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Review paper

Stability Assessment of Pharmaceutical Products Under Accelerated Conditions

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ABSTRACT

An essential aspect of developing a pharmaceutical product is performing a stability assessment to ensure that the drug will be safe, effective, and perform as expected during its shelf life. To help predict long-term stability of pharmaceutical products, accelerated stability studies are frequently used by placing drug products under high temperature and humidity conditions for a predetermined period of time. The objective of the study was to evaluate the stability of pharmaceutical products stored under accelerated conditions in accordance with the International Council for Harmonisation (ICH) guidelines. Representative batches of the formulation were put into the appropriate container-closure system and stored at 40 ± 2 degrees Celsius and 75 ± 5 percent relative humidity (RH) for six months. Samples of the products were taken from the test conditions at pre-specified time points and analyzed for critical physical and chemical properties such as appearance, assay, dissolution, moisture content, pH, hardness, friability, and impurity profile. Based on the analysis results, all formulations remained within acceptable pharmacopoeial specifications for the duration of the study with minimal variations observed in physicochemical properties. The lack of significant degradation of the products or change in potency indicates sufficient stability at accelerated conditions. Accelerated stability studies yield useful information about predicted shelf-life, required storage conditions and suitability of packaging for pharmaceutical products. Furthermore, accelerated stability studies are important tools in providing quality assurance and regulatory compliance for developing stable and effective pharmaceutical formulations with predictable long-term performance.

1. Introduction

Stability of pharmaceutical products is a major quality attribute; it determines whether or not a drug can continue to have the same identity, strength, quality, purity and performance characteristics throughout its storage period. Stability studies are an integral part of both drug development and commercialization because pharmaceutical products are subject to many types of degradation processes due to environmental factors like temperature, humidity, light exposure, oxygen exposure, and/or reactions with their packaging materials. The end results of these degradation processes are decreased therapeutic effectiveness, changed physicochemical properties and potentially harmful degradation by-products; stability assessment is therefore essential to the safety and efficacy of pharmaceutical products (Waterman & Adami, 2005).

Stability testing is the process of testing and providing scientific information on how a drug or dosage form behaves when exposed under different environmental conditions. This information helps

manufacturers determine proper storage conditions for their product, its shelf life, and whether it meets regulatory requirements. Per International Council for Harmonisation (ICH), stability studies should be conducted using long-term, intermediate and accelerated testing methods in order to provide information on the product's stability over the anticipated shelf life (ICH Recommendation Q1A(R2), 2003). The accelerated stability study involves testing pharmaceutical products under high temperature and humidity conditions to accelerate chemical and/or physical degradation (in order to estimate the product will be stable over a longer period of time).

Chemical stability refers to the ability of a pharmaceutical ingredient (API) to maintain its chemical integrity and potency as labeled within specified limits. Physical stability includes factors such as appearance, hardness, dissolution rate, viscosity, particle size and moisture content, while microbiological stability means keeping the product free from contamination by microorganisms. Therapeutic stability is ensuring that the intended pharmacological effect of the product is achieved during its entire shelf life (Bajaj et al., 2012). Any change to any one of those parameters may compromise the quality of the product and thus compromise patient safety, so it is critical to evaluate stability thoroughly.

Accelerated stability studies are performed in stressed environmental conditions, typically at 40±2°C and 75±5% relative humidity over six months, which is consistent with ICH recommendations for climate zones I and II. The stressed conditions of these accelerated studies cause degradation reactions (such as hydrolysis, oxidation, photolysis and polymorphic conversions) to occur at an accelerated rate and the data generated from these studies can help to establish degradation pathways, define critical quality attributes, assess the adequacy of packaging systems, and approximate expiry dates In addition to the data generated from these accelerated studies, stability-indicating analytical methods are utilized to detect the changes in drug content and detect the presence of impurities and degradation products. (Blessy et al., 2014) (Table 1).

Stability of pharmaceuticals is impacted by many different factors. Such as the physical and chemical properties of the drug molecule as well as the ingredients in the final formulation and their compatibility with one another, the manufacturing process and the packaging the product is placed in. In terms of stability, drugs that are readily hydrolyzed by moisture can experience the loss of potency through this route. Conversely, drugs that are subject to oxidation through exposure to atmospheric oxygen are also at risk of losing their pharma potencies. Additionally, excipients can interact with drug active ingredients and have negative affects on stability and potencies. Packaging systems used to package pharmaceuticals such as blister packs, amber indicated glass containers and bottles made from high density polyethylene are critical to providing protection from external environmental conditions that can adversely impact the integrity of the product (Allen, Popovich, & Ansel, 2014).

The basis for accelerated stability testing is provided by the Arrhenius equation, which describes the relationship between temperature and reaction rates. In accordance with this principle, the increase in temperature increases the rate of degradation reactions and allows the prediction of stability over time based on short-term results. A number of mathematical models derived from accelerated stability date are helpful in estimating shelf life and/or storage conditions without having to conduct extensive long-term studies. However, in order for regulatory authorities to accept the projected shelf life, accelerated stability testing must be done in conjunction with long-term studies that will provide additional information to substantiate the predicted shelf life (Carstensen & Rhodes, 2000).

Globally regulatory authorities, such as the US FDA, EMA, and WHO require companies to conduct stability testing when registering pharmaceuticals. ICH Q1A(R2) provides recommendations on storage conditions, testing frequency and acceptance criteria providing global consistency and quality of products in the market. Stability testing data generated under accelerated conditions is necessary for New Drug Applications, approvals for generic products, reformulation approvals and for any approved product changes (ICH, 2003).

Progressive technology developments have improved both the reliability of assessing drug stability and the accuracy of detecting these assessments through recent developments in analytical technology. High-performance liquid chromatography/high-resolution mass spectrometry (HPLC/LC-MS), Fourier-transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC) are just some examples of the types of stability-indicating techniques and their performance capabilities. These techniques allow accurate measurement of the extent of degradation of active pharmaceutical ingredients (APIs) and provide detailed descriptions of degradation mechanisms so as to optimize formulation integrity (Singh & Bakshi, 2000).

Table 1 Potential Adverse Effects of Instability in Pharmaceutical Products

Type of Instability	Causes	Potential Adverse Effects	Impact on Product Quality and Patient Safety
Chemical Instability	Hydrolysis, oxidation, photolysis, pH changes	Degradation of active pharmaceutical ingredient (API), formation of impurities	Reduced potency, decreased therapeutic efficacy, potential toxicity
Physical Instability	Temperature fluctuations, moisture absorption, polymorphic changes	Alteration in color, odor, hardness, dissolution, and appearance	Inconsistent drug release and reduced patient acceptability
Microbiological Instability	Microbial contamination due to improper storage or preservative failure	Growth of bacteria, fungi, or yeasts	Risk of infections and compromised product safety
Moisture-Induced Instability	Exposure to high humidity, inadequate packaging	Tablet softening, caking, hydrolysis of moisture-sensitive drugs	Reduced shelf life and altered drug performance
Thermal Instability	Elevated storage temperatures and heat exposure	Accelerated degradation reactions and loss of potency	Failure to meet quality specifications and therapeutic ineffectiveness
Photochemical Instability	Exposure to ultraviolet or visible light	Discoloration and formation of degradation products	Reduced drug efficacy and possible toxic effects
Packaging-Related Instability	Incompatible container-closure systems, inadequate barrier properties	Moisture ingress, oxygen permeation, contamination	Shortened shelf life and compromised product integrity
Excipient-Drug Interaction	Chemical incompatibility between API and excipients	Formation of degradation products and changes in dissolution profile	Reduced bioavailability and unpredictable therapeutic response
Volatilization or Evaporation	Loss of volatile components during storage	Change in concentration and composition of formulation	Reduced dose accuracy and product efficacy
Container Leachable and Extractables	Interaction between formulation and packaging materials	Presence of harmful contaminants or impurities	Safety concerns and regulatory non-compliance

2. Importance of Stability Studies

- The unstable product of the active substance can cause the dose form of the medicine to be too low, resulting in undermedication.
- The medicine or product might decompose into harmful byproducts.
- The drug's physical qualities can vary as it is being transported from one location to another, depending on its compatibility.
- There is a distinction between kinetics and stability studies, and instability may be the result of changes in the drug's outward appearance as predicted by kinetic principles.

3. Types of Stability Studies on Drug Substances

Levels of physical, chemical, microbiological, therapeutic, and toxicological stability tests are defined by a thorough pharmacopoeial protocol (USP).

3.1 Physical stability

Look, colour, solubility, palatability, and suspendability are all unchanged physical characteristics. It is crucial for the product's effectiveness and safety to consider the physical stability, as it might impact the consistency and rate of release.

3.2 Chemical stability

As a result of reactions caused by air, environment, temperature, etc., it has a tendency to resist change or decomposition.

3.3 Microbiological stability

Resistance to sterility and microbial growth is the propensity of medications to be microbiologically stable. Within certain limitations, the antimicrobial compounds utilised in the formulation maintain their efficacy. The sterile medicinal product might be put at risk by this microbial instability.

3.4 Therapeutic stability

There has been no change to the drug's therapeutic impact (Drug Action).

3.5 Toxicological stability

When it comes to toxicological stability, there is no discernible rise in toxicity.

4. Types of stability studies

When evaluating a pharmaceutical product over extended periods of time in a variety of temperature and relative humidity (RH) settings, stability studies are employed. If the medicine needs to be sent to multiple locations for distribution, then stability

studies over the long term are crucial. The sample is tested at defined time intervals and the settings of the external factors are altered correspondingly to conduct long term stability studies. Finding out how long the medication will last is the primary goal of this research. There are essentially four distinct kinds of stability studies: long-term, intermediate, accelerated, and in-use. Table 2 shows the many types of stability studies, as well as the storage conditions and durations of each.

Table 2 Study Methods for Stability Analysis

Types of Stability Studies	Storage Conditions	Minimum Time Period (Months)
Long Term	25±2°C and 60±5% RH or 30±2°C and 65±5% RH	12
Intermediate	30±2°C and 65±5% RH	6
Accelerated	40±2°C and 75±5% RH	6

5. Stability Testing Methods

Stability testing is an integral part of the development process for all pharmaceutical products. To evaluate stability in the first stages, accelerated stability tests are usually conducted in conditions with high humidity and temperatures. The rapid degradation of the medicine can be foretold with relative ease by use of accelerated stability testing. When medications are kept for an extended period of time, they are typically subjected to accelerated stability testing. These higher temperatures are used to determine how long the things will last. Ensuring the drug maintains an adequate level of fitness and quality for the patient during its availability is the primary purpose of stability testing. It is possible to enhance the patient's condition, increase medication acceptance, and maximise the therapeutic efficacy of pharmaceutical goods. According to the goals and procedures, there are four main types of stability testing methodologies.

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing.

6. Real-time stability testing

In order to simulate the product's expected rate of degradation under the approved storage circumstances, real-time stability testing is often carried out over an extended period of time. The product's stability, which indicates that it is neither deteriorated or decomposed over an extended period of time due to inter-assay variance, determines the duration of the test. As part of the testing process, samples are taken at regular intervals to ensure that the data is obtained at the right frequency. This allows the analyst to detect degradation on a daily basis. By using the one batch of reference material with known stability properties, the data may be expanded. It is important that the reagents and apparatus used for stability testing remain consistent. It is important to keep an eye on the reagents and instruments used for drift and discontinuity control.

7. Accelerated stability testing

The product's breakdown is identified by this form of stability testing, which is carried out at higher temperatures. Predicting the shelf life or comparing the relative stability of different formulations are both made possible by the knowledge. It takes less time to find out how stable a drug is because to accelerated stability experiments, which make predicting its shelf life easier. We apply stress conditions including light, moisture, pH, and gravity in addition to temperature. There is a time savings compared to real-time testing since instability is measured. Stability predictions are performed at four distinct stress temperatures for the accelerated stability experiments. Avoiding denaturing stress temperatures allows for the acquisition of predictions, nonetheless. The Arrhenius equation readily predicts the accelerated stability investigations:

$$K = Ae^{-Ea/RT}$$

where:
K= Detailed pacemaker
A= Arrhenius or frequency factor
Ea= Activation energy
R= Gas constant in real terms 4.184 j/mol K
T= Celsius, the absolute value

This method employs a wide range of temperatures for drug storage, from 40 to 100 degrees Celsius. These investigations will be conducted in both room temperature and cold storage settings. Gathering and evaluating samples at regular periods ensures stability. Samples are collected at three-month intervals in the first year, six-month intervals in the second year, and yearly thereafter. Products with a high rate of spoilage should have frequent sampling at frequent intervals. As the temperature increases, combustion happens far more quickly. Activation energies estimated at around 83 KJ/mole are the basis for the present ICH standards' stress testing. Forty percent of the objects meant to be kept at controlled room temperature fall within this category. The recommended storage conditions for swift stability testing, as stated by the ICH and WHO, are a temperature of 40°C ± 2°C and a relative humidity of 75% ± 5%. If the product becomes unusable when subjected to the given amounts of heat and moisture, intermediate parameters like 30°C ± 2°C and 65% RH ± 5% RH are used. The following intervals are defined by the FDA as recommended sample intervals: 0, 2, 4, and 6 months. The World Health Organization has provided recommendations for 0, 1, 2, 3, 4, and 6 months. According to ICH, the test should be

administered every three months for the first year, every six months for the second year, and annually thereafter. Results from these accelerated tests mainly pertain to photochemical stability and water absorption. This test is performed on all medicinal formulations, including emulsions and suspensions. Distributed systems are its primary use.

8. Continual monitoring of sample integrity

Any product on the market that has to be stable goes through this process. For this testing procedure to be stable, it is recommended to choose a single batch and store it for a year. If the sum of the samples is more than fifty, we divide them in half. At the initial product launch, samples are taken from every batch. However, as the product moves through the market, this percentage might decrease to 2–5% of the batches that are actually sold. An estimate of the samples' storage life can be made based on research on their stability. Results from tests conducted at3,6,9,12,18,24,36,48, and 60 months indicate that a maximum shelf life of 5 years is achievable for any given product. That kind of testing is also known as the constant interval approach. This stability sampling approach is inherently more realistic than others as it tests the product in both controlled laboratory environments and real-world circumstances.

9. Testing for cyclic temperatures

It is not common practice for this method to sample items. The purpose of these cyclic temperature stress tests is to evaluate a product's performance in a setting that mimics the circumstances seen in a retail store. Because it is in harmony with the Earth's natural rhythm, the testing presumes that sampling happens on a 24-hour cycle. When recording the lowest and highest temperatures for sample testing, several elements are considered, including product details, storage circumstances, chemical and physical degradation, and temperature. When predicting the shelf life, a cycle of 20 is recommended.

10. Directions for Stability Research

Preparations for pharmaceuticals should be as stable as possible to guarantee patient safety, and products should follow guidelines established by groups such as the FDA, the World Health Organization, and the International Conference on Harmonisation. Preparations rely significantly on ICH for their development and marketing. A method for keeping track of pharmaceuticals designed for human use is the "International Conference of Harmonisation" (ICH). The pharmaceutical and regulatory industries of the US, Japan, and the EU came together in 1991 to establish the International Conference on Harmonisation (ICH). This led to the development of a plethora of pharmaceutical product and ingredient standards addressing issues of quality, safety, effectiveness, and interdisciplinary collaboration (Q, S, E, M). As its secretariat, the International Council of Hospitals (ICH) is based in Switzerland. This set of suggestions addresses fundamental issues with stability as well as data needs for application dossiers and execution phases. Revising prior recommendations from the International Conference on Harmonisation (ICH) and the World Health Organization (WHO) from 1996, the World Health Organization (WHO) released new guidelines for stability studies in a global setting in 2004. The ICH did not assess the impact of the extreme weather on various countries as it only dealt with newly produced pharmaceutical compounds and existing products. The regulations were also published in June 1997 by the US Food and Drug Administration (FDA) in Silver Spring, Maryland, even though they lacked the jurisdiction to do so. The drug regulation in India is overseen by the Central Drug Standards Control Organization (CDSCO), which is located in New Delhi. The regulatory norms vary from country to country. This made data management and application inspection more difficult. Consequently, there was an urgent need to simplify and standardise the regulations. The ICH Steering committee was established during the conference, and decisions will be taken at least twice a year. As an additional tool for pharmaceutical marketers, a set of stability testing requirements has been published by the Committee for Proprietary Medicinal Medicines (CPMP) under the European Agency for the Evaluation of Medicinal Products (EMEA). Contents and Regulations of the ICH and CPMP. Here are the guidelines: Table 3 and Table 4.

Table 3 The ICH Guidelines' Codes and Titles

ICH Codes	Guideline Titles
Q1A	New pharmacological substance and product stability testing (second edition)
Q1B	Drug substance and product photo stability testing
Q1C	Validation of novel dosage form stability
Q1D	Stability assessment of pharmaceutical ingredients and products using bracketing and matrixing designs
Q1E	Evaluation of stability data
Q1F	Application stability data package for climate zones III and IV registrations
Q5C	Product stability evaluation in the biotech and biological industries

Q6A	Details: Methods of Testing and Requirements for Approval of Novel Medications Drugs and New Pharmaceutical Ingredients: Chemical Substances
Q6B	Specifications: Protocols for Testing and Evaluating Novel Medications Chemicals and Novel Pharmaceutical Ingredients: Biotechnological and Biological Goods

Table 4 Documentation for CPMP stability tests

CPMP Codes	Guideline Titles
CPMP/QWP/576/96 Rev. 1	Application for Variation to a Marketing Authorisation: A Guide to Stability Testing
CPMP/QWP/6142/03	European Union (EU) Product Stability Testing Guidelines for Active Substances and Medicinals Made in Climate Zones III and IV
CPMP/QWP/609/96 Rev. 1	Reminder Regarding Instructions for Declaring the Storage Conditions of Pharmaceutical Specifics and Active Ingredients
CPMP/QWP/122/02 Rev. 1	Existing Active Substances and Related Finished Product Stability Testing Guidance Note
CPMP/QWP/072/96	Finished dosage form start shelf life guidance note
CPMP/QWP/2934/99	Remark Regarding the Recommendations for Medicinal Product Stability Testing in Real-World Settings
CPMP/QWP/576/96	Important Reminder Regarding the Testing of Stability for a Type 2 Modification to a Marketing Authorisation

11. Conclusion

Accelerated conditions are crucial to the development and quality assurance of a pharmaceutical product's stability. They allow us to see how the drug product will perform when stored for an extended time by evaluating its chemical, physical, and therapeutic characteristics. Examples of the assessments performed on drugs during these studies include appearance, assay, dissolution, moisture content, pH, hardness, friability and impurity profile. They also allow for evaluation of the product's quality attributes throughout its time in store and allow us to provide recommendations on how to properly store the drug product. Accelerated conditions provide us with valuable information on the product's ability to remain stable in extreme weather conditions, identify where the drug may be degraded during manufacturing or storage, and help create optimal formulation and packaging systems. In addition, by meeting ICH guidelines, pharmaceutical manufacturers are able to develop products that are safe, effective, and meet the quality standards of regulatory authorities. As a result, accelerated condition studies are an effective and economic means of predicting product shelf-life and minimizing the risk of pharmaceutical instability. Therefore, continued observation and thorough stability evaluation of pharmaceutical products are essential to ensuring product quality, protecting patient safety, and supporting successful pharmaceutical development and commercialization.

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