

DRUG STABILITY

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Abstract- The increasing use of recombinantly expressed therapeutic proteins in the pharmaceutical industry has highlighted issues such as their stability during long-term storage and means of efficacious delivery that avoid adverse immunogenic side effects. Controlled chemical modifications, such as substitutions, acylation and PEGylation, have fulfilled some but not all of their promises, while hydrogels and lipid-based formulations could well be developed into generic delivery systems. Strategies to curb the aggregation and misfolding of proteins during storage are likely to benefit from the recent surge of interest in protein fibrillation. This might in turn lead to generally accepted guidelines and tests to avoid unforeseen adverse effects in drug delivery. Drugs are substances that change a person's mental or physical state. They can affect the way your brain works, how you feel and behave, your understanding and your senses. This makes them unpredictable and dangerous, especially for young people. The effects of drugs are different for each person and drug. Drug education helps children and young people understand that all drugs, legal and illegal, have the potential to cause harm, and that the drug experience is because of many factors including the person, the drug and the environment.

Keywords: drug stability, protein fibrillation, drug delivery system.

Introduction:

Drug Stability: The capability of a particular drug formulation in a specific container to remain within a particular chemical, microbiological, therapeutically, physical and toxicological specification in a specified period of time.

Drug Instability: The incapacity or incapability of a particular formulation in a specific container to remain within a particular chemical, microbiological, therapeutically, physical and toxicological specification.

Drug decomposition or degradation occurs during storage because of chemical alteration (reaction) of the active ingredients or additives.

Stability:

The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf-life.

Causes of Drug Stability:

The degradation of drugs and drug metabolites in samples can occur through either reversible or irreversible processes. Common factors that affect this stability include temperature, light, pH, oxidation and enzymatic degradation.

Factors affecting Drug Stability:

- pH
- Temperature
- Moisture
- Humidity
- Light
- Storage closure containers
- Oxygen
- Particle size (suspension and emulsion)
- Additives
- Molecular binding
- Diffusion of drugs and excipients [1].

Importance of Stability Studies:

Product instability of active drug may lead to under medication due to lowering concentration of the drug in the dosage form. During decomposition of active drug, the toxic product may be formed. Instability may be due to changing in physical appearance through the principles of kinetics are used in predicting the stability of the drug. To protect the reputation of the manufacturer by assuring that the product will retain fitness for use with respect to all functionally relevant attributes for as long as they are on the market [2].

CLASSIFICATION OF DRUG STABILITY

1. Physical Stability:

This type of stability covers the physical properties like appearance, color, dissolution, palatability and suspendability.

2. Chemical Stability:

The chemical stability refers to as the drugs ability to remain in the same chemical form when exposed to various environmental conditions that may cause it to deteriorate. One of the most common forms of chemical drug degradation is hydrolysis.

3. Microbiological Stability:

Sterility of the source products is retained during the aseptic preparation process and throughout the period of storage and use of the products.

4. Therapeutic Stability:

Drug stability refers to the extent to which a drug substance or product retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture.

5. Toxicological Stability:

The ability of a drug product to resist any increase in its toxicity during shelf life.

Stability studies are necessary for these following reasons:

1. Product instability or chemical degradation of active drug may lead to under medication due to lowering of the concentration of the drug in dosage form. Examples are digoxin and theophylline. If concentration of drug is not maintained in the body (or blood) through an appropriate dose, the dosage form become ineffective.
2. During decomposition of active drug toxic products may be formed. For example p-amino salicylic acid (PAS) is converted into p-aminophenol, which is toxic. Infusion of degraded penicillin G causes adverse drug reactions, because of sensitization of lymphocytes and formation of antipenicilloyl antibiotics.
3. Instability may be due to change in physical appearance. Examples of this type are, mottling of tablets, creaming of emulsions or caking of solids in a suspension.

PHYSICAL DEGRADATION OF PHARMACEUTICAL PRODUCTS

(a) Loss of Volatile Constituents:

Medicinal agents such as iodine, camphor, menthol, ethyl alcohol, anesthetic ether, chloroform have a tendency to evaporate from the product during storage. Similarly, nitroglycerine tablets may lose its potency owing to volatilization of the medicament. The preservative measures include keeping the product in well closed containers, and storage it in cool place.

(b) Loss of Water:

Loss of vehicle (water) from the product leads to decrease in weight, rises in concentration of drug and increases potency. Efflorescent substances, such as borax, caffeine and quinidine sulphate, have a natural tendency to loose water. Products such as emulsions and semisolids exhibit cracking. Loss of water depends on temperature and humidity. Preventive measures include preserving the product in a well closed container and storing it in a cool place.

(c) Absorption of Water:

Absorption of moisture from the atmosphere increases the weight of the product, dilutes the dose, and decreases the potency. Deliquescent substances, such as calcium chloride and potassium carbonate have a natural tendency to absorb water. Gelatin capsules will absorb moisture and become soft and sticky. Preventive measures include storage of such products in well closed containers.

(d) Crystal Growth:

Fluctuations in the ambient temperature (day and night or seasonal) cause crystal growth. Solutions – When temperature is lowered, the solution becomes supersaturated. Hence, precipitation and crystal growth of drug is observed. For example, 10% w/v calcium gluconate in injection is a supersaturated solution. Suspension—Particles slowly become bigger in size and finally may form a hard cake. These crystals, if present in the injection, may block the hypodermic needle. These particles produce gritty texture when applied as an ophthalmic preparation.

Polymorphism:

Polymorphs exhibit significant differences in important physicochemical properties such as solubility, dissolution rate and melting point. In general, more soluble metastable drug is employed in the manufacture. For example, cortisone acetate, Form II is more soluble (metastable) and formulated as an aqueous suspension. During storage, it may be converted into Form IV (more stable form). Such changes lead to caking of the cortisone acetate suspension. Normally suspending agents such as methyl cellulose are added to prevent the conversion owing to enhanced viscosity and limited diffusion of molecules.

Color Changes: Color changes indicates some kind of chemical or photochemical decomposition of the instability. Indigo carmine dye tends to fade rapidly in the presence of reducing substances (lactose and dextrose). Tartrazine tends to fade rapidly in the presence of additives (surface active agents) or light.

Color-development: Aspirin tablets become pink and ascorbic acid tablets turn yellowish brown. Adrenaline on exposure to air becomes red.

Preventive measures: Protect the product from light and air. Avoid using reducing substances (dextrose etc.,) as additives. Include unabsorbing substances such as 2,4-dihydrobenzophenone in the formulation (3).

Chemical decomposition of drugs-preventive measures:

All medicinal agents are to be investigated for their decomposition before being marketed. Most drugs contain one or more functional groups and therefore may undergo different chemical reactions. Ingredients present in dosage forms and environmental factors (e.g.; moisture, heat, light, radiation etc.,) affect the physical and chemical stability of drugs. A few important decomposition reactions are enumerated here.

Hydrolysis:

The principles that are generally govern hydrolysis reactions may be listed as follows:

- Drugs with ester and amide groups react with one molecule of water and undergo hydrolysis. Ester groups break faster than amide groups.
 - Drugs are either weak acids or bases. Therefore, these may be available as ionic forms or neutral molecules. Hydrolysis reaction between ionic species proceeds faster than with neutral molecules (to a large extent it is solubility related phenomenon).
 - Hydrolysis reactions are catalysed by H⁺ and (OH)⁻ ions. Hydroxyl ions catalyze hydrolysis by about 100 to 1000 times more actively than hydrogen ions.
- (1) Ester hydrolysis:
Hydrolysis of an ester into a mixture of an acid and alcohol involves rupture of a covalent linkage.
 - (a) pH:
If physiologically permissible, the pH of a formulation should be as close as possible to its pH of optimum stability.
 - (b) Type of Solvent:
Partial or full replacement of water with a solvent of lower dielectric constant reduces the velocity of hydrolysis. Ex: ethanol, glycols, glucose, mannitol solutions.
 - (c) Complexation:
Complex formation, ex; caffeine with benzocaine decreases the velocity of reaction. Similarly, caffeine complexes with local anesthetics such as procaine, tetracaine, can reduce the velocity of hydrolytic degradation.
 - (d) Surfactants:
It has been observed that nonionic, cationic and anionic surfactants stabilize the drug against hydrolysis. A 5% of sodium lauryl sulphate(anionic) causes 18-fold increase in the half -life of benzocaine.
 - (e) Modification of chemical structure;
Certain substitutes added to the alkyl or acyl chain of aliphatic or aromatic esters decreases the hydrolytic rate.
 - (1) Amide Hydrolysis:
Pharmaceutical compounds containing amide group can undergo hydrolysis.

Protection against Hydrolysis:

- Avoiding contact with moisture at time of manufacture.
- In liquid dosage form optimum pH for max stability.
- 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
- Hydrolysis susceptible drugs such as penicillin and derivatives can be prevented by formulating them in the dry powder form instead of a liquid dosage form such as solutions or suspensions.

Preventive measures or Hydrolysis:**1) Adjustment of pH:**

Rate of decomposition is critically depended upon pH. In the case of acid base catalyzed hydrolysis at minimum pH the drug stability is maximum.

2) Choice of solvent:

Aspirin is unstable in aq. Sol. So, it is formulated in alcohol.

In some cases non-aqueous. Solvent increases the instability of product e.g. Cyclamic acid in aqueous solution. Hydrolyze in slow rate while in alcohol high rate.

3) Addition of surfactants:

Addition of surfactants results into significant improvement of drug stability. Because of micelles formation. Surfactants are of two types cationic and anionic.

4) Production of insoluble form of drug:

Hydrolysis occur only with that portion of drug which is in aqueous solution.

Hydrolysis can be minimized by

- Making suspensions
- pH adjustment of the aq. Vehicle
- preparing insoluble salt of the drug

5) Modification of chemical structure:

Change of chemical structure of a chemical drug may prevent the hydrolysis.

Eg;- Alkyl to alkyl chain.

6) Presence of complexing agent:

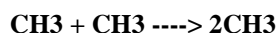
Complexing agent form water soluble complex with drug so that the rate o decomposition may be decreased.

Eg; caffeine decreases the rate of decomposition of local anesthetics such as benzocaine, procaine, and amethocaine.

Oxidation:

A number of pharmaceutical compounds undergo oxidative reaction includes vitamins, steroids, antibiotics, epinephrine etc. These reactions are mediated either by free radicals or by molecular oxygen.

Common form of oxidation is autoxidation and is defined as the reaction of any material with molecular oxygen. This may be given as follows;

**Types:**

Oxidation as two types

- Auto oxidation
- Photo oxidation

Protection against oxidation:**1. Use of Anti -oxidants:**

Antioxidants are mainly of 3 types:

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

- a. Example – tocopherol, butylated hydroxyl anisole (BHA), butylated hydroxyl toluene's (BHT). Concentration 0.001 – 0.1%.

II. 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 metabisulphite.

III. The third group, little antioxidant effect themselves but enhance the action of true antioxidant. Eg-; citric acid, tartaric acid etc.

2. Use of chelating agents:

When heavy metals catalyze oxidation.

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

- The presence of reducing agent:

Oxidation of pharmaceutical products can be retarded by the addition of reducing agents they are equally against oxidizing agents and atmospheric oxygen.

Eg:

- Potassium metabisulphites
- Sodium metabisulphites

3. Removal of oxygen:

By limiting the contact of drug with the atmospheric oxidation may be often minimized[3].

Photolysis:

Decomposition of drugs due to absorption of radiant energy in the form of light. If the molecules absorbing the radiation take part themselves, in the main reaction, the reaction said to be a photochemical one. Ex; chlorpromazine hydrochloride, hydrocortisone, prednisolone and methyl prednisolone etc.

Protection against photolysis:

- Use of amber colored bottles.
- Storing the product in dark, packaging in cartons.
- Coating of tablets with polymer films.

Racemization:

An optically active substance loses its optical activity without changing its chemical composition. The biological effect of the dextro form can be considerably less than the levo form.

Ex. Levo-adrenaline is 15-20 times more active than dextro-adrenaline. Solutions of levo adrenaline form a racemic mixture of equal part of levo, and dextro-adrenaline having pharmacological activity half than pure levo compound[4].

Influences of Light on Drug Decomposition:

Light energy, like heat, activate molecules and enhance the rate of a reaction. Drugs which undergo light induced chemical degradation are called photolabile(photosensitive) drugs. A few examples are riboflavin, tetracycline, chlorpromazine. Color development or color fading of tablets and liquids are also a few examples of photochemical degradation. A few familiar photochemical reactions are;

- (a) Conversion of ergosterol to vitamin D by ultraviolet light, and
- (b) Photosynthesis wherein carbohydrates and oxygen are produced when chlorophyll absorbs visible light.

The photochemical decomposition of pharmaceuticals is due to the absorption of sunlight particularly in the spectral region of visible blue, violet and ultraviolet wavelengths (500 to 300nm). Thus the light sources employed in the testing of drug decomposition are sunlight, artificial light and ultraviolet rays(arc light or mercury vapor lamp). A proper frequency and sufficient energy must be absorbed by the molecules in order to activate them. Therefore, strict attention has to be paid to control these parameters.

Influence of Temperature of Drug Decomposition:

The E_a values of aspirin hydrolysis, as a result of hydronium ion catalysis, intramolecular-nucleophilic catalysis, and hydroxyl-ion catalysis, were significantly different from each other when determined in the 30–40, 45–55, and 60–70°C ranges. A linear relationship observed between the calculated “differential” enthalpy and entropy values, with a slope (compensation temperature) value of about 307° K, supported a role for icebergs associated with hydrophobic groups in the formation of the activated complexes. This study illustrates that the predicted shelf life of a drug at room temperature could be erroneous if estimated

from a single E_a value which is calculated from the decomposition rate constants determined at widely spaced temperatures in the range of 10–70°C, using the Arrhenius relationship.

$$-E_a/RT$$

$$k=Ae$$

where,

- k= specific rate constant
- A= frequency factor or Arrhenius factor
- E_a = energy of activation
- R= ideal gas constant (1.987 cal/mol.deg)
- T= absolute temperature [5].

Chemical stability testing _dosage form:

In theory, the stability of pharmaceutical preparations should be evaluated by exposing the period to normal shelf conditions for a year or extended periods. The rate of decomposition is slow at room temperature. Such a method is time consuming and uneconomical. Therefore, in practice, methods are devised to accelerate the rate of degradation by keeping the product at higher temperatures.

Accelerated stability studies:

The objective of accelerated stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature. Accelerated stability studies are experimental designs.

Salient features of the experimental designs are:

1. Many pharmaceutical preparations contain different adjuvants along with the drug. Ideally, drug degradation in the mixture has to be studied individually. But its time consuming and therefore, gross picture on the stability is evaluated.
2. Some property of degradation, such as changes in the concentration of drug or the degraded substances, color etc. should be decided. In case of physical stability, changes in viscosity (examples are suspension and ointments) and number of globules (example is emulsion) are studied.
3. Mechanism of the chemical reaction need not be explored, but such a study is always advantageous to predict stability.
4. The temperature dependence on the chemical degradation must be established. A linear relationship is desirable.
5. Appropriate statistical methods should be employed to predict the shelf life with reasonable accuracy and also estimate errors.
6. Conclusions obtained by accelerated stability studies should be corroborated by results obtained at normal storage(temperature)conditions.
7. Suitable animal experiments are required to establish its efficacy, safety and toxicity[6].

Limitations:

Though accelerated stability studies have several advantages and widely used in pharmacy, it have a few limitations. The following aspects have to be considered in this study design:

- ❖ Accelerated stability studies are valid only when the breakdown depends on temperature.
- ❖ Accelerated stability studies are valid only when the energy of activation obtained in the study is about 10 to 30 kcal/mol. Reactions in solution phase, in general, have heat of activation in this range. If E_a is less than 10 kcal/mol, the rate would be fast at normal storage conditions. The elevated temperature has little influence on the decomposition. If E_a is higher than the 30kcal/mol, very high temperatures are required to enhance the degradation. Reaction at such high temperatures may not have any relevance because they do not reflect ambient storage conditions [7].
- ❖ The results (shelf life etc.,) obtained for one set of conditions for a preparation cannot be applied to other preparations of the same drug.
- ❖ Predictions will become erroneous when then order changes at elevated temperature. For example, a suspension follows a zero order at room temperature, but may become a solution that will follow first order at elevated temperatures.
- ❖ Predictions will become erroneous when the reaction changes its order during the period of study.

In spite of these limitations, temperature is still considered as an important factor in the prediction of shelf life. However, use of excessively high temperature should be avoided.

Objectives of Drug Stability:

- To determine maximum expiration date or shelf life.
- To provide better safety to the patients.
- To provide better storage conditions.
- To determine packaging components
- To gather information during preformulation stage to produce a stable product [8].

Protein drug stability: a formulation challenge

Key Points:

- Recombinantly expressed proteins are increasingly important in drug therapy. This makes it crucial to assess how their properties as proteins affect drug efficacy, targeting and side effects, as well as the ability to survive long-term storage.
- Amino-acid substitutions have led to therapeutically improved variants of, for example, insulin and interleukin-2, but modifications such as acylation and PEGylation can be just as effective, by causing a decrease in the clearing rate and reducing immunogenicity.
- Aggregation and misfolding is a fundamental issue in the long-term storage of protein therapeutics before administration. Although the mechanisms of aggregation are complex and can differ between even closely related proteins, methods have been developed to predict how amino-acid substitutions can affect this process.
- An easier approach might be to modify drug formulations. Simple additives, such as detergents, amino-acid pairs or cyclodextrins, can markedly reduce aggregation. Furthermore, judicious use of lyophilization can also provide a very reliable way to extend shelf-life [9].

Key Points of Drug Stability Analysis:

The purpose of the stability testing is to investigate how the raw materials or pharmaceutical preparations will change over time under the influence of temperature, humidity, and light, so as to provide a scientific basis for the production, packaging, storage, and transportation conditions of the drug, and to establish the validity period of the drug through the test. In addition to humidity and temperature, other factors may also affect the stability of drugs and active pharmaceutical ingredients (APIs), such as pH, excipients, API content concentration and retention time. These factors should be included in the overall stability assessment and drug development process [10].

Stages of stability methods:

Stability testing includes influencing factor testing, accelerated testing and long-term testing. The influencing factor testing is carried out with a batch of APIs or a batch of preparations. Accelerated testing and long-term testing require three batches of test products.

Generally, stability testing should start from early drug development, early formulation development. Usually, the accelerated stability test is performed first, followed by the confirmatory long-term stability test, which is considered to be the best stability research practice. Once the long-term stability data is obtained, the accelerated stability estimate can be calibrated and corrected.

Two stability research methods

If the parameters indicate that stability changes with time, regression analysis is the main method to determine stability, because time is the main factor affecting stability. The following two methods are based on the degradation rate and the influencing factors related to the degradation rate [11].

Increase antioxidants and nitrogen filling

Adding antioxidants (such as sulfite or PG, BHA and other radical blockers, VC that enhances the antioxidant effect) in the prescription can prevent the degradation of the raw material or the main drug in the preparation, and nitrogen can also prevent the degradation of the raw materials.

Reduce the introduction of metal ions:

Metal ions such as copper and iron come from excipients, coating powder, water, equipment, etc., and sometimes have a certain impact on the stability of the drug, therefore, sometimes it is necessary to consider adding metal-chelating agents, such as tartaric acid and citric acid [12].

Guidelines of stability testing:

To assure that optimally stable molecules and products are manufactured, distributed and given to the patients, the regulatory authorities in several countries have made provisions in the drug regulations for the submission of stability data by the manufacturers. Its basic purpose was to bring in uniformity in testing from manufacturer to manufacturer. The ICH was a consortium formed with inputs from both regulatory and industry from European commission, Japan and USA. The World Health Organization (WHO), in 1996, modified the guidelines because the ICH guidelines did not address the extreme climatic conditions found in many countries and it only covered new drug substances and products and not the already established products that were in circulation in the WHO umbrella countries. In June 1997, US FDA also issued a guidance document entitled 'Expiration dating of solid oral dosage form containing Iron. WHO, in 2004, also released guidelines for stability studies in global environment [1]. ICH guidelines were also extended later for veterinary products. The codes and titles covered under ICH guidance have been outlined in the Table No.2. Series of guidelines related to stability testing have also been issued by the Committee for Proprietary Medicinal Products (CPMP) under the European Agency for the Evaluation of Medicinal Products (EMA) to assist those seeking marketing authorization for medicinal products in European Union [13].

IMPORTANCE OF STABILITY IN PHARMACEUTICAL FORMULATIONS:

Stability is an essential quality attribute for pharmaceutical formulations. Evaluation of drug stability can prevent toxicity and increase safety, efficacy and quality of the final drug product. In this work, various factors affecting stability of both small molecule and biopharmaceutical compounds were investigated. However, it was found that albendazole was severely degraded by heat and

shear during extrusion. When combined with methanesulfonic acid and Kollidon VA 64, amorphous albendazole solid dispersion was successfully prepared by an alternative process, spray drying, to enhance dissolution and shelf-stability. In the second study, the stability of a caveolin-1 scaffolding domain (CSP7), which is a newly developed peptide for the treatment of idiopathic pulmonary fibrosis, was investigated in order to achieve an optimal formulation for in vivo clinical studies. This study showed the physical instability of the peptide, which was aggregation induced by moisture, and the crystallization of bulking agent on its stabilizing effect. The results showed that scuPA was stable after lyophilization (scuPA) and that both proteins were stable following reconstitution and nebulization. There were only slightly differences between the active and passive vibrating mesh nebulizers. In conclusion, from our work, the physical and chemical stability of small- and macromolecules was affected by formulation composition, processing and post-processing factors [14].

DRUG STABILITY BASED ON CONTROLLED DRUG DELIVERY SYSTEM:

Drugs which are unstable in the GI environment are not suitable candidates for controlled release systems. Drugs which are unstable in gastric pH can be designed for release in the intestine with limited or no release in stomach and drugs which are unstable in intestinal pH (alkaline pH) can be designed for release in the stomach with limited or no release in the intestine.

Similarly, there are drugs which are unstable in the intestine. Their stability can be increased significantly by making a sustained or controlled release formulation which can slowly release the drug in the stomach only. Hence, the drugs which have stability problems in any region of the gastrointestinal tract can be formulated as sustained or controlled or extended release formulation; but the release characteristics must be decided based on absorption site where the drugs are most stable. The desired physicochemical properties of a drug are summarized in the table.

Physicochemical properties of drug [15].

PHYSICOCHEMICAL PROPERTIES	DESIRED VALUE
Molecular weight / size	<1000 Daltons
Solubility	>0.1g /lt at pH 1 to 7.8
Apparent Partition Coefficient	High
Absorption mechanism	Diffusion control
General absorbability	Throughout entire GI tract
Drug release	Should not depend on enzyme and Ph

Conclusion:

Stability is a critical issue that must be assessed during the drug development process. Drug instability can occur not only in the liquid state, but also in the solid state. The common factors that must be studied include temperature, pH, moisture, oxygen, shear stress and excipients. Processing technique and device type for drug delivery can also cause drug degradation. The small- and macromolecules have both similar and different relevant factors affecting the stability of their formulations. Macromolecules tend to be less stable than the small molecules due to their complex structures and various functional groups.

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