



(REVIEW ARTICLE)



A review on drug stability

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International Journal of Science and Research Archive, 2023, 09(01), 474–485

Publication history: Received on 19 April 2023; revised on 05 June 2023; accepted on 07 June 2023

Article DOI: <https://doi.org/10.30574/ijrsra.2023.9.1.0424>

Abstract

Stability is crucial to the process of developing new drugs. Stability studies are regarded as a must for the acceptance and approval of any pharmaceutical product since they guarantee the stability of product quality, safety, and efficacy during the shelf life. This article will reduce the knowledge gap on the most important aspect for researcher or a developer who is developing a formulation by providing a complete information about drug stability, principle of drug degradation, Force degradation studies, Stability studies and their Classification, Factor Affecting Stability of Drug, Mechanism of Drug Degradation, Stability Testing, and Different ways to increase Drug Stability. As the different sources provided in this article which are mentioned above will resolve any problem regarding the stability of drug and by resolving the problem, it will influence a science oriented or research-oriented person to develop any formulation by providing the complete knowledge about this particulate topic.

Keyword: Drug Stability; Degradation; Rate of reaction; Stability guideline; Stability Testing

1. Introduction

Pharmaceutical formulation efficacy, quality, and safety require a complicated process collection that takes a lot of time, money, and scientific knowledge to develop[1]. Researchers and regulators in the pharmaceutical industry are interested in any change that takes place in a pharmaceutical product after it has been prepared and that has a negative impact on how fit a patient is to use it or on the product's quality[2].WHO (World Health Organization) states that environmental factors like ambient temperature, humidity, and light as well as product-related factors like the chemical and physical properties of the active ingredient and pharmaceutical excipient, the dosage form and its composition, the manufacturing process, the nature of the container closure system, and the properties of packaging material all affect how stable finished pharmaceutical products are[3].

Determining the drug product's shelf life is the goal of stability studies. The term "stability" refers to the amount of time that can pass before a dosage form starts to degrade. The shelf life (expiration date) of a product is calculated based on this period. The stability's goal is to demonstrate how the drug substance's (API) quality:

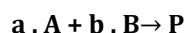
- Variations occur over time as a result of several environmental conditions, including temperature, humidity, and light.
- The stability of drug increases the established period for product.
- to increase knowledge of an API's degradation process, which may have an impact on pharma product quality [4].

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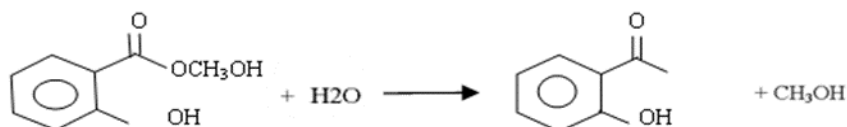
Microbiological modifications, such as the expansion of bacteria in non-sterile goods and modifications in preservative effectiveness, can also have an impact on a pharmaceutical product's stability. Additionally, the results of the stability testing are a crucial need for regulatory approval of any medicine or formulation[5][6].

1.1. Principle of Drug Degradation:[7]

The rate at which the reactants' or products' concentrations vary can be used to determine the rate of reaction:



-where A and B are the reactants, P is the product, and a and b are the molecular counts. The rate is written as $2d[A]/dt$, $2d[B]/dt$, and $2d[P]/dt$, where [A], [B], and [P] stand for concentrations and t is the time. A decrease in concentration is indicated by the negative sign. The rate is expressed in concentration-by-time units, such as $M s^{-1}$, $M h^{-1}$, or $mg ml^{-1} h^{-1}$. The total number of molecules involved in the reaction, or a plus b, determines its order. For instance, the chemical equation is followed when methyl salicylate is hydrolyzed in aqueous solution:



where salicylic acid and methanol are the end products and methyl salicylate and water are the reactants. The reaction is second order overall, but it is first order with respect to methyl salicylate and first order regarding water. A reaction that only involves one reactant molecule is referred to as unimolecular, one that involves two molecules as bimolecular, and one that involves three molecules as termolecular. Unimolecular reactions include the radioactive decay of an atom, which results in the emission of particles from the atom. Chemical reactions involving two molecules reacting to produce a product or products are known as bimolecular reactions. Ester hydrolysis is an illustration of a bimolecular process. Rare are termolecular reactions, which occur when three molecules collide simultaneously and react.

1.2. Zero - Order Reaction

Any reaction whose rate is un-affected by the concentration of the reactant is said to be zero-order:

(1.1)

$$-\frac{d[A]}{dt} = k_0$$

where k_0 is the reaction's zero-order rate constant. Although "pure" zero-order reactions are not very common, they are frequently seen in pharmaceutical products like drug suspensions. These reactions are known as apparent or pseudo-zero-order reactions. These circumstances cause the drug to decay according to first-order kinetics, yet the solid drug in the solution dissolves and keeps the concentration of dissolved drug ([A]) constant:

(1.2)

$$-\frac{d[A]}{dt} = k_1[A] = k_0$$

where [A] is the concentration of dissolved medication and k_1 is the first-order rate constant. Rearrangement of Eq. 1.1 and 1.2

(1.3)

$$[A] = [A]_0 - K_0 t$$

The total drug concentration at time zero is $[A]_0$. Plotting the evolution of [A] over time allows one to determine the rate constant.

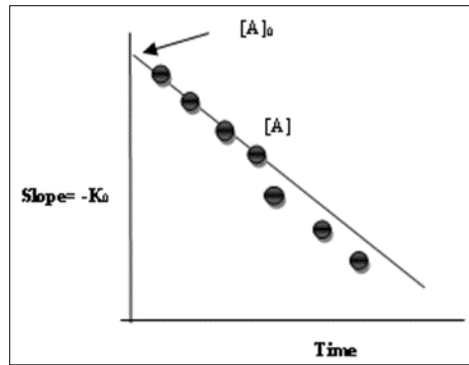


Figure 1 Zero-order plot of $[A]$ versus time . $[A]_0$ is the y- intercept.

1.3. First- Order Reaction

The first- order reactions rate is directly proportional to the reactant concentration.

(1.4)



(1.5)

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

where $[A]$ is the reactant (i.e., drug) concentration and k_1 is the first-order rate constant. Drug disappearance rates are equivalent to product creation rates.

(1.6)

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

Where $[A] = [p]$ at t_g . By rearrangement of Eq. 1.5 and integration from $t=0$ ($[A]_0$) to time t ($[A]$) gives:

(1.7)

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

(1.8)

$$-\int_{[A]}^{[A]} \frac{d[A]}{[A]} = \int_0^t k_1 dt$$

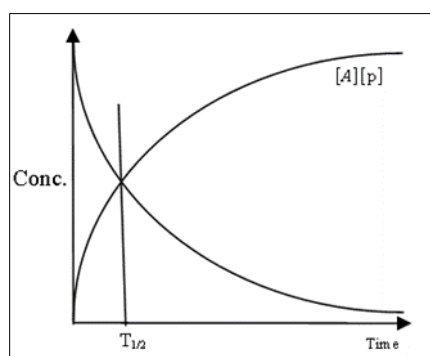


Figure 2 Plot of $[A]$ and $[p]$ versus time

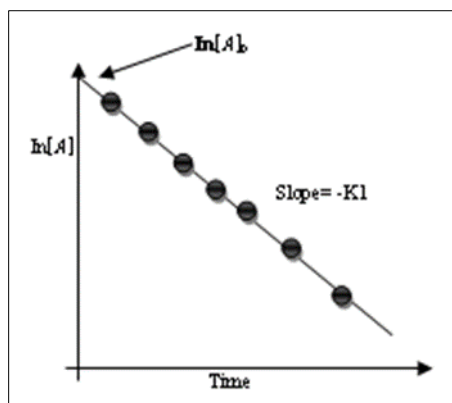


Figure 3 First-order plot of $\ln[A]$ versus time. $\ln [A]_0$ is the y- intercept.

$$[A] = [A]_0 e^{-k_1 t} \quad (1.9)$$

$$\ln[A] = \ln[A]_0 - K_1 t \quad (2.0)$$

Eq. 2.0 describes a linear plot (Fig. 1.1)

Eq. 2.0 can also be written as:

$$\log[A] = \log[A]_0 - K_1 t / 2.303 \quad (2.1)$$

$\ln[A]$ 5 2.303 $\log[A]$, for example. Older textbooks and certain drug regulatory organizations typically utilize the common logarithm (\log), which is based on 10 and is also known as the decimal logarithm, to discuss drug degradation kinetics. However, we avoid the conversion factor of 2.303 in this book by primarily using the natural logarithm (\ln) that is based on e (52.7183...).

$T_{1/2}$, T_{90} , and T_{95} for first-order reactions are unaffected by the initial drug concentration. For instance, $t_{1/2}$ (the time it takes $[A]_0$ to reach $1/2[A]_0$) may be computed as follows using Eq. 2.0:

$$\ln(1/2[A]_0) = \ln[A]_0 - K_1 t_{1/2} \quad (2.2)$$

Rearranging Eq. 2.2 give: (2.3)

$$t_{1/2} = \frac{\ln 2}{k_1} = \frac{0.693}{k_1}$$

Likewise, the following equations for t_{90} and t_{95} can be obtained:

(2.4)

$$t_{90} = \frac{0.105}{k_1}$$

(2.5)

$$t_{95} = \frac{0.0513}{k_1}$$

1.4. Second-Order Reaction

The second-order reaction is directly proportional to the concentration of two reactants:



(2.7)

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k_2[A][B]$$

Where K_2 is the constant for second-order and $[A]$ and $[B]$ are the reactant concentrations :

(2.8)

$$-\int_{[A]_0}^{[A]} \frac{d[A]}{[A][B]} = \int_0^t k_2 dt$$

Integration of Eq. 2.8 given:

(2.9)

$$\frac{1}{[A]_0 - [B]} \cdot \left[\ln \frac{[B]_0[A]}{[A]_0[B]} \right] = k_2 t$$

Eq. 2.9 can be rearranged to:

(3.0)

$$\frac{1}{t([A]_0 - [B])} \cdot \left[\ln \frac{[B]_0[A]}{[A]_0[B]} \right] = k_2 t$$

To produce a simple form of second-order reaction, when $[A] = [B]$ or if two molecules of A react:(

(3.1)

$$-\frac{d[A]}{dt} = K_2[A]^2$$

(3.2)

$$-\frac{d[A]}{[A]^2} = k_2 dt$$

(3.3)

$$-\int_{[A]_0}^{[A]} \frac{d[A]}{[A]^2} = \int_0^t k_2 dt$$

(3.4)

$$\frac{1}{[A]} - \frac{1}{[A]_0} = k_2 t$$

(3.5)

$$t = \frac{1}{k_2} \left(\frac{1}{[A]} - \frac{1}{[A]_0} \right)$$

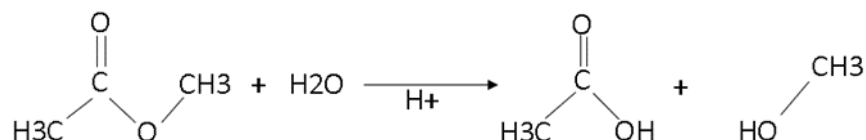
According to 3.5 the half-life is:

(3.6)

$$t_{1/2} = \frac{1}{k_2[A]_0}$$

1.5. Third-Order Reaction

The example of third-order reaction is acid catalyzed hydrolysis of an ester-



(3.7)

$$-\frac{d[\text{Ester}]}{dt} = K_3[\text{Ester}][\text{H}^+][\text{H}_2\text{O}]$$

The product of k_3 and $[\text{H}_2\text{O}]$ is constant and equal to k_2 (i.e., the second-order rate constant) because the water concentration in aqueous solutions is basically constant ($[\text{H}_2\text{O}] \approx 55.5 \text{ M}$):

(3.8)

$$-\frac{d[\text{L}]}{dt} = K_3[\text{Ester}][\text{H}^+][\text{H}_2\text{O}] = K_2[\text{Ester}][\text{H}^+]$$

Here, k_2 represents the ester hydrolysis's apparent (or fictitious) second-order rate constant.

1.6. Force degradation studies

When developing stability indicating methods, particularly when there is little information available about degradation products, force degradation studies are defined as the studies in which stress conditions or accelerated conditions are provided to the drug in bulk or product. A second goal of these studies is to learn more about the degradation pathways and degradation products that may affect during storage conditions [8][9][10].

Forced degradation studies aid in the development, manufacture, and packaging of pharmaceuticals where understanding chemical behavior may be utilized to enhance medicinal product [11][12][13].

1.7. Stability studies and their Classification

The objective of the stability study is to determine the self-life of the product. The parameters for acceptable levels of physical, chemical, microbiological, therapeutic, and toxicological stability tests are specified in a thorough pharmacopeial protocol (USP).

1.8. Physical stability

The original physical characteristics, such as shape, color, ability to dissolve, and taste. Suspend ability are still present. Physical stability is crucial for the efficacy and safety of the product since it may have an impact on uniformity and release rate.

1.9. Chemical stability

It is a propensity to resist change or degradation brought on by reactions caused by air, the environment, temperature, etc.

1.10. Microbiological stability

The medications' propensity for resistance to sterility and microbial growth is referred to as their microbiological stability. Within certain parameters, the antimicrobial agents used in the preparation retain their efficacy. The sterile medicinal product may be dangerously unstable microbiologically.

1.11. Therapeutic stability

The medicinal result (Drug Action) is unaffected.

1.12. Toxicological stability

The toxicity has not significantly increased due to toxicological stability[14][15].

1.13. Objective of Stability Studies

Due to the decrease of the medicine's dose form as a result of product instability of the active substance, undermedication may result.

The medicine or product may produce harmful by products when it breaks down.

The medication has the potential to modify its physical characteristics while being transported from one location to another.

The concepts of kinetics are employed in forecasting the stability of drugs, although there are differences between kinetics and stability studies that might cause instability to result from changes in physical appearance[16].

1.14. Factor Affecting Stability of Drug:

1.14.1. Temperature

Changes in temperature have an impact on a pharmacological substance's stability; higher temperatures speed up the rate at which medicines are hydrolyzed.

1.14.2. Moisture

When the water-soluble solid dose is absorbed into any moisture surface and loses its qualities, several physical and chemical dosage changes.

1.14.3. pH

The rate of medication deterioration in hydrolyzed solutions is affected by pH, which lowers the potency of pharmaceuticals manufactured with buffers at the pH where stability is greatest.

1.14.4. Excipient

Because of their higher water content than other excipients, starch and povidone have an impact on stability. Additionally, the chemical interactions between excipients and medications reduce instability.

1.14.5. Oxygen

Some products' oxidation is facilitated by the presence of oxygen. When exposed to oxygen, products with a greater rate of breakdown are stabilized by replacing the oxygen in the storage container with carbon dioxide and nitrogen.

1.14.6. Light

The rate of breakdown accelerates in light-exposed materials. Because some medications are photosensitive, it is possible to compare how well they hold up when stored in the dark vs exposure to light. Photosensitive medications must be stored in a dark environment and packaged in a glass amber bottle[17][18][19].

1.15. Mechanism of Drug Degradation:[20]

1.15.1. 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. 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.

1.15.2. 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.

1.15.3. 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.

1.15.4. Temperature

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

1.15.5. 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.

1.15.6. 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[21].

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.
- It is the only way to know for sure whether a drug meets the requirements for acceptance or not[22][23][24][25][26][27].

Stability Testing Method

There are four categorized methods for stability testing:

- Real-time stability testing
- Accelerated stability testing
- Retained sample stability testing
- Cyclic temperature stress testing

Real-time stability testing

Longer test periods are used for real-time stability testing. It is carried out for laboratory batches, or "primary batches," and the key elements of real-time stability testing include guidelines, a stability methodology, sample storage settings, validated rest techniques, bracketing matrixing, and results assessment.

Accelerated stability testing

Testing for accelerated stability is done at various high temperatures. Moisture, light, agitation, gravity, and pH are also administered during accelerated stability testing in addition to temperature. Since the analysis time was short and a high stress temperature was required, the stability of these tests was less unstable than real-time stability testing. Sample recovery under stressful and unstressed conditions is indicated in percent.

Based on the Arrhenius equation, the idea of accelerated stability testing was developed.

$$\ln k = \ln A + \Delta E / RT$$

Where ,

K= Degradation rate

A= Frequency factor

ΔE = Activation energy (KJ/mol)

R= Universal gas constant (0.00831 Kj/mol)

T= Absolute temperature

Retained sample stability testing

Every product that is advertised has this done to it. In this study, stability samples from at least one batch every year are chosen. If the number of batches being marketed exceeds more than half, it is advised to take stability samples. Repeat the process for each batch to ensure that the risk of degradation due to storage falls by 2% to 5%. In this study, stability samples are examined over the course of a few years depending on how long the product will remain on the market. The constant interval method is the traditional approach for gathering stability information on samples kept in storage.

Cyclic Temperature stress testing

This testing is carried out on marketed items, and the life cycle is typically 24 hours. For these tests, as well as criteria like optimum storage temperature, physical and chemical product deterioration, the lowest and maximum temperatures are appropriate. Typically, the test should consist of 20 cycles[28] [29].

Climatic Zone for Stability Testing

Every country in the world has a different climate. According to the nation's climate, stability studies for the medicine should be conducted. The five climate zones of the world are defined under the ICH criteria for stability studies.

These stability study areas were developed as a result of global differences in temperature and humidity. For pharmaceutical products, these zones have differing ICH stability conditions[30].

Table 1 ICH Stability Zone [30]

Zone	Type of Climate
Zone 1	Temperate Zone
Zone 2	Mediterranean / Subtropical Zone
Zone 3	Hot Dry Zone
Zone 4a	Hot Humid/tropical Zone
Zone 4b	Hot/higher humidity

Table 2 Stability studies storage conditions for drug products.[31]

Intended Storage Condition	Type of Stability Studies	Storage Conditions For					
		ICH			WHO		
		Temperature (°C)	Relative Humidity (%)	Time (Months)	Temperature (°C)	Relative Humidity (%)	Time (Months)
Room Temperature	Long term	25 ± 2°C	60 ± 5%	12	-20 ± 5°C	60 ± 5%	12
			65 ± 5%				
	Intermediate	30 ± 2°C	65 ± 5%	6	--	--	--
	Accelerated	40 ± 2°C	75 ± 5%	6	--	--	--
Refrigerator	Long term	5 ± 3°C	--	12	5 ± 3°C	--	
	Accelerated	25 ± 2°C	60 ± 5%	6			
Freezer	Long term	-20 ± 5°C	--	12	-20 ± 5°C		

1.15.7. Different ways to increase Drug Stability:[32]

- **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.

2. Conclusion

The purpose of this article is to enlist each and every knowledge and methods that can answer the drug stability problem and can improve it too. This article will also full fill the knowledge gap as it contains recent thought and method about stability of drugs. As it is known that drug stability is the important parameter calculated or determined while making any formulation but this field need more attention as action of drug are gradually depend on their stability.

Compliance with ethical standards

Acknowledgments

The authors are grateful to Pharmacy College, Itaura Chandeshwar, Azamgarh to carry out the present review work.

Disclosure of conflict of interest

The authors declare no conflict of interest.

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