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A REVIEW ON STABILITY OF DRUGS AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

The stability of a pharmaceutical product is a multifaceted concept that guarantees the maintenance of quality, safety, and efficacy throughout its intended shelf life. At its core, stability refers to the duration a dosage form remains within acceptable limits before it begins to degrade, which ultimately determines the product's expiration date. This degradation is governed by chemical kinetics, specifically the order of reaction, which describes how the concentration of reactants—such as the Active Pharmaceutical Ingredient (API)—influences the rate of breakdown. For instance, while zero-order reactions proceed at a rate independent of concentration, most pharmaceutical degradation follows first-order kinetics, where the rate is directly proportional to the drug's remaining concentration. These chemical processes are often driven by specific mechanisms, most notably oxidation and hydrolysis. Oxidation is considered the most significant pathway, as atmospheric oxygen can decompose substances not in their most oxidized state. Hydrolysis is equally prevalent, occurring when water performs nucleophilic attacks on labile bonds, particularly in lactam groups, esters, and amides. Beyond chemical integrity, stability is classified into several critical categories, including physical, microbiological, therapeutic, and toxicological stability. Physical stability ensures the product retains its original appearance, color, and dissolution properties, while microbiological stability prevents harmful microbial growth and maintains the efficacy of added preservatives. These characteristics are heavily influenced by environmental factors such as temperature, humidity, and light. Higher temperatures generally accelerate hydrolytic reactions, and exposure to light can cause rapid degradation in photosensitive medications, necessitating specialized packaging like amber glass bottles. Furthermore, product-related factors, such as the water content of excipients like starch or the nature of the container closure system, play a pivotal role in maintaining the API's integrity.

KEYWORDS: Drug Stability, Shelf Life, Degradation Kinetics, Rate of reaction.

INTRODUCTION

Developing a safe, effective, and high-quality pharmaceutical formulation is a complex endeavor that demands substantial scientific expertise, time, and financial investment. Once a product is manufactured, regulatory bodies and researchers closely monitor it for any subsequent alterations that could negatively affect its overall quality or render it unsafe for patient use. According to the World Health Organization (WHO), the ultimate stability of a finished pharmaceutical product relies on a combination of environmental influences such as light exposure, humidity, and ambient temperature as well as product-specific variables.[1] These product variables include the physical and chemical characteristics of the active pharmaceutical ingredient (API) and excipients, the chosen dosage form, the manufacturing techniques utilized, and the specific nature of the packaging and container closure systems.

The primary objective of conducting stability studies is to establish the product's shelf life, or expiration date, which is determined by calculating the duration a dosage form remains intact before it begins to break down.[2] Specifically, stability studies are designed to demonstrate how the quality of the API is impacted by the following:

- Environmental Stresses: Variations that occur over time due to exposure to temperature, humidity, and light.
- Lifespan Extension: Establishing and potentially increasing the documented usable period for the product.
- Degradation Insight: Expanding the scientific understanding of the API's degradation pathways, which directly affect the formulation's overall quality.

Beyond chemical and physical breakdowns, a product's stability is also significantly influenced by microbiological changes, including the proliferation of bacteria in non-sterile goods and a decline in preservative effectiveness.[3]

Consequently, providing comprehensive stability testing data is an absolute prerequisite for gaining regulatory approval for any new medication or formulation.

Fundamentals of Drug Degradation Kinetics

The rate of a chemical reaction is determined by monitoring how the concentrations of reactants or products change over a specific period of time. This relationship is mathematically expressed through the general reaction formula:

$$\mathbf{aA + bB \rightarrow P}$$

In this equation, A and B represent the reactants, P represents the resulting product, and a and b denote the number of molecules involved. The reaction rate is defined by the derivatives -d[A]/dt, -d[B]/dt, and d[P]/dt, where the brackets [A], [B], and [P] indicate molar concentrations and t represents time. A negative sign is used to signify a decrease in the concentration of reactants as the reaction progresses. These rates are typically measured in concentration-over-time units, including Ms^{-1}, Mh^{-1}, or mg/ml/h.

Reaction Order and Molecularity

The "order" of a reaction is determined by the total number of molecules participating in the process (the sum of a and b). A practical example of these principles is the hydrolysis of methyl salicylate in an aqueous solution, which produces salicylic acid and methanol. While this specific reaction is considered second-order overall, it is technically first-order regarding both the methyl salicylate and the water.[4]

Reactions are further classified based on their molecularity:

- Unimolecular Reactions: These involve only a single reactant molecule. An example is the radioactive decay of an atom, where particles are emitted from a single source.
- Bimolecular Reactions: These occur when two molecules react to create one or more products. The hydrolysis of an ester serves as a standard illustration of a bimolecular process.[5]
- Termolecular Reactions: These are rare occurrences where three separate molecules must collide simultaneously to react.

Zero-Order and Pseudo-Zero-Order Reactions

A zero-order reaction is characterized by a degradation rate that remains constant regardless of the reactant's concentration. This relationship is mathematically represented as:

$$- \frac{d[A]}{dt} = k_o$$

In this equation, k_0 represents the zero-order rate constant. While "pure" zero-order reactions are relatively rare in chemistry, they occur frequently in pharmaceutical science, particularly within drug suspensions.[6]

Pseudo-Zero-Order Kinetics in Suspensions

In a suspension, the drug exists in both solid and dissolved states. As the dissolved drug molecules degrade according to first-order kinetics, additional solid drug dissolves to replace them, thereby maintaining a constant concentration of the dissolved drug ([A]). This phenomenon is known as an apparent or pseudo-zero-order reaction.[7] The rate equation for this process is expressed as:

$$- \frac{d[A]}{dt} = k_1[A] = K_o$$

Here, k_1 is the first-order rate constant and [A] is the steady concentration of the dissolved medication.

Calculating the Rate Constant

By rearranging the rate equations, we can determine the concentration of the drug at any given time (t) using the following formula:

$$[A] = [A]_0 - k_0 t$$

In this linear equation, $[A]_0$ signifies the total drug concentration at the initial time (time zero). When the evolution of [A] is plotted against time, the resulting straight line allows researchers to calculate the rate constant from the slope.[8]

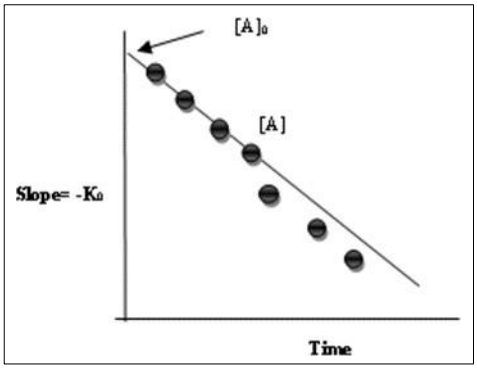

Figure 1: Zero-order plot of [A] versus time. $[A]_0$ is the y- intercept.

Stages of Stability Studies

Stability study is performed at various stages of the drug development process. There are 6 different stages:

Stage 1: Early stage, i.e., stress and accelerated testing with drug substances.

Stage 2: Stability on pre-formulation batches.

Stage 3: stress test done on scale-up batches.

Stage 4: Accelerated and long-term testing for registration purposes.

Stage 5: Enduring stability testing.

Stage 6: follow up studies.

Importance of Stability Studies

The significance of stability testing in pharmaceutical development cannot be overstated, as it serves as a critical safeguard for both patient health and manufacturer integrity. Primarily, the degradation of an active pharmaceutical ingredient (API) leads to a reduction in drug concentration within the dosage form, which can result in sub-therapeutic dosing and a failure to achieve the intended clinical outcome. Furthermore, the chemical breakdown of a drug is not merely a loss of potency; it can lead to the formation of harmful degradation products that increase the risk of toxicity.[9,10] Beyond chemical changes, instability often manifests as alterations in the physical appearance of the medication. By applying the principles of chemical kinetics, scientists can accurately predict these stability trends over time. Ultimately, these studies are essential for protecting a manufacturer's brand reputation, providing the necessary assurance that a product will remain safe, effective, and functionally intact for as long as it is available on the commercial market.[11,12]

Objectives of Stability Studies

The primary objective of stability testing is to provide a comprehensive, evidence-based understanding of how a pharmaceutical product's quality evolves under the continuous influence of environmental variables such as temperature, humidity, and light. Crucially, these findings guide the selection of optimal formulations and the most effective container closure systems, ensuring the drug remains protected throughout its lifecycle.[13] Moreover, this data is instrumental in defining accurate storage requirements and substantiating the declared shelf life, providing a scientific basis for the product's expiration date.

Beyond initial development, stability testing serves as a vital quality control mechanism to verify that any subsequent modifications to the manufacturing process or formulation do not inadvertently compromise the product's integrity. Accelerated stability testing, in particular, plays a strategic role by enabling researchers to predict a drug's long-term stability profile through exposure to high-stress conditions. This allows for a reliable estimation of shelf life before the product is officially launched into the market, ensuring that safety and efficacy are guaranteed from day one.[14]

Types of Drug Stability

- **Physical Stability**

This implies that the drug product remains unchanged throughout its shelf life with no alteration in its physical properties that include its appearance, organoleptic properties, hardness, brittleness, and particle size. This stability is essential to ensure drug efficacy, safety and should be maintained during all the stages of the drug product formulation, manufacturing, packaging, storage and carefully monitored and evaluated.[15]

❖ **Chemical Stability**

This refers to the lack of any alteration in the chemical composition of the drug formulation. The chemical stability of drug is of great importance since it becomes less efficient as it undergoes degradation via chemical reactions such as hydrolysis, oxidation, and photolysis. Such results can lead to decrease in the active ingredient concentrations of the drug as well as the formation of undesired by-products. This, in turn, can cause the drug to have lower or no therapeutic effect or even to contain a harmful or toxic substance. The chemical degradation can also happen to preservatives and excipients included in the drug products as well as their packages leading to the same unwanted chemical instability.[16]

It has been noticed that the solid dosage forms are more stable than liquid dosage forms since they undergo slower chemical degradation.

❖ **Microbiological Stability**

This refers to the sterility of the drug formulation and lack of contamination by different types of microorganisms (e.g., fungi and bacteria). Naturally, microbial growth in a drug product can lead to severe effects. Because of their high moisture content, solutions and water-based semi-solids drugs are more liable to suffer from microbial contamination.[17] This makes the addition of antimicrobial preservatives to those drug dosage forms essential to ensure their sterility. To prevent the contamination of the formulation during the storage, it is preferable to use single dose container.

Guidelines for 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 primary purpose was to bring in uniformity in testing from manufacturer to manufacturer. These guidelines include fundamental issues related to stability, the stability data requirements for application dossier and the steps for their execution. Such guidelines were initially issued in the 1980s.

These were later harmonized (made uniform) in the International Council for Harmonization (ICH) in order to overcome the bottleneck to market and register the products in other countries. The ICH was a consortium formed with inputs from both regulatory and industry from the European Commission, Japan, USA and various guidelines for drug substance and drug product came into existence regarding their quality, safety, and efficacy. These guidelines are called as quality, safety, efficacy and multidisciplinary (also called as Q, S, E, and M) guidelines. The World Health Organization (WHO) 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. Further, different test condition and requirements have been given in the guidance documents for active pharmaceutical ingredients, drug products or formulations and excipients. The codes and titles covered under ICH guidance have been outlined in Table 1.

Series of guidelines related to stability testing has also been issued by the Committee for Proprietary Medicinal Products (CPMP) under the European Agency for the Evaluation of Medicinal Products (EMEA) to assist those seeking marketing authorization for medicinal products in European Union.

Table 1: Codes and titles used in ICH guidelines.

ICH CODE	GUIDELINE TITLES
Q1A	Stability testing of New Drug Substances and Products (Second Revision)
Q1B	Stability testing : Photostability Testing of New Drug Substances and Products
Q1C	Stability testing of New Dosage Forms
Q1D	Bracketing and Matrixing Designs for stability testing of Drug Substances and Products
Q1E	Evaluation of stability data
Q1F	Stability data package for Registration Applications in Climatic Zones III and IV
Q5C	Stability testing of Biotechnological/Biological Products

Drug Shelf Life

The shelf life, or expiration date, of a pharmaceutical product represents the critical time interval during which its essential characteristics specifically its potency, purity, and overall strength—are guaranteed to stay within rigorous, pre-approved regulatory specifications. It is a measure of the product's longevity from the moment of manufacture until it is no longer considered safe or effective for use.

Establishing an accurate shelf life is a complex task because the actual stability of a drug is not a fixed constant; rather, it behaves as a random variable due to inherent batch-to-batch variations. Even when produced under similar conditions, different batches may degrade at slightly different rates depending on a multitude of factors, including the drug's intrinsic chemical stability, the precise storage temperature, ambient humidity levels, exposure to light, and the quality of the container closure system.[18]

Consequently, the fundamental objective of any stability study is to analyze these variables and establish a conservative shelf life that can be reliably applied to all future batches produced under the same manufacturing conditions. This ensures that every unit of the medication reaching the consumer will maintain its therapeutic integrity throughout the duration of its stated lifespan.

Estimation of Shelf Life

The goal of shelf life estimation is to predict the time when the drug stability is no longer within the approved specification limit. Estimation of the expiration date of every newly released drug product in the market is one of the essential stages required by law to prove its safety. The shelf life is determined from the data obtained from the long-term storage studies. The data is first linearized, and test for goodness of fit is applied.[19] The linearized data is then analyzed to see that the slope and the intercepts are matching. For determination of the significance of the difference in case of slope or intercept, statistical tests like t-test should be applied. The data is available in the form of only five data points, i.e., 0, 3, 6, 9 and 12 months, either pooled from the three batches or from the three individual batches if they are not fit for pooling. In case data is not fit for pooling, stability estimates are to be made on the worst batch. The shelf life/expiry date is determined from the regression line of this five- point data based on a calculation of 95% one- sided confidence limit. For reading the expiry date, 90% drug concentration is considered as the lowest specification limit and the point where the extension line cuts the 95% confidence limit line is taken as an expiry date. Because shelf life derived from the intersection of the lower 90% confidence bound and 90% potency value has a 95% confidence level, therefore there is only a 5% chance that our estimate of the shelf life will be too high. For new drugs, it is a general practice to grant only two-year expiry initially, which is based on satisfactory one-year long- term and 6 months accelerated stability data. The expiry date for third and later years is allowed only on production of real-time data for the subsequent year.[20] Most pharmaceutical products are characterized by only one shelf life. However, in

some cases a product may be, e.g. a freeze-dried (lyophilized) protein product may have only 1 shelf life, say 2 years and for the product stored in the dry condition have 2 shelf life, say 2 days, for the product when it has been reconstituted with the appropriate vehicle and is ready for injection.

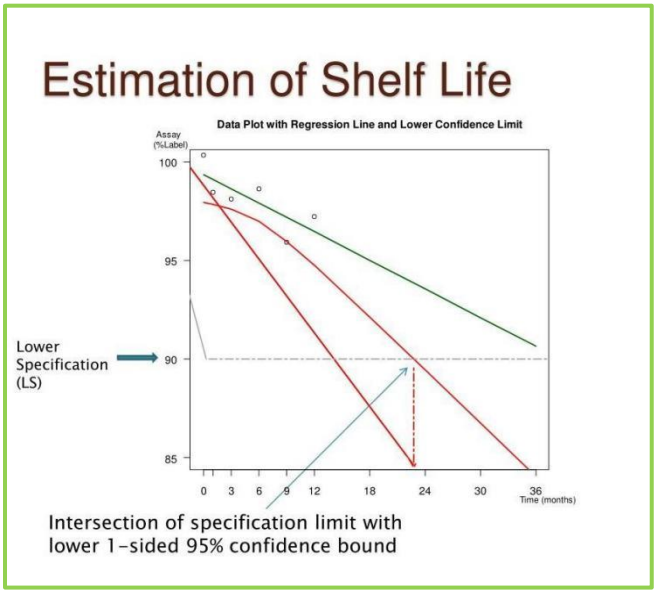

Figure 2: Estimation of shelf life.

The expiration date period must be obtained through a rigorous experimental analysis with several batches of the product. The analytical procedures and conclusions derived from the analysis have to be carefully monitored and well supervised.

In order to predict the shelf life, accelerated studies are used for estimating the rate of chemical and physical degradation. For this, the order of reaction has to be determined. For example, a zero order equation represents a linear relationship between the drug characteristic and time, whereas in the first order the logarithmic transformation of the drug characteristic which is a linear function of time. After the order of the reaction is determined, the Arrhenius equation is then applied to decide the relationship between the rate of degradation and the temperature, as Arrhenius equation describes the linear relationship between log (degradation) and reciprocal of the absolute temperature.[21]

Drug Dosage Forms and Stability

The stability of a pharmaceutical product encompasses its physical, chemical, microbiological, therapeutic, and toxicological integrity, though these specific requirements vary significantly across different dosage forms. To ensure patient safety and therapeutic efficacy, FDA guidelines mandate specialized stability testing tailored to each unique formulation type to maintain its specific attributes throughout its shelf life.

Dosage Form Specificity and Physical Integrity

For solid dosage forms, essential characteristics like hardness, brittleness, and dissolution rates must be strictly maintained. These properties are monitored via specialized tests during the manufacturing process to verify that the drug's essential qualities remain intact.

- Tablet Hardness: This is a fundamental physical property used to measure tablet strength.
- Mechanical Resistance: Evaluated during formulation, hardness ensures the product remains stable and resists

breaking during packaging, shipping, dispensing, or consumer handling.

- Diametrical Compression Test: In the pharmaceutical industry, hardness is defined as the force needed to fracture a tablet. This is measured by placing the tablet between two anvils and increasing pressure until it breaks; the force recorded at the point of fracture is the hardness value.

Strength, Potency, and Regulatory Requirements

Shelf life is primarily determined by a drug's primary characteristics, most notably its strength.

- Defining Strength: This refers to either the concentration of the active drug substance or its therapeutic potency.
- Quantitative Measures: According to regulatory guidelines, strength is a quantitative assessment of the active ingredients as well as other critical components like preservatives and alcohol content.
- Combination Products: If a drug is intended to be mixed with another—such as in parenteral or aerosol applications stability studies must be performed on the final mixture rather than just the individual components.

Influencing Factors

The stability of any specific dosage form is highly sensitive to external conditions and materials.

- Storage Environment: Factors such as temperature, humidity, light, and air exposure can drastically alter a product's stability profile.
- Packaging Materials: The type of container used, such as high-density polyethylene (HDPE), plays a crucial role in protecting the drug's characteristics over time.[22]

Table 2: Drug characteristics for different dosage forms.

Dosage form	Drug Characteristic
Tablets	Appearance, friability, hardness, color, odor, moisture, strength, dissolution.
Capsules	Strength, moisture, color, appearance, shape, brittleness, dissolution.
Emulsions	Appearance, color, odor, pH, viscosity, strength.
Oral solution and suspension	Appearance, strength, pH, color, odor, redispersibility, dissolution, clarity.
Oral powder	Appearance, pH, dispersibility, strength.
MDI aerosols	Strength, delivered dose per actuation, number of metered doses, color, clarity, particle size, loss of propellant, pressure, valve corrosion, spray pattern.
Topical and ophthalmic preparations	Appearance, clarity, color, homogeneity, odor, pH, re- suspendibility, consistency, particle size distribution, strength, weight loss.
Small volume parenterals and large volume parenterals	Strength, appearance, colour, clarity, particulate matter, sterility, pyrogenicity, Ph.
Suppositories	Strength, softening range, appearance, dissolution.

Factors Affecting Drug Stability

To keep medications stable and effective, it is crucial to understand their unique chemical structures and how they react to various physical, chemical, microbiological, and environmental conditions. This knowledge allows us to establish the best storage and transportation methods to prevent the drug from losing its potency for instance, knowing exactly how temperature impacts a drug ensures it is kept safe during shipping.

Ultimately, drug stability is compromised when environmental elements (like heat, moisture, light, and oxygen) or product-specific variables (such as formulation ingredients, manufacturing processes, and packaging) alter the medication's physical and chemical makeup. These alterations speed up the drug's breakdown. While the exact rate of degradation depends heavily on the specific dosage form, similar types of formulations are generally affected by these factors in comparable ways.[23]

Table 3: Factors Affecting Drug Stability.

Category	Specific Factors	Impact on Drug Product
Inherent Characteristics	Drug structure; physical, chemical, microbiological, and toxicological profile	Determines the necessary storage conditions, transportation modes, and precautions needed to maintain efficacy.
Environmental Factors	Heat (temperature), moisture, light, oxygen	Alters physicochemical properties, which can expedite the degradation of the drug.
Product-Related Factors	Formulation composition, manufacturing process, packaging	Influences overall stability; specific degradation rates vary depending on the dosage form.

Factors that commonly affect the stability of various dosage forms are summarized below:

A. Liquid Dosage Form

The stability of liquid medications is heavily dependent on a variety of chemical, physical, and environmental variables. Liquid dosage forms stability is influenced by the following factors:

- pH Levels: The acidity or alkalinity of a solution directly dictates the rate of hydrolysis. Strong acids and bases can cause rapid degradation. Because weakly acidic or basic drugs decompose much faster when they are in an ionized state, pinpointing the exact pH where the formulation is most stable is a critical step in development.
- Temperature: Elevated temperatures typically accelerate the hydrolytic breakdown of drugs in solution. Certain formulations, such as insulin and injectable penicillin, are unstable even at room temperature and strictly require continuous cold storage to remain viable.
- Ionic Strength: While electrolytes are frequently added to liquid formulations to achieve the correct tonicity, these dissolved ions can inadvertently alter the chemical stability of the drug.
- Solvent Selection: For some medications, substituting water with non-aqueous solvents like alcohol or propylene glycol successfully prevents hydrolysis. However, this approach is not universal; for certain drugs, changing the solvent can actually speed up the degradation process.
- Oxygen Exposure: Oxygen drives oxidative degradation in sensitive drugs. This reaction can be minimized by optimizing packaging to reduce the empty headspace above the liquid, or by flushing the container with inert gases like nitrogen or carbon dioxide to displace the oxygen entirely.
- Surfactants: The addition of non-ionic, cationic, or anionic surfactants can improve stability by forming protective micelles around the drug particles. These micellar structures act as a physical shield, blocking hydrolytic agents (like hydroxyl ions) from reaching the active pharmaceutical ingredient and thereby slowing down hydrolysis.

Table 4: Factors Affecting Liquid Dosage Form Stability.

Factor	Mechanism of Impact	Preventive / Formulation Strategy
pH	Dictates hydrolysis rate; ionized forms of weakly acidic/basic drugs degrade more rapidly.	Formulate the solution at the specific pH level that offers maximum stability.
Temperature	Heat accelerates the hydrolytic breakdown of dissolved drugs.	Implement cold storage conditions for temperature-sensitive medications.
Ionic Strength	Electrolytes added for tonicity adjustment can chemically destabilize the solution.	Carefully evaluate and control the concentration of added electrolytes.
Solvent	Aqueous environments naturally promote hydrolysis in certain active ingredients.	Replace water with solvents like alcohol or propylene glycol, provided it does not cause adverse degradation.
Oxygen	Drives the oxidation of the drug product.	Minimize packaging headspace; replace oxygen with inert gases (nitrogen or carbon dioxide).
Surfactants	Can trap drug particles within micelles, shielding them from hydrolytic groups (e.g., OH^-).	Add appropriate surfactants to physically block degradation and decrease the hydrolysis rate.

B. Solid Dosage Form

The integrity of solid medications is largely governed by how they interact with their immediate environment and the materials they are blended with:

- Moisture Exposure: When water-soluble solids encounter humidity, they can behave like liquid dosage forms, triggering chemical breakdowns such as the hydrolytic cleavage of ester or amide bonds.[24] Controlling humidity during production and utilizing moisture-resistant packaging is vital to preventing this.
- Role of Excipients: A drug's stability is often linked to the moisture levels inherent in its inactive ingredients. Excipients like starch, povidone, and magnesium trisilicate naturally hold higher water content, which can facilitate degradation. Additionally, direct chemical reactions between the drug and its excipients can further compromise the formulation.
- Temperature Effects: Heat can physically alter a product by causing components to melt or shift into different polymorphic forms. It also plays a secondary role by fluctuating the relative humidity within a container, which indirectly speeds up chemical decomposition.
- Light and Oxygen: Many active ingredients are sensitive to photodecomposition or oxidation. Because water itself can be a carrier for oxygen, maintaining bone-dry storage conditions is a primary defense against both oxidative and hydrolytic damage.

Table 5: Factors Affecting Solid Dosage Form Stability.

Factor	Mechanism of Impact	Preventive / Formulation Strategy
Moisture	Induces hydrolytic cleavage of chemical bonds (esters/amides) in water-soluble drugs.	Strict humidity control during manufacturing; use of desiccants and specialized packaging.
Excipients	High-moisture excipients (e.g., starch) provide water for degradation; possible chemical incompatibility.	Select low-moisture excipients; perform compatibility studies to ensure ingredients don't react.
Temperature	Causes physical changes like melting or polymorphism; alters local relative humidity.	Maintain stable, cool storage temperatures to prevent physical and indirect chemical changes.
Light & Oxygen	Triggers photolysis or oxidative pathways that break down the drug's molecular structure.	Use opaque or amber-colored containers; ensure dry storage to limit oxygen exposure via moisture.

Mechanism of Drug Degradation

Drug products of different dosage forms such as liquid, solid, and Semisolid dosage forms can usually undergo some kind of chemical degradation or breakdown with time. Such change in the dosage form may change either the physical drug appearance such as discoloration or its chemical structure with a consequent difference in its potency or safety.

Several modes of degradation have been identified include;

- Hydrolysis
- Oxidation
- Isomerization
- Photochemical decomposition
- Polymerization.

The mode of degradation that will take place is determined by the type of the chemical groups that are present in the drug molecules. Some drugs can undergo more than one mode of degradation.

❖ **Oxidation**

The most significant drug breakdown pathway is oxidation. Oxygen is present everywhere in the atmosphere and exposure to oxygen will decompose drug substance that are not in their most oxidized state through auto- oxidation.

There are two main categories of oxidative degradation of pharmaceuticals: reaction with molecular oxygen and reaction with other oxidizing agents present in the formulation. Electrons, oxygen, or hydrogen are transferred from one substance to another during oxidation and reduction reactions.[25] oxidation in tablet dosage form relies on the tablet hardness or on the presence of coating as either of these might impact the oxygen penetration rate.

❖ **Hydrolysis**

Hydrolytic reactions are among the most common pathway for drug breakdown. The medication in solution is subjected to nucleophilic attacks by water on labile bonds during hydrolysis events. The reactions involving lactam groups are fastest and are followed by those involving esters, amides and imides in that order and follow first order. These reactions are catalyzed by presence of divalent metal ion, ionic hydrolysis, heat, light solution, and high drug concentrations.

❖ **Microbial Instability**

Product contamination can result in significant product damage or, in certain cases, no damage at all. For instance, mould spores may exist in a latent state and never create spoilage or affect the patient who takes the medication. Salmonella can, however, infiltrate a drug undetected and yet pose a major health risk to those who take it.

❖ **Temperature**

Temperature has a significant impact on a wide range of processes, and an increase in temperature typically speeds up these reactions.

❖ **pH**

Acidic and alkaline pH levels affect how quickly most medications break down. A pH increase or drop might harm the formulation of a medicinal product. So, during the production of formulation concern should be taken regarding the pH correction.

❖ **Stability Testing**

Stability tests are a standard procedure used in the various stages of medicinal substance and product development. Accelerated stability tests are used in the early phases to assess the kind of deteriorated goods discovered after extended storage. The primary goals of the pharmaceutical stability test are to make sure that goods are fit for consumption until the last pharmaceutical unit is consumed and remain on the market for the duration of their acceptable fitness or quality.

Importance of Stability Testing

- The breakdown of active medications may result in the formation of toxic compounds.
- The breakdown of active medications may result in the formation of toxic compounds.
- Ensuring that the brand is appropriate for usage for the duration that it is on the market and that it has all functionally acceptable features to preserve the manufacturer's good name.
- To confirm that no adjustments to the manufacturing process or formulation strategy have been made that would

have a detrimental effect on product stability.

- It provides a database that might be used for selecting excipients, formulations, and container closing strategies for growing current products.
- Gaining knowledge of how API degradation may impact the pharmaceutical product's quality.

Different ways to increase Drug Stability

- pH adjustment: The stability of a medication solution can be impacted by pH changes. In certain circumstances, raising the pH can increase stability, whereas in other circumstances, lowering the pH may be required.
- Use of antioxidants: By scavenging free radicals and reactive oxygen species that might lead to oxidation, antioxidants can aid in preventing the breakdown of medications.
- Use of stabilizers: To aid stop deterioration, stabilizers can be added to medicinal formulations. These may contain ingredients that can aid in stabilizing the medication molecule, such as carbohydrates, amino acids, or proteins.
- Freeze-drying: A medication solution is frozen during the freeze-drying procedure, and it is subsequently dried under vacuum. By eliminating water, this can assist to stabilize the medicine by decreasing the chance of deterioration.
- Packaging: The stability of a medicine can also be increased with proper packaging. For instance, keeping a medicine in a container that is sealed and has a desiccant inside can assist to stop moisture from getting in and causing deterioration.
- Chemical modification: In some circumstances, a drug's stability can be increased by changing its chemical composition. This might entail altering the formulation to make it more stable or adding functional groups that can stop deterioration.

CONCLUSION

The conclusion of this review article emphasizes that pharmaceutical stability is a foundational parameter that must be rigorously calculated and determined during the formulation process, as the clinical action of a drug is fundamentally dependent on its stability over time. This comprehensive review has consolidated essential knowledge and methodologies designed to address and mitigate drug stability challenges, filling a critical knowledge gap by incorporating contemporary thoughts and methods in the field. To ensure that a drug remains fit for consumption until the final unit is used, stability testing must serve as a standard procedure throughout all stages of medicinal substance and product development. By monitoring physical, chemical, microbiological, therapeutic, and toxicological characteristics, manufacturers can prevent under-medication and the formation of toxic degradation products, thereby safeguarding patient safety.

Furthermore, the integration of kinetic principles, such as zero- and first-order reaction rates, allows researchers to predict degradation patterns and establish accurate shelf lives. The use of specialized testing including real-time, accelerated, retained sample, and cyclic temperature stress testing provides a robust database for selecting the most appropriate excipients, formulations, and container closure systems. Ultimately, adhering to these rigorous stability standards and ICH climatic zone guidelines is the only definitive way to confirm that a drug meets the requirements for regulatory acceptance and market fitness. As the pharmaceutical industry evolves, this field requires continued attention to ensure that every manufactured batch maintains its intended strength and purity throughout its commercial lifespan.

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