EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 10
85-92
Year: 2024

A REVIEW ARTICLE ON STBILITY INDICATING METHOD DEVELOPMENT

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Article Received on 07/08/2024 **Article Revised on 28/08/2024** **Article Accepted on 17/09/2024**

ABSTRACT
A stability-indicating method is a quantitative approach that has been validated over time, as per an FDA guidance statement. Stability testing aims to establish a retest period for drug substance or shelf life for drug product, as well as recommended storage conditions. It further understands the chemistry of the drug substance and drug product and facilitates the development of stability indicating analytical methodology. Regulatory guidance in ICH Q1AR2, Q3BR2, Q6A and FDA 21 CFR Section 211 requires validated stability-indicating methods. Stability indicating methods of drug substance and products have the ability for separation, identification, qualification, and quantification of all impurities associated with drug substance and drug product at any storage Conditions to give the exact concentration of drug substance or analyte at any time point over the shelf life of products and beyond.

KEYWORDS: HPLC, forced degradation, stability indicating method.

1. INTRODUCTION[1,2]

Drug products are defined as various marketed formulations of drug substances that are easily administered to patients to show the necessary therapeutic effect. Drug substances are defined as active ingredients used in the treatment and mitigation of various diseases and disorders. For each of these, a thorough analysis of their stability was necessary in order to determine their shelf life and retest interval. The capacity of a drug or product to maintain its identity, quality, and purity across the course of its life cycle under specific storage conditions is known as balance.

The development of stability testing methodologies for the registration of novel drug substances and products in the United States, Japan, and the European Union has been directed by ICH standards. For each of the four climate zones, it lays out the requirements for three different kinds of stability testing: long-term stability studies, expedited stability studies, and intermediate stability studies. In order to establish thresholds, ICH recommendations also serve as a guide for the qualification, identification, and quantification of impurities in drug substances and drug products.

An analytical technique called a stability indicating method (SIM) is used to measure how much of the active pharmaceutical ingredient (API) in a drug product is lost as a result of degradation. A stability-indicating method is a quantitative approach that has been validated over time, as per an FDA guidance statement. When there is no interference from excipients, other degradation products, or other contaminants, a stability-indicating method can detect changes in the concentration of the active components with accuracy. When nothing is known about a possible degradation product, stress testing is used to show the designed method's specificity in measuring changes in drug substance concentration. The foundation for pre-formulation studies, stability studies, and the creation of appropriate storage requirements is provided by the development of an appropriate stability indicating method.

1.1Types of stability studies[3]

Stability studies are mainly of four types.

i. Long term stability
ii. Intermediate stability
iii. Accelerated stability
iv. In-use stability

1.2 Objectives of Stability Studies[4,5]

i. To determine the API's shelf life and storage requirements.
ii. To demonstrate the extent to which temperature, humidity, and light, among other environmental conditions, affect the quality of API over time.
iii. To create stable formulations by resolving issues related to stability.
iv. To separate degradation products connected to drug products from those originating from the non-drug product in a formulation.
v. To determine the inherent stability of a pharmaceutical ingredient inside the formulation.
vi. To determine the mechanisms of hydrolysis, oxidation, thermolysis, and photolysis that occur during the degradation of the drug material and drug product.
vii. To provide a degradation profile that is similar to what would be observed in a formal stability study conducted in compliance with ICH criteria.
viii. To develop more stable formulae. It also helps determine the expiration date of a particular composition.

1.3. Need, and Purpose of Stability Studies[3]

i. Because the active medication's lozenge form lowers attention, product insecurity of the medicine may result in underdosing.
ii. Poisonous compounds may arise when an active medication becomes contaminated.
iii. Even though the concepts of kinetics are used to predict the stability of medicine, there are differences between stability studies and kinetics that may contribute to feelings of insecurity.

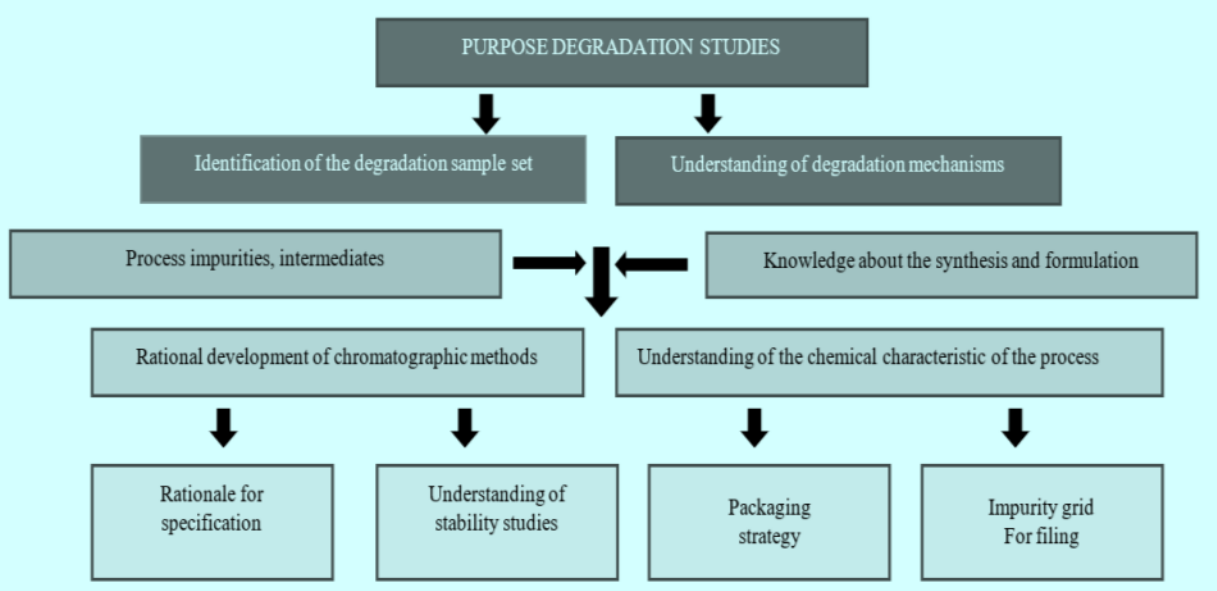

Fig 1: Purpose of Degradation Studies.

1.4. Importance of Stability Indicating HPLC Method[6,7]

Importance of Stability Studies:

i. Because the concentration of the drug in the dosage form lowers as a result of product instability of the active ingredient, undermedication may result.
ii. A hazardous product may arise during the active drug's breakdown.
iii. The drug's stability may be predicted using kinetics principles, which may account for changes in the drug's physical appearance.
iv. To safeguard the manufacturer's brand by guaranteeing that the product will remain fit for use in terms of all functionally significant aspects for the duration that it is sold.

Pharmaceutical manufacturing now includes strict quality control measures to reduce batch-to-batch variations and guarantee product quality. Stability is currently the primary and most important criterion for pharmaceutical product quality. Precise delivery is ensured by stable preparations, which provide a strong focus on product quality. Moreover, analytical research in both typical and stressful circumstances determines the drug formulation's shelf-life duration. In order to identify the degradation products using validated stability-indicating analytical methods, ICH drug stability testing guideline Q1A (R2) emphasizes that samples of active pharmaceutical ingredients that are subjected to stress conditions should be analyzed to establish their inherent stability characteristics. Particular assay techniques known as stability-indicating assay methods (SIAMs) assess the medication in the presence of its breakdown products, excipients, and additives.

Stability testing aims to establish a retest period for drug substance or shelf life for drug product, as well as recommended storage conditions. It also provides evidence on how the quality of drug substance or drug product varies with time under the influence of various environmental factors, such as temperature, humidity, and light.

2. ANALYTICAL INSTRUMENT USED IN STABILITY INDICATING METHOD DEVELOPMENT[2]

The development of the SIM is facilitated by the advancements in analytical instrument techniques. The drug material, its contaminants, and degradant products should be well separated. Possessing a high degree of sensitivity in determining the minimal concentration of drug material is expected. Some of the techniques with high sensitivity and resolution power to produce the effective stability indicating method 30 are TLC, HPLC-DAD, HPLC-UV, HPTLC, HPLC-MS, LC-MS/MS, and LC-NMR. The TLC method has an advantage over HPLC in that a large number of samples can be evaluated in a single plate using the densitometry method, and the mobile phase amount required is minimal. While HPLC is less sensitive than TLC, HPTLC is more sensitive than TLC.

The advantages of HPTLC include the ability to put a large number of samples on a single plate and its cost-effective analysis due to the tiny amount of mobile phase needed. The most popular technique for developing stability indicating methods is HPLC UV, which is more sensitive than TLC and HPTLC methods but has a limit to its ability to detect. There is a broad spectrum of detection with HPLC-PDA or DAD. The wavelength at which all impurities, degradant products, and drug substance exhibit absorbance may be found, making it simple to detect, separate, and quantify all contaminants and related compounds and providing precise drug concentration at any moment during storage. HPLC-MS has higher sensitivity to analyze the small quantity of analyte also. In such a way the HPLC-MS/MS shows to study the fate of a drug in human biological fluids, *i.e.* drug plasma concentration level. LC-NMR is also a highly sensitive technique to have the ability of separation of enantiomers in which one of them considered as an impurity of drug substance.

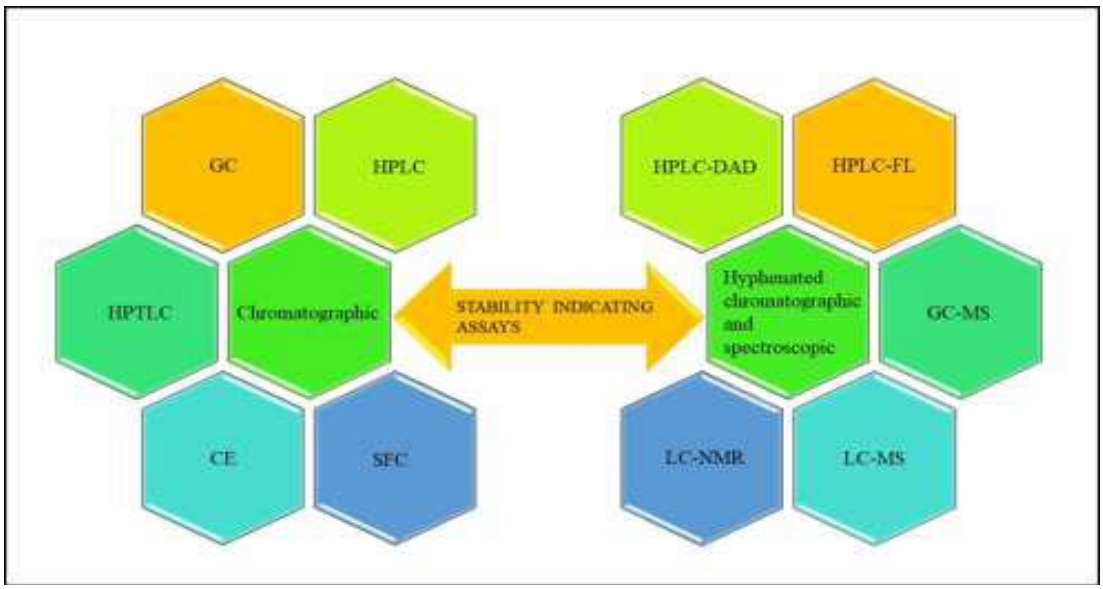

Fig 2: Stability Indicating assays for pharmaceuticals.

3. GUIDELINES FOR STABILITY TESTING[7]

The regulatory bodies in a number of nations have included provisions in their medication legislation for manufacturers to submit stability data in order to ensure that the production, distribution, and administration of molecules and products that are ideally stable reach the patients. Its main goal was to standardize testing procedures across manufacturers. These recommendations include fundamental stability-related concerns, the stability data requirements for application dossiers, and the procedures for carrying them out. These rules were first published in the 1980s.

Later on, these were harmonized (rendered uniform) at the International Conference on Harmonization (ICH) to get around the obstacle of having to register and promote the products abroad. The European Commission, Japan, and the United States of America provided regulatory and industry input to construct the ICH consortium. The World Health Organization (WHO) changed the guidelines because the ICH guidelines only covered new drug substances and products, not established ones that were already in use in the WHO umbrella countries, and they failed to address the extreme weather conditions found in many countries. The India Drug Manufacturers Association has also published a technical monograph on stability testing of drug substances and products that are legally available in India. Further, different test condition and requirements have been given in the guidance documents for active pharmaceutical ingredients drug products or formulations and excipients.

4. ICH GUIDELINES[7,8]

The ICH principles are used by other nations, but they have been incorporated into the legal systems of the US, Japan, and the EU. Since these regulations mirror general

inspection trends, they are legally binding. These regulations are titled Quality, Safety, Efficacy, and Interdisciplinary Guidelines (QSEM). In 1996, WHO updated these recommendations. This is because only new active ingredients and goods have been recorded; the ICH rules do not account for the extreme climatic conditions of several nations, and he has not yet utilized the items sold by WER in any of the countries. Specifications and test conditions for active pharmaceutical ingredients (APIs), drug substances, drug products, and excipients are developed in guidance documents.

Table 1: The codes and titles of the stability studies covered by ICH guidelines.

ICH Code and their Guideline title	
Q1A	Stability testing of New Drug Substances and Products (Second revision).
	Stability testing Photo stability testing of New Drug Substances and products.
Q1C	Stability testing of New Dosage Forms.
	Bracketing and Matrixing Designs for stability testing of Drug substances.
Q1E	Evaluation of stability data.
	Stability data package for Registration Applications in Climatic Zones III and IV.
Q5C	Stability testing of Biotechnological/Biological Products.

4.1. ICH Q1A (R2): Stability testing of new drug substances and products

According to these laws, the registration application must contain details regarding new molecular entities and related medical goods. The Q1A guidelines' Section 2.1.2. Section ICH Q1A covers the testing of stability for innovative pharmaceutical substances and their products. When creating methods to evaluate the stability of medications, these suggestions are helpful. According to Q1A, degradation depends on the specific drug molecules as well as the composition of the drug products. To perform these forced decomposition tests on pharmaceutical substances and their derivatives, a number of accelerated conditions were suggested. These conditions included the effects of oxidation, photolysis, a broad range of Ph (solution/suspension), humidity (75% relative humidity), and temperature (>50°C).

4.2. Q1B: Photo stability testing of new drug substances and products

These methods are usually used to predict the photostability of medicinal compounds during the drug development phase. These guidelines provide guidance on how to assess the photostability of compounds under investigation for stability investigations. Regulations and the necessity for forced drug degradation, respectively, both called for the forced breakdown of drug molecules and their byproducts. Forcible degradation investigations are helpful in confirmatory research to find photolytic degradants.

4.3. Q1C: Stability testing for new dosage forms

These guidelines address a suggestion regarding the stability of new dosage forms made by the original applicant after the initial application for innovative pharmacological substances and products. The parent stability guideline should serve as the foundation for the concept of stability for a new dosage.

4.4. Q1D: Bracketing and matrixing design

This point of view suggests using bracketing and matrixing instability research. This tip suggests using bracketing and matrixing instability research. The technique of developing a stability schedule known as bracketing involves evaluating only samples consistently up to the boundaries of layout factors such as strength, container size, or full design filling.

Matrixing is the process of creating a stability schedule that indicates which subsets of the total number of samples should be verified later and which subsets should be investigated for all conceivable factor combinations at a specific time point.

4.5. Q1E: Evaluation of stability data

When and how to consider extrapolation is explained in this guideline for a re-assessment length for the drug substance or drug product shelf life that extends beyond the time period covered by "long term storage conditions information accessible from the stability research".

4.6. Q1F: Stability data package for registration applications in climatic Zone III and IV: The ICH regions were required to follow these documents after they were approved by the ICH Steering Committee in February 2003. This guideline establishes the storage requirements for stability testing in climatic zones III (hot and dry) and IV (hot and humid). By reducing the number of storage circumstances, it describes standardized international stability testing techniques to promote drug accessibility.

4.7. Q5C: Stability testing of biotechnological/biological products

This advice is limited to proteins and clearly defined polypeptides; it does not apply to products and derivatives made using r-DNA technology or that have been extracted from tissues, cell cultures, physiological fluids, or other sources.

5. CLIMATIC ZONES FOR STABILITY TESTING

The world has been split into four zones (I through IV) for stability testing purposes based on the types of environmental conditions that pharmaceutical products are expected to encounter while being stored. The average yearly temperature and relative humidity for

these areas have been used to calculate these conditions. Accelerated stability testing conditions as well as long-term or real-time stability testing conditions have been derived from this data.

Table 2: The Standard Climatic Zones For Use In Pharmaceutical Product Stability Studies.

Climatic zone	Climatic definition	Major countries/region	MAT*/Mean annual partial water vapor pressure	Long-term testing conditions
I.	Temperate	United Kingdom, Northern Europe, Russia, United states	<150C / < 11hPa	21°C/45%RH
II.	Subtropical and Mediterranean	Japan, Southern Europe	>15-22°C / > 11-18hPa	25°C/60%RH
III.	Hot and Dry	Iraq, India	>22°C / < 15hPa	30°C /35%RH
IV.	Hot and Humid	Iran, Egypt	>22°C / >15-27hPa	30°C /65%RH
	Hot and very humid	Brazil, Singapore	>22°C / > 27hPa	30°C /75%RH

6. APPLICATIONS OF SIAMS[9]

1. Stability studies are utilized to ascertain the shelf life of the finished product and the re-test period of the active ingredient, which is the length of time it may be stored and used without being immediately inspected.
2. In order to account for possible variations during storage or degradation of the active component, the product's release and shelf-life parameters may change.
3. The International Conference on Harmonization (ICH)'s drug stability test guideline Q1A (R2) requires that stability samples be analyzed utilizing SIAMs, or established stability-indicating analytical techniques.
4. It also suggests stress testing the drug substance to ascertain its intrinsic stability properties and to bolster the acceptability of the recommended analytical procedure.
5. Using the validated SIAMs, the stability samples of the drug substance and drug product will undergo extensive testing.

7. FACTORS AFFECTING MEDICINE STABILITY[3]

a) Temperature: A medication's stability is impacted by temperature variations; a rise in temperature causes a medication's rate of hydrolysis to increase.

b) Humidity: When the water-answerable solid remedy absorbs into any humidity face and so loses its packages, certain physical and chemical lozenges change.

c) PH: The rate at which hydrolyzed pharmaceuticals deteriorate is determined by pH, which lowers the effectiveness of medications that are designed with buffers at the pH of maximum stability.

d) Excipients: Excipients with lower water contents, such as starch and povidone, improve the stability of a mixture by emphasizing the water content. Similarly, there exist chemical interactions between medications and excipients that result in decreased insecurity.

e) Oxygen: In certain compounds, the presence of oxygen promotes oxidation. When exposed to oxygen, products with advanced corruption rates are stabilized by replacing oxygen in the storage tank with carbon dioxide and nitrogen.

f) Light: The rate of corruption rises in the presence of light. Because some medications are photosensitive, it is possible to compare how stable they are in the dark or when exposed to light. Medication that is photosensitive needs to be stored in a dark area and packaged in a glass amber bottle.

8. STABILITY INDICATING ASSAY METHOD[8]

A stability indicating method (SIM) is an analytical technique used to quantify the amount of active pharmaceutical ingredient (API) that is lost as a result of deterioration in a drug product. "A validated quantitative analytical approach that can detect the changes with time in the pertinent properties of the drug substance and drug product" is what the FDA guideline document defines as a stability-indicating method. A stability-indicating approach precisely evaluates variations in the concentration of the active ingredients without the impact of extra degradation products, impurities, or excipients. Stress tests are performed to demonstrate how well the developed approach works in situations where there is limited knowledge of potential degradation products in terms of assessing changes in medication substance concentration. The development of a suitable stability indicating method underpins the pre-formulation studies, stability studies, and establishment of suitable storage requirements.

a. Preparation of sample

The proper preparation of the sample is an essential stage in the stability indicating assay technique. Understanding the drug's structure and how it breaks down is crucial to selecting the right strategy. Since the processed sample is used for stress testing, understanding its breakdown profile, related contaminants, and based products from previous samples can help create an efficient stability indicating assay method. To obtain samples for the stability indicating assay process, the API is pushed to deteriorate under conditions more severe than accelerated degradation settings. It involves the hydrolytic, oxidative, photolytic, and thermal conditions discussed earlier for drug degradation. Forced degradation of API in solid state and solution form is

carried out to generate degradation products that are expected to occur under real storage conditions. After that, a SIM is created with this example.

b. Method selection

The method's selectivity and specificity, or how delicately it can assess the given material, determine which approach is best. The methodology is selected after a careful analysis of the literature for a sample that is anticipated to be used and for which procedures have already been developed. It relies on the method's ability to discriminate between the drug's deteriorated outcome and its active pharmaceutical components (API), as well as any associated impurities.

c. Method development and optimization

Finding the pKa value, log P, solubility, and max of the pertinent drug is the first step in developing a procedure. It is standard procedure to use HPLC in a reverse phase technique for pharmaceutical separation. A mobile phase consisting of acetonitrile, water, and methanol can be used in different ratios for the initial phases of separation. Methanol or acetonitrile should be selected for the organic phase based on the solubility of the analyte. The water:organic phase ratio can be first adjusted at 50:50 to provide a good separation of peaks, and as trials progress, pertinent changes can be made. Finding a specific column and mobile phase that may successfully divide the active component and its associated product is a step in the method development process. In order to optimize the parameters and achieve a successful separation, developing a method may need a process of trial and error. The developed method is considered homogeneous if the drug peak's area under the curve and percentage remain unchanged, but the degradation peak is observed. If the area % of the drug peak and degradant peaks do not change, then the drug peak is considered homogeneous. It would be acceptable if it turned out that the co-eluting degradant was not produced under conditions of rapid and extended storage. The process is then optimized to isolate tightly eluting peaks by varying the injection volume, flow rate, column type, and mobile phase ratio. Once these parameters have been optimized, the study's procedure will be validated in compliance with ICH guidelines.

9. METHOD VALIDATION

When verifying a procedure, the ICH guidelines are adhered to. The accuracy, precision, linearity, LOQ, LOD, robustness, and roughness of each recently created novel technique are assessed. As per the recommendations provided by ICH, the RSD number need to be below 2%. Once it is determined that the degradants above the identification threshold (about 0.1%), they need to be separated, identified, and quantified. If the method fails to meet the validation's acceptance requirements, it is changed and revalidated.

10. RELATION BETWEEN FORCED DEGRADATION AND STABILITY[8]

Forced degradation studies yield more items than normal stability tests. It can be difficult to identify true degradation products during stability testing because of their restricted potential. From this perspective, studies on forced deterioration minimize this problem. The procedure can be viewed as a stability signaling approach since it is assumed that the medicinal ingredient is stable under the given stress conditions if no degradation products are produced. Forced deterioration analysis can also be used to study the proper storage conditions for specific pharmaceuticals. More significantly, forced degradation studies are useful in determining the mechanism of degradation of many pharmaceutical substances.

11. RECENT ADVANCEMENTS IN STABILITY TESTING AND DEGRADATION STUDIES[10]

The effectiveness and dependability of stability testing and degradation studies have been improved by recent developments in analytical instrumentation, technique, and data analysis.

High-volume screening: High-throughput screening of drug formulations has been made possible by automation, robotics, and downsizing, which has sped up stability testing and degradation investigations. Rapid examination of a large number of samples is made possible by high-throughput technologies, which helps with regulatory submission and formulation development decision-making.

Advanced analytical techniques: The sensitivity, selectivity, and resolution of analytical methods used in stability testing and degradation studies have been increased by developments in chromatography, spectroscopy, mass spectrometry, and imaging techniques. Comprehensive characterization of degradation products, contaminants, and excipients in medication formulations is made possible by these approaches.

Predictive modeling: Degradation pathways, stability trends, and degradation kinetics are being predicted more and more by computational modeling and data-driven techniques including Artificial Intelligence (AI) algorithms and Quantitative Structure-Activity Relationship (QSAR) modeling. In addition to helping with formulation optimization and risk assessment, predictive modeling improves the effectiveness of stability testing.

CONCLUSION

The stability-indicating method is an analytical technique that may distinguish any degradation (decomposition) product(s) created under certain storage conditions during the stability evaluation period from the principal active (intact) pharmaceutical ingredients (API). To guarantee the stability of drug substances and drug

products over their retest period and the shelf life of the final product, a technique must be developed and validated. In order to ensure that the product is used safely and effectively, it entails stress testing to determine the degradation pathway and stating any limits of specification existing in the finished product during its shelf life.

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