**CHEMICAL STABILITY OF DRUGS**

**Ashu1, Kavita Sapra2, Ankush Kumar1**

1. Department of pharmaceutical sciences, Maharshi Dayanand University, Rohtak, Haryana
2. Amity institute of Pharmacy, Amity University, Gurugram, Haryana

**ABSTRACT**

Stability of drug is the capacity of the pharmaceutical dosage form to maintain the chemical, physical, microbial and therapeutic properties during the time of storage and usage by the patient. Stability studies are done to determine the expiry date of products and to choose formulations and container closure techniques that are appropriate in terms of stability in order to assess storage needs and shelf life. There are various types of stability studies which we can consider to determine shelf life of pharmaceutical products like Physical stability, Chemical stability and microbiological stability. All of these are important but among them Chemical stability is more important as changes in chemical structure leads to loss of therapeutic activity of drug.

**KEY WORDS**: Chemical Stability, Shelf life, Expiry date determination, Structural changes

**INTRODUCTION**

It is the ability of the pharmaceutical dosage form to maintain the chemical, physical, microbial and therapeutic properties during the time of storage and usage by the patient.

As defined by the United States Pharmacopeia (USP), the extent to which a drug substance or product "retains, within the stipulated conditions, the same traits and attributes that it possessed at the time of its manufacture," is known as the stability of the drug product. Also, Stability of drugs is determined by the rate of changes that occur in the pharmaceutical dosage forms.

The phrase "drug stability" describes how well a pharmaceutical substance can maintain its therapeutic characteristics over the course of its storage or shelf life. Drug manufacturers are required to do routine stability testing on their medications in accordance with FDA standards known as Current Good Manufacturing Practices, or CGMPs, to assure their efficacy. As novel medication compounds arise, ongoing research is needed to create formulation strategies and stability testing techniques.

• **Expiry date**: Expiry date on every formulation indicates that drug cannot be used after this date because the amount of drug is lowered and become less than its therapeutic concentration. In addition, some products which are resulted from drug degradation are harmful and toxic to patients.

**Note!**In cases of some pharmaceutical formulations, the expiry date will be lesser after opening of drug container due to decrease in concentration of drug during usage and some external factors. Example:

1. **Eye drops and ear drops**: can be used only for one month after opening thedrops.

2. **Syrups and suspension of antibiotics**: can be consumedwith in one week by storage in room temperatureand 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 presenceof preservatives.

**Importance of Stability studies of drugs:**

1. The decomposition of the active medicine could result in the formation of the harmful product.
2. To maintain the product's strength for use with regard to all functionally linked features during the duration that it is on the market, protecting the manufacturer's reputation.
3. Due to a decreased concentration of the medicine in the dosage form, the instability of the active drug and its products may result in undermedication.
4. The stability of the medicine is predicted using the kinetics principles of changes in physical appearance brought on by instability.
5. To establish commercial expiration date of the drugs
6. To support the stability of the drug product used in clinical and non-clinical investigations
7. To establish the control limits for lot release and establish levels for specified requirements (such as API, preservatives, etc.)

**Objectives of Stability studies of drugs:**

1. To determine the shelf life of the drug product.
2. To choose formulations and container closure techniques that are appropriate in terms of stability in order to assess storage needs and shelf life.
3. To determine how the changes in the quality occurs under the presence of several environmental factors ( pH, humidity, light and temperature) with time.
4. To ensure that no alterations to the formulation or manufacturing process have been made that could impact the drug's stability.
5. The primary goal of a stability research is to create a drug product's stability profile so that a prediction of the product's shelf life may be produced before it is introduced to the market.

**Adverse effects of instability of drugs**:

1. Loss of active drug.
2. Loss of content uniformity.
3. Production of toxic material.

**Factors affecting drug stability:**

**1.Temperature**: High temperature increases oxidation, reduction and hydrolysis reaction which leads to drug degradation.

**2. pH**: Stability of drugs is also affected by pH.

• 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 watermiscible 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.

**3.Moisture:**

a. Moisture acts as catalyst for chemical reactions such as oxidation, hydrolysis and reduction reaction.

b. Water also promotes microbial growth.

**4.Light**: affects drug stability through its energy or thermal effect which lead to oxidation.

**5.Drug incompatibility**: There may be chances of reactions between components of pharmaceutical dosage forms itself orbetween these components and cover of the container.

**6.Oxygen**: Exposure of drug formulations to oxygen affects their stability.

**Types of Stability of drugs**

There are three types of stabilities of drugs which must be considered:

1. Physical stability

2. Microbiological stability

3. Chemical stability

**1.Physical stability of drugs**

Possibilities due to physical instabilities are:

1. **Formation of crystals in pharmaceutical preparations**:

Causes:a. Polymorphism phenomena: i.e., Chloramphenicol (change of amorphous to crystallineform.

b. Saturated solution: by different temperature precipitation of solute may occur.

c. In suspension: when very fine powder is used a part of suspending agent will dissolve then

precipitate as crystal.

b. **Loss of volatile substances from pharmaceutical dosage forms**:

Examples:

a. Aromatic waters

b. Elixirs

c. Spirits

d. Some types of tablets which contain aromatic water (Nitro-glycerine tablets)

c. **Loss of water:**

This can be seen in the following dosage forms:

a. Saturated solution

b. Emulsions

c. Creams

d. Pastes

e. Ointments

Humectants are added to these dosage forms to absorb water from atmosphere and prevent its loss from the dosage forms.

Examples: Glycerin

d. **Absorption of water**:

This phenomenon can be seen in the following pharmaceutical forms:

a. Powders: powders may liquify or degrade after absorption of water.

b. Suppositories:In case of suppositories, Bases made from hydrophilic substances such as Glycerin, Gelatin, polyethylene glycol.The consistency of these forms becomes jelly-like appearance.

e. **Change in crystalline form**:

Example: Cocoa butter which is capable of existing in four polymorphic forms.

**2.Microbiological stability**:Microbial contamination is a verybig problem for all formulations containing moisture. There are different sources for microbial contamination.

**Sources of Microbial Contamination**:

1. Water

2. Air

3. Raw materials, containers and closures

4. Instruments and apparatus

**3.Chemical stability**

The most easily understood form of drug instability is loss of drug due to chemical reaction results in decrease in potency of drug.Shelf-life of a pharmaceutical product is affected by degradation of the drug by chemical reaction. There may be degradation of other substances presents in the formulation, such as antioxidants orpreservatives which may also affect the shelf life of a product.

In some cases, the products obtained by degradation may be toxic which affects the shelf life of a product.For example, flucytosine which is an antifungal drug is degraded to fluorouracil which can cause cancer.Sometimes, products obtained after degradation provide an undesirable appearance for example, epinephrine on oxidation give highly coloured products.

In most of the cases, there is no spontaneous chemical degradation in drugs but it occurs due to presence of some other reactive molecules present in dosage form.Generally, it occurs due to presence of water.The main aim in designing of dosage form is preservation of dosage form from chemical degradation.

**Chemical degradation reactions:**

1. **Hydrolysis:**

Hydrolysis is the reaction of compound in presence of water. Pharmaceutical products contain water which may be present as a contaminant or as an ingredient, and most common reason for chemical degradation is hydrolysis.Hydrolytic reactions are common in carboxylic acids derivatives likeesters and amides.

Ester on hydrolysis give a carboxylic acid and an alcohol (Fig 1). Bond polarization by anadjacent oxygen atom makes the carbon of carboxyl group electron deficient.Therefore, chances of nucleophilic attack by water areincreased at this carbon atom. For example, aspirin(acetylsalicylic acid)is hydrolysed to salicylic acid and acetic acid ([Fig. 2](https://clinicalgate.com/chemical-stability-in-dosage-forms/#F0015)).



**Fig. 1** hydrolytic reactions, **(a)** Esters **(b)** Amides.



**FIG. 2** Aspirin to salicylic acid and acetic acid

Hydrolytic reactions of amides, esters and related molecules are catalysedin the presence ofan acid and base. For example, in case of ester hydrolysis in presence of base as catalyst, there is nucleophilic attack by hydroxyl ion at the electron deficient carbon atom and produce a tetrahedral intermediate (Fig. 3 a, b). which is further followed by ejection of the alcohol (Fig 3 c).



**FIG. 3** Ester hydrolysis in the presence of base as catalyst.

In ester hydrolysis in presence of an acid as catalyst, first step involves the protonation of carbonyl group. (Fig 4 a) andgive resonance structures (Fig 4 b, c). Positively-charged carbon atom promotes nucleophilic attack by water (Fig 4 c) and produce a tetrahedral intermediate (Fig 4 d). Transfer of H+ within a molecule (Fig 4 e) causes the loss of the alcohol (Fig 4 f).



**FIG. 4** Ester hydrolysis in presence of acid as a catalyst.

Amides are more prone to hydrolysis than the esters because the oxygen atom is more electronegative than the nitrogen atom in the amide. Drugs containing amides include paracetamol and lidocaine. Chloramphenicol which is an antimicrobial drug also contain amide and chances of hydrolysis are more in chloramphenicol than other amides (Fig 5) because of high polarization of the amide bond by adjacent chlorine substituents which are highly electronegative. Therefore, eyedrops of chloramphenicol need to store in a refrigerator.



**FIG. 5** Hydrolysis of chloramphenicol

Because penicillin and cephalosporin antibiotics contain the lactam group, a cyclic amide, and because this group is highly hydrolyzable, it is crucial. The four-membered -lactam ring's bond strain is what gives the molecule its reactivity. Different hydrolysis products are produced. A significant hydrolysis product for benzylpenicillin is benzylpenicilloic acid (Fig 6). The side chain of penicillins contains an amide group, however this group is less prone to hydrolysis than the -lactam ring. Because of how quickly it is hydrolyzed by the stomach's acidic environment, benzoylpenicillin cannot be given orally. Penicillins that can be usedorally, such amoxicillin, are comparatively less prone to hydrolysis.

**FIG. 6** Hydrolysis of the *β*-lactam ring of benzylpenicillin to give benzylpenicilloic acid.

1. **Oxidation:**

An increase in the number of carbon-to-oxygen bonds or a decrease in the number of carbon-to-hydrogen bonds occurs during oxidation processes. These processes frequently lead to the chemical instability of medicines. Vegetable oils, which are sometimes employed in pharmaceutical products as a solvent or as an emollient in emulsions and creams, also degrade due to them. Oxidation reactions are frequently intricate and result in a wide range of degradation products. Table 1 compiles typical cases.

**Table 1**

**Drug oxidation reactions**



Autoxidation is the term for oxidation involving molecular oxygen that occurs at room temperature. Free radicals, which are chemical entities that have an unpaired electron, are involved in the majority of these reactions. Although free radical oxidations are frequently complicated, there are three primary steps. The oxidation of numerous medicines and vegetable oils is summarised in the diagram below.

Low concentrations of free radicals are formed during the beginning phase. The production of free radicals for the medication RH can be shown as:



Light and the presence of heavy metals, which are invariably detected as trace impurities inmedicinal products, encourage initiation.

Free radical concentration rises dramatically during the propagation phase



Hydroperoxides (ROOH), which arise when oxygen is present, then react further to produce stable oxidation products. Degradation quickens during this phase, which could have devastating effects for the product.

1. **Isomerisation:**

The process of conversion of drugs into its optical or geometrical isomersis known as isomerisation. The obtained isomers are of less therapeutic quality. This type of conversion may be regarded as form of drug degradation.

For example: In acidic conditions, the tetracyclines undergo epimerisation to form 4- epi tetracycline which is toxic.

1. **Photochemical decomposition**:

Many pharmaceutical compounds like phenothiazine tranquilizers, hydrocortisone degrade on exposure to light which causes loss of potency of drug. Photodecomposition does not occur only during storage it may occur during the usage of the product.

1. **Polymerisation**:

The process by which two or more molecules combine together to form complex molecules is known as polymerisation. Polymerisation generally occurs during storage of dosage forms. For example: Formaldehyde hydrate may polymerise in aqueous solution to form paraformaldehyde, which deposits as white precipitates in the solution.

**Stability-indicating Method:**

A sensitive, accurate, and stability-indicating test and approach that does not allow for interference from other peaks and enough to identify and analyse the degradation products/impurities. Under specific storage conditions, a stability-indicating method is a quantitative analytical process that has been verified to be able to identify changes over time in the relevant properties of the drug substance and drug product. For the long-term stability study trending to be accurate, stability-indicating assay analytical methodologies need to be discriminating and confirmed.

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