EFFECTS OF OXIDATION AND HYDROLYSIS ON CHEMICAL STABILITY OF DRUGS

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# ABSTRACT

**A guide for chemical stability of drugs to hydrolysis and oxidation is presented. This chapter covers general discussion on stability, oxidation and hydrolysis. Various functional groups and structural moieties present in drug molecules, which can undergo hydrolysis, and oxidation were discussed. Solid, semisolid and liquid dosage forms discussed with formulation changes. Major strategies have been explained for prevention of oxidation and hydrolysis, which has the major role in causing degradation of the pharmaceutical dosage forms.**

**Keywords** – Cyclodextrin, Surfactants, Lyophilization**,** hydrolysis

# INTRODUCTION

Pharmaceutical stability refers to the ability of a drug substance or formulated product to maintain its specified identity, potency, and purity throughout its shelf life. It involves ensuring that the product retains its intended properties and characteristics during storage and use. Various factors during manufacturing, processing, and storage can influence the chemical and physical integrity of the drug substance, leading to degradation. Chemical reactivity refers to processes that modify the drug molecule through covalent bond cleavage or formation, resulting in the creation of new chemical entities. In his chapter will focus on the how chemical stability of drug substances are affected by degradation. The chemical stability of a drug substance is crucial for ensuring that the product remains effective and safe. A pharmaceutical product must remain stable under different conditions, such as varying temperatures and humidity levels. Chemical instability of pharmaceuticals can lead to changes in therapeutic effectiveness and toxicity or potential harmful effects. Understanding the conditions that cause degradation of the drug substance helps establish appropriate controls during manufacturing, processing, and product storage to maintain its stability [1]**.**

Understanding the chemical stability of a drug is crucial for determining appropriate storage conditions, considering factors like light, temperature, and humidity. It also helps predict potential interactions with other drugs or excipients. Stable medications are essential for pharmacists in terms of marketing, storage, and distribution. For physicians and patients, drug stability ensures safety and efficacy. Regulatory agencies and quality control analysts rely on stability data to assess the drug's quality, strength, purity, and identity. Many tablets contain derivatives of carboxylic acid or are composed of compounds based on this moiety, such as esters, amides, lactones, lactams, imides, or carbamates. Consequently, various chemical reactions can cause drug degradation. These reactions include hydrolysis, oxidation, photochemical reactions, polymerization, isomerization, racemization, and dehydration [2]**.**

Pharmaceutical products have different molecular structure; therefore, it has different degradation pathways based on molecular structure drug instability can be predicted. Degraded products are not acceptable they are assumed to be adulterated if changes occur in colour and odour with time. For example, epinephrine on oxidation forms adrenochrome (red Colour material). Epinephrine when adulterated form pink colour. Therefore, it is essential to know about the degraded products and how much toxicity it is causing. To know about how much of drug is lost with time. It reduces efficacy and potency of the drug product. Among these reactions, oxidation and hydrolysis are the primary ones that significantly influence drug stability. They both are causes for most frequently occur degradation in pharmaceutical products therefore it is important to prevent them [3]**.**

Acceptable stability is a major challenge during the formulation of dosage forms. Stability refers to no change in the chemical composition of the formulation. In the pharmaceutical world, the term “stability” more often refers to the storage time allowed before any degradation product in the dosage form achieves a sufficient level to represent a risk to the patient. Based on this time, the shelf life of a product is determined. (Accelerated aging). For obtaining chemical stability of new drug molecules, forced degradation studies can be done. Drug formulations are continuously, analysed during their development stage, with a specific focus on the stability of the drug. Stability methods can be developed for those degradation products this in turn will be helpful for maintaining stability [4, 5].

# HYDROLYSIS

Hydrolysis is a common chemical reaction in which a water molecule cleaves a bond in the substrate. It is a prevalent degradation pathway observed in pharmaceuticals for two main reasons. Firstly, various functional groups and structural moieties present in drug molecules can undergo hydrolysis. Drug substances containing ester, amide, lactam, carbamate, or sulphonamide functional groups often experience hydrolytic degradation. This reaction has been extensively studied and is a major degradation pathway for many pharmaceuticals. Water molecules are widespread and can be present as moisture in solid dosage forms, as liquid in aqueous liquid formulations, or as crystal water in crystalline drug substances. Ester compounds are typically hydrolysed through nucleophilic attack by hydroxide ions or water on the ester bond. Some well-known pharmaceuticals that undergo hydrolytic reactions include aspirin, benzocaine, procaine, and atropine. Amide bonds are less susceptible to hydrolysis compared to ester bonds because the carbonyl carbon in an amide bond is less electrophilic. The resonance between the lone-pair electrons of the nitrogen and the carbonyl group in amide bonds provides them with partial double-bond character, contributing to their stability. However, certain drug substances like acetaminophen, indomethacin, chloramphenicol, lidocaine, and β-lactam antibiotics can still undergo hydrolysis despite containing amide bonds[1]**.**

The hydrolysis reaction of esters occurs at a faster rate than that of amides and can be catalysed by both acidic and basic conditions, with the rate being dependent on the pH of the aqueous solution. In the body, the metabolism of drugs containing esters and amides is also facilitated by hydrolytic enzymes present in various tissues and plasma. The reason behind the difference in hydrolysis rates between esters and amides lies in their structural dissimilarities. Esters have an oxygen atom in their functional group, while amides have a nitrogen atom at the same position. This structural contrast results in the carbon atom of the carbonyl group (C=O) in esters being even more positively charged than in amides, leading to a stronger attraction between this carbon and a water molecule. Conversely, the presence of the nitrogen atom in amides reduces the positive charge on the carbonyl carbon atom, making it less capable of attracting incoming water molecules. This difference in the hydrolysis behaviour of esters and amides is by comparing the local anaesthetics lidocaine and procaine. Procaine, containing an ester group, is now rarely used as a local anaesthetic due to its short-lasting effect caused by rapid hydrolysis of the ester bond. On the other hand, lidocaine, which contains an amide bond, is less susceptible to hydrolysis than procaine's ester. This, along with lidocaine's bulkier structure, contributes to its longer-lasting local anaesthetic effect [3].

# STRATEGIES TO INHIBIT HYDROLYSIS

Hydrolysis can be prevented or minimized through various methods. While it can be challenging to prevent hydrolysis during in vivo metabolism, there are strategies that can be employed during the early drug development stage. One approach involves chemically modifying the structure of the active compound, provided that the issue of hydrolysis is identified early enough. For inherently unstable drugs, preventive measures can involve altering the dosage form in several ways. By changing the drug's form and utilizing techniques like surfactants, cyclodextrin, and lyophilization, the chemical stability of drugs can be enhanced. Crystalline drugs, which generally exhibit higher resistance to hydrolysis compared to other drug forms like salts and polymorphs with stronger lattice energies, tend to be more stable. Moreover, drug forms with greater hydrophobic characteristics may offer improved hydrolytic stability. In the case of hydrophobic drugs, surfactants can be used to solubilize them in surfactant-based micelles or liposomes, providing protection against catalytic acid and base and stabilizing the drug. This effect is particularly significant with non-ionic surfactants, although charged micelles and liposomes have, also shown some effects. Hydrolysis rates generally decrease from zero to about four- fold in these cases. For more polar drugs, they may not be as deeply enveloped in the hydrophobic core of the micelles, leading to a reduced stability improvement.

# Surfactants

Surfactants for hydrophobic drugs, solubilization in surfactant-based micelles or liposomes can provide protection from catalytic acid and base, thereby stabilizing the drug. This effect has been most pronounced with non-ionic surfactants; however, effects have been observed with charged micelles and liposomes. Decreases in hydrolysis rates from zero to about four-fold are generally observed. With more polar drugs, the molecules are presumably less deeply enveloped in the hydrophobic core of the micelles and the resulting stability improvement is diminished.

# Cyclodextrin

Cyclodextrins (CDs) are valuable pharmaceutical excipients that can enhance the chemical stability of drugs and extend the shelf life of pharmaceutical products. When used in aqueous solutions, CD complexation has been demonstrated to impede various degradation processes, including hydrolysis, oxidation, photo degradation, isomerization, and enzyme-catalysed degradation of dissolved drugs. This ability makes CDs effective in preserving the integrity of drugs in solution. However, it is important to note that

some drugs, such as β-lactam antibiotics, may undergo CD-catalysed degradation under specific conditions when present in aqueous solutions. Additionally, while certain drugs benefit from stabilization by CDs in aqueous solutions, the same CDs can have a destabilizing effect on these drugs when incorporated into solid dosage forms. Due to these variations in the effects of CDs on drug stability, it is essential to thoroughly test and verify their impact in the final drug formulation and under the recommended storage conditions. This ensures that CDs are used effectively and safely as excipients to improve the stability and shelf life of pharmaceutical products. HPβCD also improves chemical stability of drug, and hence enhance bioavailability [6,7]**.**

# Lyophilization technique

Lyophilization is a technique that involves removing most of the water and reducing the mobility of the drug. While it increases drug stability, it requires a more complex manufacturing and end-use procedure. For many drugs, lyophilization remains the preferred method to create a stable formulation resistant to hydrolysis. For instance, ENA (N-epoxymethyl-1,8-naphthalimide), a synthetic antiproliferative agent, is susceptible to hydrolytic degradation, and therefore, it is commonly formulated as lyophilized powders or nonaqueous solutions in the pharmaceutical industry to minimize hydrolysis. (Solubilization and reformulation of poorly water-soluble and hydrolysis-susceptible N-epoxymethyl-1,8-naphthalimide (ENA) compound) [8].

In liquid dosage forms, the hydrolysis of drugs is influenced by the presence of water. To minimize hydrolysis, storing drugs as dry powders and reconstituting them in water before dispensing is recommended. If a drug is known to be susceptible to hydrolysis at room temperature, storing it in a cool place is advised, and patients can be counselled on this practice. Proper labelling on packaging by pharmacists is crucial. Additionally, the rate of hydrolysis is temperature-dependent, so heat sterilization of such drugs could be problematic. For hydrolytically labile drugs in liquid formulations, forming suspensions can increase stability. Reducing drug solubility in the formulation decreases the concentration of the drug in solution and subsequently reduces the overall degradation rate. An example is converting highly water-soluble but extremely labile penicillin G into poorly water-soluble procaine penicillin G while maintaining the same hydrolytically active centre. This method has proven successful for many penicillin and cephalosporin derivatives.

In semi-solid dosage forms such as ointments and creams, the stability of the active ingredient can be controlled by altering the nature of the ointment or cream base in the formulation. Similarly, the sensitivity of a drug to hydrolysis in a solid dosage form can be managed by preparing a less hygroscopic salt of the drug or by reducing the water content in the excipients used in the formulation [3]**.**

# OXIDATION

Pharmaceutical products can undergo degradation through oxidation reactions, which are characterized by atoms increasing their bonds to oxygen, reducing bonds to hydrogen, or losing electrons. The oxidative pathways involved are intricate and influenced by various factors. Once triggered, the process initiates the gradual formation of radicals, followed by peroxides and hydroperoxides, which are the main by-products of oxidation. These reactive and unstable species can continue propagating, eventually breaking down into secondary oxidation products like small organic acids, aldehydes, and ketones. The speed and extent of these reactions can differ based on the delivery system (liquid, solid, biphasic) and the concentration of oxidation-prone substrates. (excipient, drug, and or antioxidants) [9].

The primary mechanisms responsible for the oxidative degradation of pharmaceutical products are autoxidation (radical- mediated), nucleophilic/electrophilic reactions (peroxide-mediated), and oxidation mediated by single electron transfer to dioxygen. Autoxidation refers to the oxidation of a substrate by molecular oxygen (O2), initiating a chain reaction where the oxidized substrate generates reactive species that further attack other substrate molecules. This process, also known as a radical chain reaction, results in the formation of hydroperoxides and associated peroxyl radicals upon the addition of oxygen. The second most common oxidation mechanism, peroxide-mediated reactions, occurs when pharmaceutical drugs react with hydrogen peroxide (H2O2). Peroxides are often found in excipients commonly used in pharmaceutical formulations, leading to these reactions in products susceptible to oxidation. These reactions are slow and typically occur during extended storage. The third mechanism involves oxidation mediated by single electron transfer to dioxygen. Certain compounds can undergo this process, wherein a weakly acidic hydrogen atom in the compound is cleaved to form a carbanion in a basic environment. In summary, pharmaceutical products can undergo oxidative degradation through different pathways, including autoxidation, peroxide-mediated reactions, and single electron transfer to dioxygen. Understanding and controlling these mechanisms are essential for maintaining the stability and shelf-life of pharmaceutical formulations[4,5] .

In many cases, pharmaceutical drugs remain stable in their pure form, but when they are combined with excipients, instability issues can arise. Excipients can contain trace-level impurities, particularly peroxides, which can react with the drug molecules. These peroxides encompass organic peroxides and hydroperoxides, all of which have a very weak O–O bond that can easily break, leading to the formation of hydroxyl and alkoxy radicals. Additionally, other reactive oxygen species like superoxide anion, hydrogen peroxide, and hydroperoxides can result from peroxides and radicals. As previously mentioned, the stability of a drug product is greatly influenced by the pharmaceutical excipients used, as they contain impurities, particularly hydroperoxides and organic peroxides, which can contribute to the oxidative degradation of the drug. Hydroperoxides are commonly found as trace-level impurities in excipients such as

polyethylene glycol (PEG), povidone, hydroxypropyl cellulose, and polysorbate. Completely eliminating these impurities from the final product poses a challenging task. [5].

# STRATEGIES TO INHIBIT OXIDATION

1. **Antioxidants**

Utilizing antioxidants is one of the methods utilized in the drug product formulation. Antioxidants are substances that can stop other molecules from oxidizing. They can be: (a) Initiation inhibitors, based on their antioxidative mechanism of action. As they interact with the catalysts of radical chain reactions, antioxidants can stop them from happening. Ethylenediaminetetraacetic acid (EDTA), which also functions as a heavy-metal chelating agent, is the most widely used member of this category. Additionally, the type of metal that is complexed with EDTA must be taken into consideration. Iron-EDTA complexes are created when EDTA is added in the presence of iron ions, which paradoxically speeds up the production of hydroxyl radicals. Contrarily, the Fenton reaction is not speed up by an iron complex containing diethylenetriaminepentaacetic acid. However, all of the investigations that are discussed here were carried out in aqueous solutions, therefore it is impossible to conclude that the same holds true for solid dosage forms without further testing. (b) Terminators of radicals. Some antioxidants, like butylhydroxyanisole (BHA) and butylhydroxytoluene (BHT), can interact with radicals to prevent the radical chain reaction from proceeding to the propagation stage. There are many phenolic compounds in nature that have a propensity to form rather persistent radicals after one electron oxidation. The stability of the radical electron increases when bulky alkyl groups, like t-butyl in the case of BHA and BHT, are added to the aromatic ring. Such anti-oxidants usually create relatively harmless radicals, which stop the chain process. -tocopherol is more efficient than propyl gallate, which is more effective than BHA at preventing the oxidative breakdown of lovastatin in an aqueous solution. [5].

# Chelating Agents

Chelating agents are employed in pharmaceutical formulations to hinder oxidation by sequestering catalysing metals like iron and copper. The commonly utilized chelating agents in pharmaceuticals include EDTA, citric acid, various amino acids, weak phosphoric acid, and tartaric acid. Their role is to bind and remove these catalysing metals, thereby preventing them from catalysing oxidation reactions and preserving the stability of the pharmaceutical products[10].

# Use of amber or coloured glass containers

Amber glass is designed to block light with wavelengths of 470 nm and provides partial protection to light-sensitive compounds. Additionally, specific formulations like metered dose inhalers, which are utilized in asthma treatment, are carefully crafted to shield the drug from both light and oxygen. These formulations involve dissolving or suspending the drug in a propellant and storing it in a sealed aluminium container, thereby ensuring enhanced protection for the medication from potential degradation caused by light exposure and oxygen exposure [11].

**CONCLUSION**

One of the primary challenge is adequate stability of product during development process. Need of accelerated studies has increased due to increase in formulation development. Hydrolysis and oxidation are most common degradation pathways in almost every pharmaceutical products. For the development of new drug molecule or product, it is important to understand oxidation and hydrolysis reaction at every step. Forced degradation study will be helpful in providing information about the degradation causes. Therefore, main aim is to control the degradation causing parameter and avoid its occurrence in the main product. It is time to do a rational design of more pharmaceutically resistant oxidation formulation.

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