

EFFECTS OF OXIDATION AND HYDROLYSIS ON THE CHEMICAL STABILITY OF DRUGS

Abstract

A guide for the chemical stability of drugs to hydrolysis and oxidation is presented. This chapter covers a 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 are discussed with formulation changes. Major strategies have been explained for the prevention of oxidation and hydrolysis, which have a major role in causing degradation of the pharmaceutical dosage forms.

Keywords: Cyclodextrin, Surfactants, Lyophilization, hydrolysis

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I. INTRODUCTION

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

Understanding chemical stability 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 and are composed of compounds, which are based on the moiety such as amides, lactones, esters, lactams, carbamates or imides. Consequently, drug degradation is caused by various chemical reactions. These reactions include hydrolysis, photochemical reactions, oxidation, 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 forms a pink colour. Therefore, it is essential to know about degraded products and how much toxicity it is causing. To know how much of a drug is lost with time. It reduces the 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 of the more frequently occurring 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 world of pharmaceuticals, 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. The shelf life of a product is determined based on this time. (Accelerated ageing). To obtain the chemical stability of new drug molecules, forced degradation studies can be done. During their development stage drug, formulations have been continuously analysed, with a specific focus on the stability of the drug. Stability methods can be developed for those degradation products this in turn will help maintain stability [4, 5].

II. HYDROLYSIS

Hydrolysis is defined as a 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 drug molecules undergo hydrolysis due to functional groups and structural moieties present in them. Drugs 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].

III. 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, some strategies 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.

- 1. Surfactants:** Drugs that are hydrophobic can be stabilized by solubilization in liposomes or micelles made of surfactants to protect against catalytic acid and base. However, effects have also been seen with charged micelles and liposomes. This effect has been particularly noticeable with non-ionic surfactants. In general, hydrolysis rates decrease from zero to roughly four times. The molecules are probably less thoroughly encapsulated in the hydrophobic core of the micelles with more polar medicines, which reduces the stability improvement.
- 2. Cyclodextrin: Cyclodextrins (CDs)** are valuable pharmaceutical excipients that can increase 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, isomerization, photodegradation, 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. HP β CD also improves the chemical stability of the drug and hence enhances bioavailability [6,7].
- 3. Lyophilization Technique:** Lyophilization is a technique that involves removing the majority of the H₂O and minimizes the drug mobility. While it increases drug stability, it requires a more difficult manufacturing. Lyophilization remains the preferred method for several drugs to create a stable formulation resistant to hydrolysis. For instance, ENA (N-epoxymethyl-1,8-naphthalimide), which is a synthetic antiproliferative agent, is susceptible to hydrolytic degradation, and therefore, it is commonly formulated as the lyophilized powders or as a nonaqueous solutions in the pharmaceutical industry to minimise hydrolysis. Reformulation and solubilization and of poorly water-soluble and hydrolysis-susceptible N-epoxy methyl-1,8-naphthalimide (ENA) compound [8].

In liquid dosage forms, the hydrolysis of pharmaceutical products is greatly influenced by the presence of H₂O. To minimize hydrolysis, storing drugs as dry powders and reconstituting them in water prior to dispensing is recommended. If a drug which is prone to hydrolysis at room temperature, storing it in a cool place is highly

recommended, and patients should be counselled for this practice. Proper labelling on packaging by pharmacists is crucial. Additionally, the rate of hydrolysis depends on temperature, so heat sterilization of such pharmaceutical drugs could be problematic. In a liquid formulations, some hydrolytically labile drugs forming suspensions increase stability. By reducing drug solubility in the formulation decreases the amount of the drug in the solution and generally decreases the overall rate. An example is conversion of highly water-soluble and extremely labile penicillin G into procaine penicillin G which is poorly water-soluble. By maintaining the same hydrolytically active centre. This method has proven successful for a number of penicillin and cephalosporin derivatives. Semi-solid dosage forms, the stability of the ingredients can be controlled by altering the nature or cream base used in the formulation such as in an ointments and creams. Similarly, those drugs which are sensitive to hydrolysis in a solid dosage form can be managed by by reducing the water content in the excipients used in the formulations or preparing a less hygroscopic salt of the drug [3].

IV. OXIDATION

Most of 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 radicals formation, hydroperoxides and peroxides as the main by-products. Reactive and unstable species can continue propagating, eventually breaking down in a secondary oxidation products like small organic acids, ketones, and aldehydes. Based on the delivery system and concentration of excipients, drug or antioxidants, the speed and extent of these reactions can differ [9].

Primary mechanisms responsible for the oxidative degradation of pharmaceutical products are autoxidation (radical-mediated) or nucleophilic and electrophilic reactions (peroxide-mediated), and oxidation mediated by transfer of single electron to dioxygen. Autoxidation refers to oxidation of a substrate by oxygen (O₂) molecule, initiating a chain reaction where this oxidized substrate generates reactive species which further attack other substrate molecules. This process, is also called as radical chain reactions, results in the formation of hydroperoxides and associated peroxy radicals upon the addition of oxygen. The second most common oxidation mechanism, peroxide-mediated reactions, occurs when pharmaceutical drugs react with (H₂O₂) Hydrogen peroxides. Peroxides often found in commonly used excipients in pharmaceutical formulations, leading to these reactions in products which are susceptible to oxidation. These reactions occur slowly and typically during extended storage. The third mechanism involves oxidation which is mediated by single transfer of electron to dioxygen. Certain compounds can undergo this process, where in a hydrogen atom (weakly acidic) compound get cleaved and 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 containing impurities,

in a trace-level particularly in peroxides, which react with the molecules of drug. These peroxides encompass organic peroxides and hydroperoxides, all of which form a 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 mentioned, previously 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 molecule. Hydroperoxides are commonly found as impurities in various excipients such as polyethylene glycol (PEG), hydroxypropyl cellulose, povidone and polysorbate. Eliminating the impurities from the final product poses a challenging task. [5].

V. 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 the antioxidative mechanisms. They interact with the catalysts of radical chain reactions, antioxidants can stop them from happening. (EDTA) which is Ethylenediaminetetraacetic acid, which functions as a chelating agent, is the most widely used member of this category. Additionally, this type of metal 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 for solid dosage forms without further testing. (b) Terminators of radicals. Some antioxidants, like butyl hydroxyl anisole and butylhydroxytoluene, interact with radicals to prevent the radical chain reaction from proceeding to the propagation stage. Many phenolic compounds in nature have a propensity to form rather persistent radicals after one-electron oxidation. 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 antioxidants 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].
- 2. Chelating Agents:** Chelating agents are employed in pharmaceutical formulations to hinder oxidation by sequestering and 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].
- 3. 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].

VI. CONCLUSION

One of the primary challenges is the adequate stability of the product during the development process. The need for accelerated studies has increased due to an increase in formulation development. Hydrolysis and oxidation are the most common degradation pathways in almost every pharmaceutical product. For the development of a new drug molecule or product, it is important to understand oxidation and hydrolysis reactions at every step. A forced degradation study will help provide information about the degradation causes. Therefore, the 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 a more pharmaceutically resistant oxidation formulation.

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