INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Review On Drug Stability

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ARTICLE INFO

Received: 07 May 2024
Accepted: 11 May 2024
Published: 18 May 2024
Keywords:
Drug Stability; Degradation; Rate of reaction; Stability guideline; Stability Testing
DOI:
10.5281/zenodo.11214813

ABSTRACT

This includes drug stability studies Important parameters for new drugs and new drug development pharmaceutical formulation. Durability prediction plays a big role All dosage forms and their drug development Helps determine and suggest storage conditions for each Label description. Ensuring drug stability research Maintain product quality, safety and effectiveness throughout Durability is a prerequisite for acceptance Drug approval. These studies are necessary It will be implemented according to the guidelines issued by ICH. WHO or other institution 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.

INTRODUCTION

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture. Shelf life of the product can be defined as the substance reduces to

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

90% of its original concentration. Shelf life is a technical term used to denote the stability of the product and it is expressed as expiry date. Expiration varies for each pharmaceutical preparations. The expiry of the pharmaceutical dosage form depends on various environmental factors such as temperature, humidity, light, radiations etc. and many physical and chemical active substances in the formulation, the nature of container-closures used and the storage conditions. Literature data on the decomposition process and degradability of active substances are generally available together with adequate analytical methods. Thus, stability studies may be restricted to the dosage form. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products. Stability of a pharmaceutical product can also be affected because of microbiological changes like growth of microorganisms in non sterile products and changes in preservative efficacy. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation. The Shelf life of the pharmaceutical drug products is established by the stability studies. Stability testing of pharmaceuticals is known to be a complex set of procedures which involves significant cost, time and scientific proficiency to generate safety, in quality and efficacy in a drug formulation. Pharmaceutical formulation efficacy, quality, and safety require a complicated process collection that takes a lot of time, money, and scientific knowledge to develop. 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. 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.

Importance of stability studies

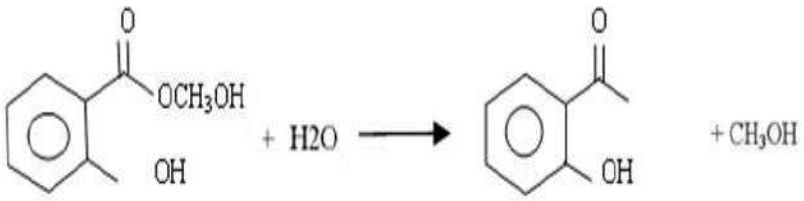
- Stability testing is an important step in the drug approval process and how the quality of a drug or drug (including packaging) changes over time under the influence of environmental factors such as temperature, humidity and light
- The toxic product may be formed during the decomposition of active drug.
- Stability storage and testing studies are performed to simulate climatic effects. The studies are based on where the products are going to be sold. Knowing all the ways a finished product or active pharmaceutical ingredients (APIs) could be affected by degradation is crucial in the storage of these products.
- In addition, stability testing establishes the shelf life and recommended storage conditions of the finished drug, as well as the drug substance retest period.
- It provides a database that might be used for selecting excipients, formulations, and container closing strategies for growing current products
- The breakdown of active medications may result in the formation of toxic compounds.
- To confirm that no adjustments to the manufacturing process or formulation strategy have been made that would have a detrimental effect on product stability.

Principle of Drug Degradation:

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

a . A + b . B→ P

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 Ms-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.

Zero – Order Reaction

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

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

……(1.1)

where k0 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:

$$-\frac{d[A]}{dt} = k_1[A] = k_0 \quad \text{……(1.2)}$$

where [A] is the concentration of dissolved medication and k1 is the first-order rate constant. Rearrangement of Eq. 1.1 and 1.2

$$[A] = [A]0 - K0t \quad \textbf{…….(1.3)}$$

The total drug concentration at time zero is [A]0. Plotting the evolution of [A] over time allows one to determine the rate constant.

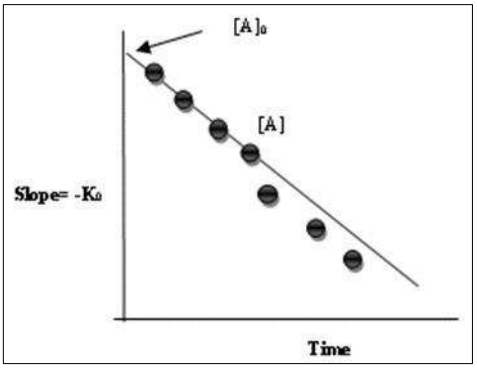


Figure 1 Zero-order plot of [A] versus time . [A]0 is the y- intercept.

First- Order Reaction

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

$$A \rightarrow P \quad \text{..... (1.4)}$$

$$\frac{d[A]}{dt} = k_1[A] \quad \text{.....(1.5)}$$

where [A] is the reactant (i.e., drug) concentration and k1 is the first-order rate constant. Drug disappearance rates are equivalent to product creation rates.

$$-\frac{d[A]}{dt} = \frac{d[P]}{dt} = K_1[A] \quad \text{.....(1.6)}$$

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

$$-\frac{d[A]}{dt} = \frac{d[P]}{dt} = K_1[A] \quad \text{.....(1.7)}$$

$$-\int_{[A]}^{[A]} \frac{d[A]}{[A]} = \int_0^t k_1\, dt \quad \text{.....(1.8)}$$

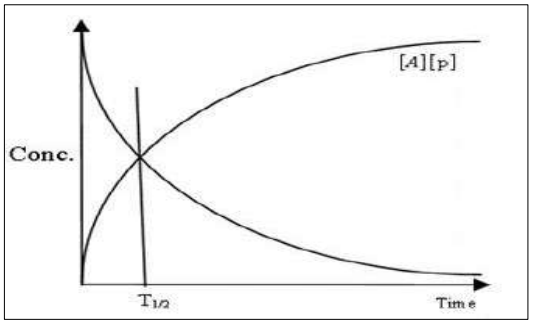


Fig 2: Plot of [A] and [p] versus time

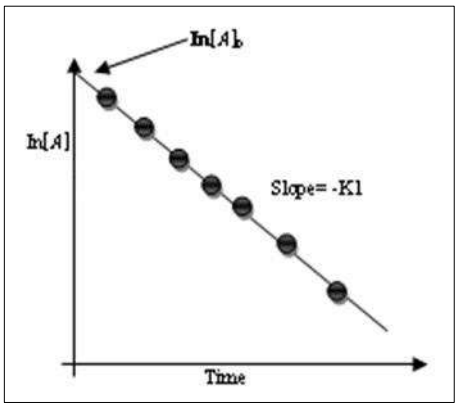


Fig 3: First-order plot of In versus time. In 0 is the y- intercept.

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

$$In[A] = In[A]_0 - K_1 t \quad \text{.....(2.0)}$$

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

Eq. 2.0 can also be written as:

log = log – K1t/ 2.303 .....(2.1)

ln[A] 5 2.303log[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...). T1/2, T90, and T95 for first-order reactions are unaffected by the initial drug concentration. For instance, t1 /2 (the time it takes [A]0 to reach 1 /2[A]0) may be computed as follows using Eq. 2.0:

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

Rearranging Eq. 2.2 give

$$t_{\frac{1}{2}} = \frac{In^2}{k_1} = \frac{0.693}{k_1} \quad \textbf{.....(2.3)}$$

Likewise, the following equations for t90 and t95 can be obtained:

$$t_{90} = \frac{0.105}{k_1} \quad \textbf{.....(2.4)}$$

$$t_{95} = \frac{0.0513}{k_1} \quad \textbf{.....(2.5)}$$

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

$$-\int_{[A]_0}^{[A]} \frac{d[A]}{[A][B]} = \int_0^t k_2\, dt \quad \text{..... (2.8)}$$

Integration of Eq. 2.8 given:

$$\frac{1}{[A]_0 - [B]} \cdot \left[In \frac{[B]_0[A]}{[A]_0[B]}\right] = k_2 t \quad \text{..... (2.9)}$$

Eq. 2.9 can be rearranged to:

$$\frac{1}{t([A]_0 - [B])} \cdot \left[In \frac{[B]_0[A]}{[A]_0[B]}\right] = k_2 t \quad \text{.....(3.0)}$$

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

$$-\frac{d[A]}{dt} = K_2[A]^2 \quad \text{..... (3.1)}$$

$$-\frac{d[A]}{[A]^2} = k_2\, dt \quad \text{.....(3.2)}$$

$$-\int_{[A]_0}^{[A]} \frac{d[A]}{[A]^2} = \int_0^t k_2\, dt \quad \text{..... (3.3)}$$

$$\frac{1}{[A]} - \frac{1}{[A]_0} = k_2 t \quad \text{..... (3.4)}$$

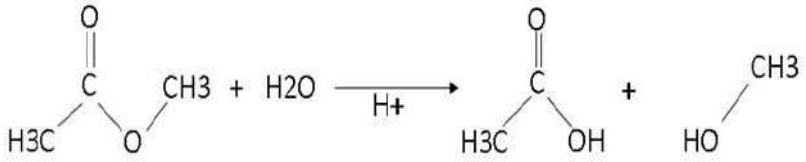
$$t = \frac{1}{k_2}\left(\frac{1}{[A]} - \frac{1}{[A]_0}\right) \quad \text{..... (3.5)}$$

According to 3.5 the half- life is:

$$t_{1/2} = \frac{1}{k_2[A]_0} \quad \text{..... (3.6)}$$

Third-Order Reaction

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



$$-\frac{d[\text{Ester}]}{dt} = K_3[\text{Ester}][H^+][H_2O] \quad \text{.....(3.7)}$$

The product of k3 and [H2O] is constant and equal to k2 (i.e., the second-order rate constant) because the water concentration in aqueous solutions is basically constant ([H2O] 5 55.55 M):

$$-\frac{d[L]}{dt} = K_3[\text{Ester}][H^+][H2O] = K_2[\text{Ester}][H^+]$$

.....(3.8)

Here, k2 represents the ester hydrolysis's apparent (or fictitious) second-order rate constant.

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 degradations products that may affect during storage conditions.

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

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).

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.

Chemical stability

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

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.

Therapeutic stability

The medicinal result (Drug Action) is unaffected.

Toxicological stability

The toxicity has not significantly increased due to toxicological stability.

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.

Factor Affecting Stability of Drug:

Temperature

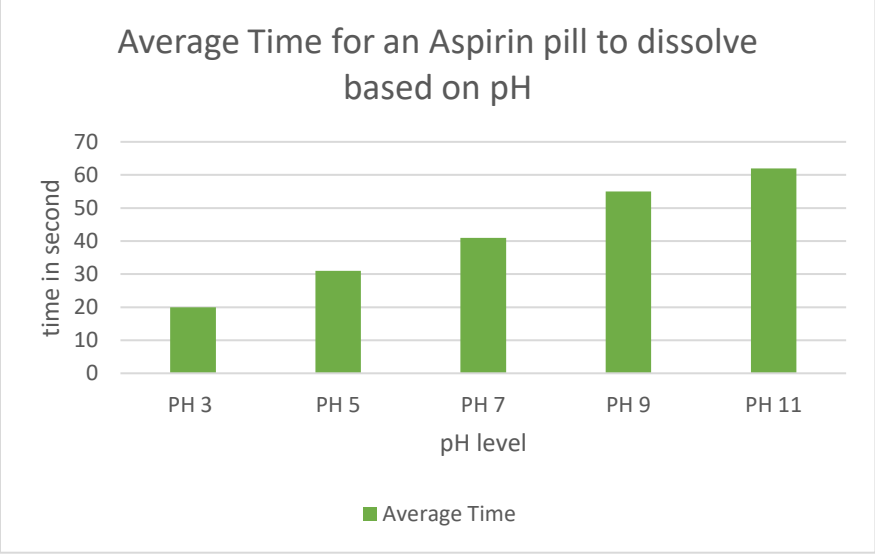
Changes in temperature have an impact on a pharmacological substance's stability; higher temperatures speed up the rate at which medicines are hydrolyzed.

Moisture

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

pH Rate Profile

The pH rate profile is the pH dependence of a particular rate constant for the decomposition of a compound. Sometimes referred to as the pH stability profile or rate-pH profile, it is easily represented by a log (k) vs. pH plot. The pH profile helps develop more stable solution formulations, and the lyophilized product also provides insight into the catalytic properties of the reaction. Many drug degradation reactions are usually plotted in a pH rate profile that is subject to certain common acid-base catalysis, following an apparent primary reaction rate. General acid-base catalysis needs to be corrected by buffer components by extrapolation to zero buffer concentration if he catalysis effect is significant. Analysis of a pH-rate profile can be started by assuming all possible pathways and writing down the corresponding rate equations The presence or absence of a certain mechanism can then be verified by analyzing the kinetic data Like as pH rate profile of aspirin



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.

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.

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.

Mechanism of Drug 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. 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.

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

Real-time stability tests are usually performed over a long period of time to allow significant product deterioration under the recommended storage conditions. The duration of testing a product depends on the stability of the product. This clearly shows that the product does not deteriorate or deteriorate over time due to variability between assays. During the test, samples are collected on a regular basis, so data is collected at an appropriate frequency and analysts can identify daily degradation. Data can be increased by including a single batch of reference material with established stability. The reagents and equipment used should be consistent throughout the stability test. Control of drift and discontinuity results due to reagent and equipment changes should be monitored. 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. In this method the drugs are stored at different temperatures such as 40°C, 60°C, 70°C, 80°C, 100°C etc. These studies are to be done at room temperature and at refrigerator temperatures. During different intervals the samples are collected and examined for the stability. The sampling is done at 3 months in the first year and 6 months interval the next year and yearly thereafter. The products which degrade very fast for them regular sampling at short duration of time should be done. When the temperature increases the decomposition of the substance is also very rapid. The stress tests used in the current ICH guidelines (40% for products are to be stored at controlled room temperature) were developed from a model that assumes energy of activation of about 83 KJ/mole. As per ICH and WHO the storage condition for accelerated stability studies is 40°C ± 2°C 75% RH ± 5% RH. If the product is unstable on the prescribed temperature and humidity intermediate conditions are used i.e. 30°C ± 2°C 65% RH ± 5% RH. FDA prescribes the sampling testing for 0, 2, 4, and 6 months respectively. WHO prescribes for 0, 1, 2, 3, 4, and 6 months. ICH prescribes the test to be performed for every 3 months in a year, 6 months in 2 years and yearly thereafter. These accelerated tests are mainly done for photochemical stability and moisture absorption. This test is performed for all the pharmaceutical preparations but mainly this is a test used for dispersed systems like pharmaceutical emulsions and suspensions

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

$$Ink = InA + \Delta E/RT$$

Or

$$k = -\frac{E_a}{RT} + ln\ A$$

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 method is not widely used for product sampling, testing is carried out on marketed items, cyclic temperature resistance tests are designed with product knowledge in mind to mimic marketable storage conditions. 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.

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.

Table 1 ICH Stability Zone

Zone	Type of Climate	Long-term testing conditions
Zone I	Temperate Zone	21^0 C/45%RH
Zone II	Mediterranean / Subtropical Zone	25^0 C/60%RH
Zone III	Hot Dry Zone	30^0 C/35%RH
Zone IV a	Hot Humid/tropical Zone	30^0 C/65%RH
Zone IV b	Hot/higher humidity	30vC/75%RH

Table 2 Stability studies storage conditions for drug products.

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

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.

- **Storage Conditions:**

Implementing appropriate storage conditions, such as temperature and humidity control, throughout the supply chain and at pharmacies to maintain drug stability.

- **Monitoring and Testing:**

Regularly monitoring drug stability through stability testing under various conditions to identify potential degradation pathways and develop appropriate strategies to mitigate them.

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. The review concluded that stability studies were used on the product to be formulated to predict shelf life, shelf life, determine appropriate storage conditions, and recommend labeling guidelines label.

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HOW TO CITE: Ganesh U. Chavan, Vitthal R. Gawade, Vaibhav P. Chopade, Shubham V. Wankhede, Sahil D. Nivangune, Dattatray B. Gatade, Review On Drug Stability, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 5, 954-965. https://doi.org/10.5281/zenodo.11214813