROPICAL AND MEDITERRANEAN CLIMATE	25°C/60 % R.H
III	HOT , DRY CLIMATE	30°C/35 % R.H
IV	HOT , HUMID CLIMATE	30°C / 70% R.H

India: Climatic Zone IV (a): 30°C/65%RH

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Climatic zones	Climatic conditions	Mean kinetic temperature	Yearly average relative humidity
Zone I	Moderate/ Temperate	21°C	45 % RH
Zone II	Mediterranean/ Subtropical	25°C	60 % RH
Zone III	Hot and dry	30°C	35 % RH
Zone IVA*	Hot and humid/ Tropical	30°C	65 % RH
Zone VIB*	Hot and very humid	30°C	75 % RH

* Earlier to 2005, Climatic Zone IVA and IVB were designated as Climatic Zone IV

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Climatic Zones / Storage Conditions: CONTD...

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C / 60% ± 5% RH or 30°C ± 2°C / 65% ± 5% RH.	12 months
Intermediate	30°C ± 2°C / 65% ± 5% RH.	6 months
Accelerated	40°C ± 2°C / 75% ± 5% RH.	6 months

Drug Substances - Intended for Storage in A Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C / 60% ± 5% RH.	6 months

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Climatic Zones / Storage Conditions: CONTD...

Drug Substances/Product- Intended for Storage in Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	-20°C ± 5°C	12 months

Drug products - General case

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C / 60% ± 5% RH. or 30°C ± 2°C / 65% ± 5% RH.	12 months
Intermediate	30°C ± 2°C / 65% ± 5% RH.	6 months
Accelerated	40°C ± 2°C / 75% ± 5% RH.	6 months

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Accelerated Stability Studies:

- To predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature.
- Storage condition of 40^0C and relative humidity of 75% has been recommended for all the four zones for drug substances and drug products.
- **Time duration: 3 to 6 months.**

Salient features:

1. **Gross picture on the stability**
2. **Properties of degradation**
3. **Mechanism of chemical reaction**
4. **Establish an analytical method for estimation of drug & degraded product**
5. **The temperature effect on the chemical degradation is estimated**
6. **To establish efficacy, safety and toxicity**

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Accelerated Stability Studies: CONTD...

Storage Condition	Testing Condition
Controlled room temperature $20\text{-}25^0$C	40^0C and 75% RH for 6 months
Refrigerated condition $2\text{-}8^0$C	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:

1. **Garret and Carper method**
2. **Free and Blythe method**

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Stability Protocol

Format No.: HU/FP/NBT/SP/001	**Protocol No.:** S/T/AC/XY/001	**Page:** 1 of 1
Product Name: XY Tablets		**Strength:** 50 mg
Batch No.: NTJ-(12)-11-A	**Batch Size:** 1,00,000 Tablets	**Mfg. Date:** 02/02/2009
Packaging Details:	**Container Material and Type:** High density polyethylene (HDPE) bottle **Capacity:** 80 cc **Closure Material and Type:** HDPE child resistant caps **Pack Size:** 100 tablets per bottle **Desiccant Present:** Yes **Absorbent Cotton Present:** No	
Storage Conditions: 40°C temperature and 75% relative humidity		
Stability Initiation Date: 03/02/2009		
Stability Testing Time Points: 0,1, 2, 3 and 6 months interval		

Sr. No.	Test to be Performed	Specifications
1.	Physical Appearance	White colored, round, film coated tablet
2.	Assay (by HPLC method)	99.8 - 99.9%
3.	Dissolution Testing on 12 tablets Media: 900 ml of 0.1N HCl Time Points: 5,10, 15 and 30 min.	>85% of drug must dissolve in 30 min or less
4.	Disintegration Time	Less than 5 min
5.	Moisture Content	1.87 – 2.05%
6.	Hardness	70 N
7.	Friability	0.12%
8.	Content Uniformity Test	98.5 - 99.8%
9.	Related Substance Test i) known impurity A ii) known impurity B iii) total unknown impurity	 0.002% 0.005% 0.007%

Prepared By
Signature: Neeraj
Date: 1 Jan 2012

Checked By
Signature: Shadab
Date: 1 Jan 2012

Approved By
Signature: Gaurav
Date: 1 Jan 2012

Fig. 28.18: Typical stability protocol for tablet dosage forms

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Question Bank:

2 Marks

1. Define the term stability & shelf life.**
2. Define stability. State different advantages of conducting stability studies.***
3. Define stability. State different reasons for conducting stability studies.
4. Explain auto-oxidation of ascorbic acid.*
5. Effect of temperature on drug decomposition.*

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Question Bank: CONTD...

5 Marks

1. Describe the physical degradation of pharmaceutical products.****
2. Describe effect of light, pH and temperature on the decomposition on pharmaceutical products.*
3. Define oxidation. Add note on approaches to prevent oxidation.
4. Explain hydrolytic degradation with suitable examples. What measures should be taken to protect the drug against hydrolysis.

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Question Bank: CONTD...

10 Marks

1. Describe the ester and amide hydrolysis of drugs with suitable examples. Add note on protection of drugs against hydrolytic degradation.****
2. What is oxidation? Write about protection against oxidation and hydrolysis.
3. Discuss in detail chemical pathways of drug degradation.
4. Explain physical degradation of pharmaceutical products. What is the effect of pH and light on drug decomposition?

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