

Drugs Degradation Pathways And Stabilities Studies: A Compressive Review

Shubhada Ganjare*, Rohini Gaikwad, Sneha Patil, Hitanshi Darji, P. N. Sable

Department Of Pharmaceutical Quality Assurance, S.S.P Shikshan Sanstha's Siddhi College Of Pharmacy, Chikhali, Pune, Maharashtra – 411062

ABSTRACT

Drug degradation is the chemical or physical breakdown of medication into lower-quality products, reducing efficacy and potential safety. Driven by factors like heat, light, moisture, and pH, it leads to reduced active ingredients and sometimes toxic by products. Key pathways include hydrolysis (water), oxidation, and photolysis (light), to the of a new drug substance or drug product under conditions that are more severe than normal accelerated stability conditions. These studies help researchers understand the chemical behavior of the molecule and drug which supports the development of suitable formulations and packaging systems. Although regulatory guidelines recommend forced degradation studies, they provide only limited details regarding how these studies should be performed. Stability plays a vital role in the development of new pharmaceutical products. Stability studies are essential for the approval and acceptance of any drug product because they ensure that the product maintains its quality, safety, and effectiveness throughout its shelf life. This review highlights current approaches and trends in drug degradation studies, discusses strategies for investigating degradation mechanisms, and describes analytical methods that are useful in developing stability-indicating methods.

Keywords: Degradation conditions, Degradation product, drug degradation, Stability indicating method, Stability studies.

INTRODUCTION

The chemical stability of pharmaceutical molecules is extremely important because it directly influences the safety, quality, and effectiveness of a drug product. According to guidelines issued by the U.S. Food and Drug Administration and the International Council for Harmonisation, stability testing data are required to evaluate how the quality of a drug substance or drug product changes over time when exposed to different environmental conditions such as temperature, humidity, and light.^{Error! Reference source not found.} Drug degradation is a technique in which drug substances and drug products are exposed to conditions that are more severe than accelerated stability conditions.

This process produces degradation products that help researchers better understand the stability and degradation behavior of the molecule. Stability studies generally include long-term studies conducted over 12 months and accelerated studies carried out for 6 months.^{Error! Reference source not found.}

In some cases, intermediate studies lasting 6 months may also be performed under conditions that are less harsh than accelerated conditions.

Samples obtained from drug degradation studies are useful in developing stability-indicating analytical methods. These methods can later be applied to analyze samples generated during accelerated and long-term stability studies.

According to ICH guidelines, stress testing is performed to identify possible degradation products, determine the intrinsic stability of the molecule, establish degradation pathways, and validate the stability-indicating procedures used for pharmaceutical analysis.^{Error! Reference source not found.,Error! Reference source not found.}

Objective:-

1. Drug degradation refers is the chemical or physical breakdown of medication into lower-

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quality products, reducing efficacy and potential safety. Error! Reference source not found.

2. These studies help researchers understand the chemical behavior of the molecule, which supports the development of suitable formulations and packaging systems. Error! Reference source not found.
3. To establish stability indicating nature of a developed method.
4. To understand the chemical properties of drug molecules.
5. To generate more stable formulations.
6. To establish degradation pathways of drug substances and drug products.
7. To differentiate degradation products that are related to drug products from those that are generated from non-drug product in a formulation. Error! Reference source not found.,Error! Reference source not found.
8. To elucidate the structure of degradation products.
9. To determine the intrinsic stability of a drug substance in formulation
10. To solve stability-related problems.

Limits for degradation:-

- I. The question of how much degradation is sufficient has been the topic of many discussions amongst pharmaceutical scientists.
- II. It is not necessary that forced degradation would result in a degradation product. Error! Reference source not found.
- III. Protocols for generation of product-related degradation may differ for drug substance and drug product due to differences in matrices and concentrations. Error! Reference source not found.
- IV. It is recommended that maximum of 14 days for stress testing in solution (a maximum of 24 h for oxidative tests) to provide stressed samples for methods development. Error! Reference source not found.

V. No such limits for physicochemical changes, loss of activity or degradation during shelf life have been established for individual types or groups of biological products. Error! Reference source not found.

Strategy for Selection of Degradation Conditions:-

A well-planned strategy is essential for conducting effective degradation studies. The commonly recommended stress conditions include acid and base hydrolysis, thermal degradation, photolysis, and oxidation. Error! Reference source not found.

In some cases, additional stress conditions such as freeze-thaw cycles and shear stress may also be included depending on the nature of the drug substance and formulation. Error! Reference source not found.

Using moderate stress conditions over a longer period is generally preferred over applying extremely harsh conditions for a short time. This approach offers several advantages. First, very harsh conditions may alter the natural degradation mechanism of the drug, leading to unrealistic degradation pathways. Second, highly concentrated acidic or basic solutions can create practical difficulties during sample preparation, as they often require neutralization or dilution before injection into the HPLC system. Forced degradation studies are mainly performed to generate representative degraded samples that can be used in the development of stability-indicating analytical methods for both drug substances and drug products. Error! Reference source not found.,Error! Reference source not found.

However, regulatory guidelines do not clearly specify the exact pH, temperature, or oxidizing agents that should be used during these studies. Therefore, the selection of conditions depends largely on the physicochemical properties of the drug molecule and scientific judgment. Error! Reference source not found.

Analyzing samples at early time points is also important because it helps distinguish primary degradation products from secondary degradation products. This provides a clearer understanding of the degradation pathway of the molecule.

In another commonly used approach, the drug substance is initially considered highly unstable, and

degradation studies are performed under conditions likely to cause degradation in order to identify possible breakdown products quickly. Drug degradation studies should be repeated whenever

there are changes in the formulation, manufacturing process, or analytical method, since such changes may result in the formation of new degradation products or altered degradation behaviour.^{Error! Reference source not found.}

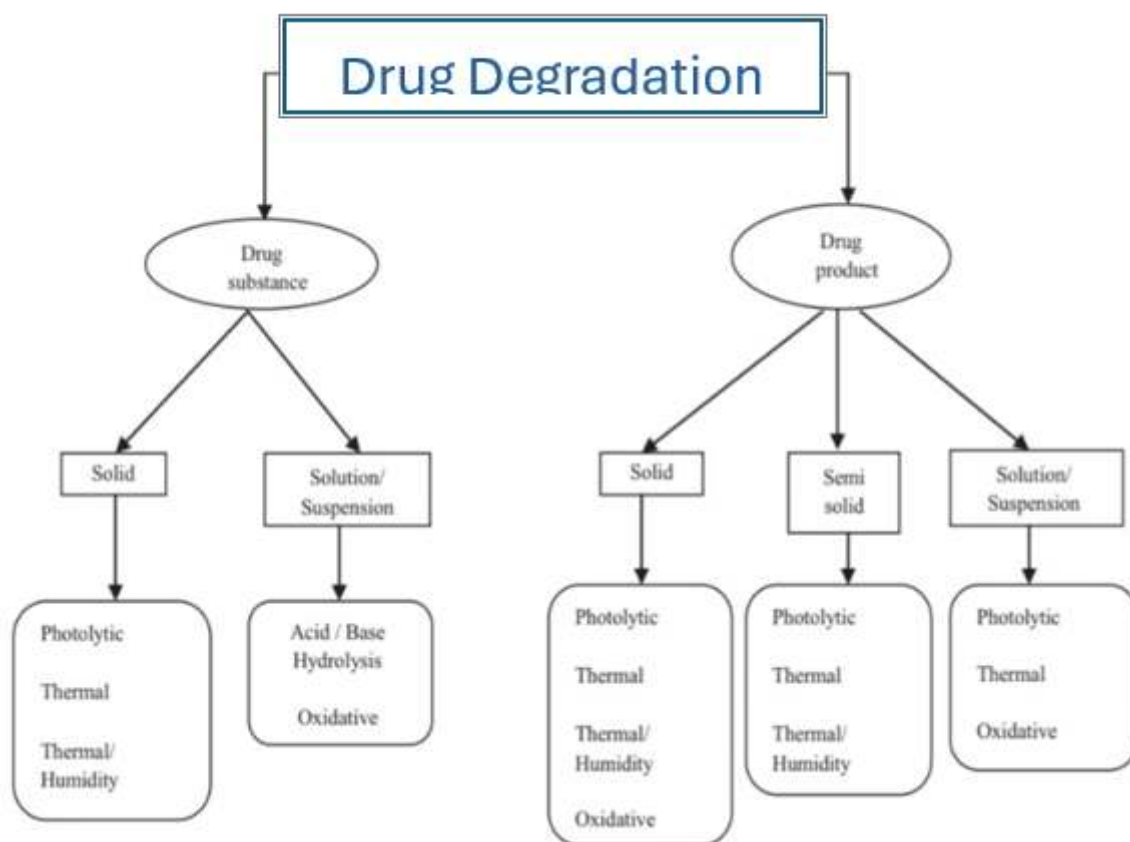


Fig.no1: Flowchart describing various condition used for degradation of new substance and drug product.

Degradation Conditions

1. Hydrolytic Conditions :-

Hydrolysis is one of the most common chemical degradation reactions observed in pharmaceutical substances over a wide pH range.^{Error! Reference source not found.}

- It is a chemical process in which a compound decomposes through its reaction with water.

Hydrolytic degradation studies are generally performed under acidic and basic conditions to evaluate the stability of ionizable functional groups present in the drug molecule.^{Error! Reference source not found.}

- Acid and base stress testing involve exposing the drug substance to acidic or alkaline conditions to

generate degradation products within a suitable range. The choice of acid or base, along with its concentration, depends on the stability characteristics of the drug substance.^{Error! Reference source not found.}

- Commonly used reagents include hydrochloric acid (HCl) and sodium hydroxide (NaOH). If the drug substance has poor water solubility, suitable co-solvents may be added to dissolve the compound before stress testing.^{Error! Reference source not found.}
- The selection of the co-solvent depends on the chemical structure and properties of the drug molecule. Stress studies are usually initiated at room temperature, and if no significant degradation is observed, the temperature may be

increased to 50–70 °C to accelerate the degradation process. Error! Reference source not found.

- Generally, stress testing should not continue for more than seven days. After degradation, the sample is neutralized using an appropriate acid, base, or buffer solution to prevent further decomposition before analysis.

2. Oxidation Conditions :-

The selection of an oxidizing agent, its concentration, and experimental conditions depends on the nature and stability of the drug substance. Error! Reference source not found.

- Hydrogen peroxide is the most commonly used oxidizing agent in forced degradation studies.
- However, other oxidizing agents such as metal ions, oxygen, and radical initiators like azobisisobutyronitrile (AIBN) may also be employed. Error! Reference source not found.
- Oxidative degradation usually occurs through an electron transfer mechanism, resulting in the formation of reactive cations and anions. Certain functional groups are more susceptible to oxidation, particularly those containing labile hydrogen atoms. Error! Reference source not found.
- These include benzylic carbon, allylic carbon, tertiary carbon atoms, and α -positions adjacent to heteroatoms. Oxidation of these groups can lead to the formation of hydroperoxides, alcohols, or ketones.

3. Photolytic Conditions :-

- Photostability studies are conducted to evaluate the effect of light exposure on drug substances and to generate photolytic degradation products. Error! Reference source not found.
- These studies help determine whether exposure to light causes unacceptable changes in the drug product. Photolytic degradation is generally carried out using ultraviolet (UV) or fluorescent light. Error! Reference source not found.
- The most widely accepted wavelength range for photostability testing is 300–800 nm. According

to recommended guidelines, the maximum light exposure is usually around 6 million lux hours. Error! Reference source not found.

- Certain functional groups are more prone to photodegradation and may increase the photosensitivity of drug molecules. These include carbonyl groups, nitro aromatic compounds, N-oxides, alkenes, aryl chlorides, sulfides, polyenes, and compounds containing weak C—H or O—H bonds. Error! Reference source not found.

4. Thermal Conditions :-

- Thermal degradation studies are performed to evaluate the effect of temperature on the stability of a drug substance or product.
- The relationship between temperature and the rate of degradation is commonly explained using the Arrhenius equation. Error! Reference source not found., Error! Reference source not found.
- Increased temperature generally accelerates chemical degradation reactions, allowing prediction of the stability and shelf life of pharmaceutical products under normal storage conditions. Error! Reference source not found., Error! Reference source not found.
- Where k is specific reaction rate, A is frequency factor, E_a is energy of activation, R is gas constant (1.987 cal/deg mole) and T is absolute temperature. Thermal degradation study is carried out at 40–80 °C. Error! Reference source not found.

Stability-Indicating Method (SIM):-

According to guidance from the U.S. Food and Drug Administration, a stability-indicating method (SIM) is a validated quantitative analytical procedure used to determine how the quality and stability of drug substances and drug products change over time. Error! Reference source not found.

A properly developed SIM can accurately measure the concentration of the active pharmaceutical ingredient (API) without interference from degradation products, impurities, or excipients present in the formulation.

The development of a suitable stability-indicating method is essential during pharmaceutical development because it supports preformulation studies, stability studies, and the establishment of appropriate storage conditions for the product.^{Error! Reference source not found.}

Among the available analytical techniques, reverse-phase high-performance liquid chromatography (RP-HPLC) is the most widely used method for separating and quantifying impurities and degradation products. RP-HPLC is commonly coupled with a UV detector for routine analysis.^{Error! Reference source not found.}

The development of a stability-indicating method generally involves three major steps:

1. Sample generation
2. Method development and optimization
3. Method validation

1. Sample Generation:-

Sample generation involves subjecting the drug substance to different stress conditions such as hydrolytic, oxidative, photolytic, and thermal degradation. Forced degradation studies are carried out on the API in both solid-state and solution forms to produce degradation products that are likely to form under normal storage conditions.^{Error! Reference source not found.} The degraded samples generated during these studies are then used for the development of a stability-indicating analytical method.^{Error! Reference source not found.}

2. Method Development and Optimization

Before initiating HPLC method development, it is important to understand the physicochemical properties of the drug, such as pKa, log P, solubility, and absorption maximum. These properties provide the foundation for selecting suitable chromatographic conditions.^{Error! Reference source not found.}^{Error! Reference source not found.}

A reverse-phase column is usually selected initially because degradation studies are commonly performed in aqueous solutions. Methanol, acetonitrile, and water are frequently used as components of the mobile phase in different proportions. The choice between

methanol and acetonitrile mainly depends on the solubility and chromatographic behavior of the analyte.^{Error! Reference source not found.}

Method development often begins with a 50:50 ratio of aqueous and organic phases, followed by gradual optimization to achieve better peak separation and symmetry. Buffers may be added later if required to improve chromatographic performance.^{Error! Reference source not found.}

During method optimization, impurity or degradation peaks may co-elute with the drug peak, making peak purity analysis necessary. Peak purity analysis helps establish the specificity of the method. This can be performed directly using photo diode array (PDA) detection or indirectly by changing chromatographic conditions such as the mobile phase composition or column type. If the degradation peaks and the area percentage of the drug peak remain unchanged after modifying conditions, the drug peak can be considered homogeneous and free from co-eluting impurities.^{Error! Reference source not found.}

3. Other Analytical Methods Used for SIM Development

Stability-indicating methods are designed to evaluate the potency, purity, and biological activity of pharmaceutical products. Since the selection of analytical methods depends on the type of product being studied, several analytical techniques may be employed during SIM development.^{Error! Reference source not found.}

These methods include electrophoretic techniques such as SDS-PAGE, immunoelectrophoresis, Western blotting, and isoelectric focusing. High-resolution chromatographic methods such as reverse-phase chromatography, size exclusion chromatography (SEC), gel filtration, ion exchange chromatography, affinity chromatography, and peptide mapping are also commonly used. An ideal analytical method should be sensitive enough to detect impurities at very low levels, typically around 0.05% or lower of the analyte concentration, while maintaining detector linearity.^{Error! Reference source not found.}^{Error! Reference source not found.}

It should also be capable of detecting all degradation products formed during formal stability studies within

the threshold limits recommended by the International Council for Harmonisation. For the identification and characterization of degradation products, both conventional chromatographic methods and advanced hyphenated techniques may be used. These include techniques such as LC–MS and LC–NMR, which provide detailed structural information about impurities. Error! Reference source not found. Unknown impurities observed during stress testing, pharmaceutical development, or stability studies can be separated and analyzed using chromatographic techniques such as RP-HPLC, thin-layer chromatography (TLC), gas chromatography (GC), capillary electrophoresis (CE), capillary electrochromatography (CEC), and supercritical fluid chromatography (SFC).

The use of these advanced analytical methods provides a deeper understanding of impurity structures and helps identify potential genotoxic impurities, enabling better impurity control and safer pharmaceutical products. Error! Reference source not found.

CONCLUSION

Degradation products generated from drug degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in the developing stability indicating method.

It is better to start degradation studies earlier in the drug development process to have sufficient time to gain more information about the stability of the molecule. This information will in turn help improve the formulation manufacturing process and determine the storage conditions. The aim of any strategy used for forced degradation is to produce the desired amount of degradation i.e., 5–20%. A properly designed and executed forced degradation study would generate an appropriate sample for development of stability indicating method.

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