

CHEMICAL STABILITY OF DRUGS

Abstract

Pharmaceutical stability refers to a substance's capacity to maintain the predetermined levels of identity, potency, and purity over the period of its shelf life. It measures how well a product maintains its original attributes and traits during storage and use, if certain parameters are met. A pharmacological material may be subjected to situations that could significantly affect its chemical and physical integrity during synthesis, processing, and storage. A medicinal substance's chemical stability is extremely important. A marketable medicine must maintain its stability under a range of circumstances, such as extremes in temperature and relative humidity. Pharmaceuticals' chemical instability affects their therapeutic efficacy and toxicological effects. Determining the proper controls to implement during product production, processing, and storage can be made easier with knowledge of the factors that cause the parent chemical to degrade. This chapter talks about various factors affecting chemical stability of drugs and parameters to meet the chemical stability requirement of the drug or formulation.

Keywords: Chemical Stability, Prodrugs, Chemical Reactions, Drug.

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I. INTRODUCTION

Drug stability is the extent to which a drug substance or product maintains, within specific bounds and during the duration of storage and use, the same qualities and characteristics that they did at the time of their manufacture. The basic types of stability include chemical, physical, microbiological, therapeutic, and toxicological. Drug stability can be divided into pre-market and commercial (marketed product) stability. In order to support the clinical research, where drug products are maintained under diverse circumstances for safety and efficacy assessment, pre-market stability is frequently carried out during the clinical trial and during the filing period. Continuous assurance of post-approval batches for continuous drug product stability monitoring is known as commercial stability. To assess the retest window (for pre-market stability) and shelf life (for commercial stability), drug substance or drug product testing using a stability-indicating method is often needed.

The substance utilised to make the drug product, typically along with excipients, is referred to as the drug substance (also known as the active pharmaceutical ingredient [API] as per USP-NF definition¹). Drug ingredients may be created chemically, come from plants or animals, or be produced biologically or using recombinant technology. The drug material may also include other contaminants or product- and process-related chemicals in addition to the API. Information on drug substance stability has been a crucial component of medication research since the very beginning. Data on the physical, chemical, and other properties of the drug ingredient are useful for designing formal stability studies as well as methodologies that suggest the stability of the drug product.

In the final packaging intended for marketing, a drug product (also known as a dosage form or completed product according to USP-NF definition 1) contains one or more drug compounds, typically with excipients. In order to support the stability of the drug product used in clinical and non-clinical studies, to determine the commercial expiration date, to determine the levels for specifications (such as API, preservatives, etc.), and to set the control limits for lot release, stability studies on the drug product are performed. A number of factors, some related to the environment and others to the properties of the drug itself, have an impact on a drug's stability. According to FDA regulations known as Current Good Manufacturing Practises, or CGMPs, drug manufacturers are required to do routine stability testing on their medications to ensure their efficacy.

Chemical stability is a crucial component of product quality that is closely related to a drug product's potency, purity, efficacy, and safety during its shelf-life and usage by the patients. It is measured by rate of changes that takes place in the pharmaceutical dosage forms. Chemical stability in chemistry refers to a chemical system's thermodynamic stability. When a system is in its lowest energy state or in chemical equilibrium with its surroundings, thermodynamic stability occurs. Temperature, light, pH, oxidation, moisture, concentration, drug incompatibility and enzymatic degradation are common elements that have an impact on its stability. High temperature accelerates oxidation, reduction and hydrolysis reactions which leads to degradation. Physical stability describes modifications to the physical properties of a drug product's formulation components, such as the drug's phase transformation or excipients. Polymorphic conversion, hydration/dehydration, crystallization/amorphization, salt-to-free form conversion, and other mechanisms are examples of common phase changes. These phase changes may affect a pharmacological product's quality characteristics and processing

behaviours since the physical, chemical, and mechanical qualities of distinct solid forms can vary widely. For instance, during processing operations, partial or complete phase change may happen, leading to higher levels of crystal defects or the production of amorphous phase, both of which can be harmful to chemical stability. Consequently, the design of a manufacturing process should be founded on knowledge of the characteristics of the drug ingredient and how those characteristics interact with each unit operation.

The knowledge of the medicine, its molecular structure, prior experience, and theoretical calculations may frequently be used to forecast a drug's molecule's susceptibility to degradation to a great extent. Therefore, the formulation and procedure should be created with an understanding of the drug material to resolve or control issues with chemical or physical instability. For instance, desiccants could be incorporated into the container closing mechanism, moisture, and pH control in the formulation, or using a dry production process could all be considered when designing the product to reduce hydrolysis. An antioxidant and oxygen scavenger may be included in a formulation or container closure system to reduce oxidative deterioration. The right choice of the unit operation or ingredient(s) that inhibit phase shifts may be taken into consideration in order to prevent or control process-induced phase transitions that could have an impact on product quality. In a perfect world, the solid form and suitable excipients would be chosen to minimise or prevent deterioration and eliminate the need for further stability control techniques throughout formulation, processing, and packing.

One of the most common forms of chemical drug degradation is hydrolysis. It is the chemical breakdown of the drug which occurs when it reacts with water or moisture. Many pharmaceutical compounds contain functional groups those are the atoms which react with other atoms of the molecule by forming bonds with them. These functional groups have tendency to undergo hydrolysis causing the drug to undergo breakdown. One of the most challenges in the research area in terms of developing the stable drug is to formulate the protecting shield in the molecular structure itself to prevent the hydrolysis of the drug.

Sometimes the drug degrades into the products which may be toxic to our body. So, it is essential to know the amount of drug lost with time along with degradants formed. These degradants may be of known or unknown toxicity. However reactive intermediates formed are also known or suspected to be toxic. A product's degradation could render it aesthetically unappealing. If noticeable changes in a product's colour or odour over time, for example, they are assumed to be adulterated. Most of the drugs are stable at neutral pH values found in small intestine but are found to be unstable at pH values found in stomach. Despite of drug's stability is found in the intended formulation; the given drug should be stable at pH found in gastrointestinal tract. ^{[1] [2] [3]}

II. FACTORS AFFECTING CHEMICAL STABILITY

1. Moisture: Moisture content has a significant impact on the chemical and physical characteristics of medicinal compounds and final solid dosage forms. In two ways, moisture can impact the stability of medicinal substances. First, the uptake of water, which may be adsorbed to the crystal surface or present in stoichiometric quantities within the crystal lattice, may cause the medication to deteriorate and change in potency.

Second, excessive moisture levels may have a negative impact on how well drugs dissolve, thereby lowering their bioavailability.

Water molecules can interact with crystalline solids through a variety of ways, which can promote chemical deterioration and shorten a product's shelf life. Water molecules can function as either reactants in chemical reactions that result in hydrolysis or other bimolecular reactions or as promoters of drug degradation. A monolayer or many layers of water molecules may develop on the crystal surface in this scenario, allowing the drug molecules to dissolve there. Water molecules can be absorbed into the flaws and variously disordered regions found in pharmaceutical crystalline solids, acting as a plasticizer to increase molecular mobility and improve drug breakdown. While tightly bound water molecules are thought to have reduced activity because they are integrated into the crystal lattice to produce a stable crystal form (i.e. hydrate), loosely bound water molecules are thought to stimulate chemical processes.^[4]

- 2. Temperature:** The main factor influencing temperature is how it affects the chemical stability of medications. Higher temperatures often speed up chemical reactions by increasing molecular mobility. The Arrhenius equation, which describes the link between the rate of a reaction and temperature, is the most used formulation for analysing chemical stability and reaction:

$$k = A \exp\left(-\frac{E_a}{RT}\right)$$

where k is the rate constant, A is the pre-exponential factor or frequency factor (i.e. the likelihood of collisions between reactants, regardless of energy), T is the absolute temperature, R is the universal gas constant, and E_a is the activation energy. There is an equilibrium between the reactants and a specific collision complex, known as the activated complex, when a reaction takes place. The activation energy is the force needed to carry the reactants to the activated compound. Therefore, projections can be constructed to connect the quantity of degradation products as well as the rise of individual degradation products at the stress temperature to the long-term storage temperature under the assumption of Arrhenius kinetics and appropriate energies of activation. A temperature increase speeds up most responses. Most pharmacological compounds typically degrade with activation energies in the range of 12–24 kcal mol⁻¹^[5]
^{[6][7]}

- 3. Pharmaceutical Processing:** During the production of pharmaceuticals, mechanical and thermal stressors may cause physical and/or chemical transformations that could affect the performance and quality of the finished product. The unit operation of milling is frequently used in the manufacture of medications to minimise particle size. The size of pharmaceutical powders is frequently reduced using fluid energy, impact, or screen mills. Depending on the type of mill and the conditions of the milling, heat might range from 450 to 10. The mill chamber creates chemical stability and reaction by using mechanical energy to physically break down coarse, individual, and/or agglomerated particles. Phase transitions such polymorphic transformations, hydration, or dehydration, and partial or total amorphization may be brought on by the creation of heat and the application of mechanical energy. Crystal flaws arise and then accumulate as a result of the continuous flow of mechanical energy from the mill to the medicinal material. In this case, the milling procedure is referred to as mechanically transforming the material or activating it.

For several different pharmacological compounds, including piroxicam, naproxen, and indomethacin, milling has been found to cause amorphization. Pharmaceutical substances are prone to chemical deterioration due to the potential rise in crystal flaws. According to experimental findings, medications that are partially and wholly amorphous degrade chemically much more quickly than equivalent pharmaceuticals in crystal form. From this perspective, the analysis of the chemical breakdown of cefoxitin sodium crystals in comparison to its amorphous analogue is particularly instructive. When cefoxitin sodium is in its crystalline form, hydrolysis is the primary mechanism for degradation; the presence of water restricts the rate and degree of breakdown.^{[8] [9]}

III. WAYS TO PREVENT CHEMICAL REACTIONS

Different methods are used to increase chemical stability because there are many factors that can affect medication breakdown. Appropriate formulations can reduce chemical instability during long-term storage to a larger extent. To reduce moisture adsorption or to separate pharmacological substances that are incompatible, for instance, tablet coating technique may be used. Excipients are a class of pharmacological ingredient that can interact with the drug itself, serve as all-purpose acid-base, nucleophilic, or electrophilic catalysts, alter the dosage form's moisture content, and/or alter the pH of the microenvironment. The stability of pharmaceutical products can also be preserved by choosing the right packaging, which offers protection and compliance for a medication up until it is administered.^[10]

IV. FORMULATION-RELATED APPROACHES

Oxygen-sensitive or photosensitive chemicals need to be made more stable by removing oxygen, metal ions, and light. Antioxidants and chelating agents are frequently added in the formulation or packaging to achieve this. Antioxidants particularly react with oxygen, preventing oxidative destruction of the component of interest. The best antioxidant should be chosen, though, depending on knowledge of the oxidation process. While free-radical scavengers like butylated hydroxytoluene (BHT) are better for autoxidation, ascorbic acid might be more suitable for nucleation or electrophilic kinds of oxidative reactions. When metal ions play a significant role in the oxidation process, chelating agents like citric acid or ethylenediaminetetraacetic acid (EDTA) may be required.

V. PRODRUGS

The prodrug technique permits chemical modification to boost an active component's chemical stability. Prodrugs are chemically inert drug molecules that must undergo a chemical change within the body in order to exhibit their therapeutic or pharmacological effects. The versatile, promising prodrug approach to drug development can be applied with a range of drug administration methods and parent drug molecule compositions. Prodrugs are roughly one in ten of the drugs sold on the market today, and in 2008, a third of the newly approved low molecular weight molecules were prodrugs. Prodrugs fall into one of two categories: either carrier-linked prodrugs or bio-precursor prodrugs. A bio-reversible covalent bond connects the active molecule and the carrier in a carrier-linked prodrug. The carrier-linked prodrug experiences a biotransformation inside the body, releasing both the carrier and the active pharmacological component. Esters and amides are two common families of carrier-linked prodrugs. Bio-precursor prodrugs are created by molecularly altering the active

molecule itself and do not include a carrier or promoiety. Bio-precursor prodrugs are converted metabolically or chemically to the active medicinal ingredient through hydration, oxidation, or reduction. Comparing the prodrug to the parent active molecule, the solid-state chemical stability of the prodrug is improved. It increases the parent compound's permeability through biological membranes. ^{[11][12][13]}

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