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# Stability Indicating Assay Method

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**Abstract**-:

Pharmaceutical stability is the ability to sustain the product's identity, quality, purity, and safety over the course of its shelf life. A stability-indicating assay method is a validated quantitative analytical approach that may detect changes over time in the chemical, physical, or microbiological features of a drug substance or drug product in particular manner that allows the concentration of the active components and product degradation to be measured accurately and unaffectedly.

A Stability Indicating Method (SIM) is a validated analytical peptide testing procedure that accurately and precisely assesses active ingredients (drug substance or drug product) free from process impurities, excipients, and degradation products, in accordance with FDA guidelines (Guidance for Industry, Analytical Testing Procedures and Methods Validation, FDA, 2000). A stability indicating method's crucial aim is to maintain a close watch on the final results of stability research in order to safeguard their safety, potency, and quality. The primary goal of stability indicating methods in contemporary times is to provide details about the facts of stress testing with the aim to estimate the stability of pharmaceutical substances and products.

**Key words-**stability indicating assay methods, stress testing, ICH guidelines.

## Introduction-

For secure and effective use, it is vital that drug quality continues to exist across the product life cycle. The arrival of various stability assessment methods is an outcome of the necessity for constantly monitoring the pharmaceutical ingredient and product for quality and purity.[1] Applying these techniques, the amount of drug substance in the presence of additional pollutants excipients, and degradation products can be determined without the separation of these components. Small molecule medicines' chemical stability studies are assessed mainly by employing chromatographic or other separation assays that are able to separate and quantify significant impurities and degradation products.A quantitative or analytical method called the stability indicator assay method is based on the chemical and structural characteristics of each active ingredient[2]

The stability indication assay method is a quantitative/analytical technique that relies on the structural and chemical features of each active component that makes up a medicinal product and that will recognize each active ingredient synthesis with the objective to accurately measure the active ingredient concentration. A stability indicating assay method's significant objective is to constantly keep an eye on the results of stability investigations in order to ensure their safety, efficacy, and quality.[3] To bring consistency to the stability assessment requirements for pharmaceutical products across different geographical regions, the ICH stability testing guideline was set up. Pharmaceutical companies used an array of conditions for prolonged testing prior to the acceptance of the ICH guidelines, sometimes lacking time or temperature control. This yielded

unpredictable results and made it challenging to determine the stability of products from various companies.[4]

A SIM, according to the FDA, is "an analytical procedure that is able to detect changes in the composition of a drug substance or drug product that may affect its safety or efficacy." To put it another way, a SIM must be able to recognize the development of degradation products that can endanger patients.[5]

The active ingredient(s) of a drug substance or drug product can be precisely and accurately measured using a SIM, which is a validated analytical process. SIMs are employed to monitor pharmaceutical product stability and to spot probable degradation products.[6]

The stability program's early-stage objective is to compile data on the stability of the therapeutic substance in its purest form. The drug product is designed using this knowledge, and the ideal dose form and container closure system are chosen. Consideration should also be given to the effects of pH, moisture, air (oxygen), and light on the stability of the medicinal ingredient. All of these elements may quicken the breakdown of medication ingredients. The formulation team should choose a dosage form and a vehicle that will shield the drug component from these elements.[7]

Although it has an influence on both the safety and efficacy of the medicinal properties. product, the chemical stability of pharmaceutical ingredients is an important cause of concern. Pharmaceutical compounds that are not stable can breakdown, lose their medicinal value, or generate harmful byproducts[8]. This could result in a variety of difficulties, such as:

Reduced efficacy: A drug's ability to have the desired medical influence may be reduced if it is not stable. This could result in the patient's condition becoming worse and the treatment fail.

Negative consequences Pharmaceutical compounds may dissolve down into dangerous byproducts that can harm patients. These side effects might be fatal in certain situations and can range from mild to severe.

Infection risk: Degradation products of pharmaceutical molecules can also provide a breeding ground for bacteria and other microorganisms. This can increase the risk of infection in patients.

**objectives of stability studies-**

1. Stability studies are carried out to determine the API and product's shelf life and storage requirements. They involve subjecting the medication product to various environmental factors over time, including heat, light, and humidity, while keeping an eye on its chemical and physical characteristics. This data is utilized to assess the stability of the medication product and establish storage conditions that will guarantee its security and effectiveness.[9]

2. Stability testing is crucial to the process of creating new drugs. It contributes to the safety and efficacy of pharmaceutical goods for the purposes for which they are designed, safeguards the reputation of the manufacturer, and complies with regulatory agency criteria. The results of stability testing can also be utilized to create novel pharmaceutical formulations.[10]

3.Identify any potential stability issues that could lead to degradation of the drug product or the formation of harmful byproducts. This information can then be used to take corrective action, such as reformulating the drug product or changing the storage conditions.[11]

4.Provide data that may be of value in formulation of other products. The data from stability testing can be used to develop formulations that are more stable and have a longer shelf life.[12]

**REGULATORY STATUS OF STABILITYINDICATING ASSAYS-**

The stability evaluation of new drug substances and products is governed under ICH guideline Q1A. illustrates the need for accepted stability-indicating methods of testing to be used for determining features that are likely to change during storage and may have an effect on quality, safety, or efficacy. Analytical procedures termed stability-indicating assays (SIAs) will detect changes in a drug substance or pharmaceutical product that could affect its safety or efficacy. To ensure that SIAs are accurate, dependable, and reproducible, they must be

validated.[13]Stability-indicating assays should be used to assess the following characteristics of drug substances and drug products, accordance to the ICH Q6A guideline.[14]:

Identity: The assay need to be able to tell the drug substance or drug product from its contaminants.

Purity: The assay should be able to accurately measure the concentration of the drug substance or drug product.

Potency: The assay should be able to accurately measure the efficacy of the drug substance or drug product.

Stability: The assay should be able to detect changes in the drug substance or drug product over time.

The Q7A guideline states that the test procedures used in stability testing should be able to detect changes in the API that could affect its quality, safety, and efficacy. The test procedures should also be validated to ensure that they are accurate, reliable, and reproducible[15].The ICH Q7A guideline also provides a list of specific test procedures that can be used for different types of APIs. These tests are considered to be appropriate for most cases, but they may not be suitable for all APIs. In some cases, it may be necessary to develop a new test procedure that is specifically designed for the API in question.

**STEPS INVOLVED DURING THE DEVELOPMENT OF STABILITY—INDICATING ANALYTICAL METHODS (SIAMs)-**

The FDA recommends that all assay content methodologies for stability studies be stability indicating. According to FDA regulations, a SIAMs is defined as a fully validated method that accurately and precisely measures API free from potential interferences like degradants, biproducts, intermediates, and excipients.[16]

The following stages are taken while developing stability-indicating analytical methods (SIAMs):

step 1:Pick an appropriate analytical technique. Choosing a good analytical strategy for the SIAM is the first step. The technique must be able to measure the concentration of the drug substance or drug product over time with accuracy and dependability. Additionally, it should be tailored to the particular medication ingredient or drug product in question and unaffected by modifications to the formulation oror by the environmental conditions under which the stability testing is conducted.

**1.determination of limit of quantification (LOQ)**-The assessment of the method's Limit of Detection (LOD) and Limit of Quantification (LOQ) is closely related to the determination of the degree of deterioration. According to ICH Q3B (R2), these limits should be directly tied to the reporting, identification, and qualification of degradation products.[17] It is typical to require analytical methods to be validated for their capacity to quantify possible degradation products and medication contaminants with a LOD and LOQ at least as high as as perceptive as the ICH threshold (see Figure.1.)

Figure 1: ICH Q3B for New Drug Applications' degradation product levels

**Reporting threshold**

| Maximum Daily Dose | Threshold |
|---|---|
| < 1.g | 0.1% |
| >1.g | 0.05% |

**Identification threshold**

| Maximum Daily Dose | Threshold |
|---|---|
| <1mg | 1.0% or 5µg TDI, whichever is lower |
| 1mg-10mg | 0.5% or 20ug TDI, whichever is lower |
| >10mg-2g | 0.2% or 2mg TDI,whichever is lower<br>0.10% |

**Qualification threshold**

| Maximum Daily Dose | Threshold |
|---|---|
| <10 mg | 1.0% or 50ug TDI, whichever is lower |
| 10 mg-100 mg | 0.5% or 200ug TDI, whichever is lower |
| >100mg-2g | 0.2% or 3mgTDI, whichever is lower |
| >2g | 0.15% |

**2) Excessive or inadequate stress-** the utilization of an effectively planned and carried out forced degradation research will produce representative samples that will aid must make sure the final technique adequately reflects long-term stability.[18] It is advised to include alkaline and acidic in the text design when discussing the forced degradation (or stress test, both names will refer to the same thing). oxidation, humidity, photolysis, hydrolysis, and climate stress.When there is insufficient or excessive deterioration, circumstances might be changed to be harder or softer. As unusual degradants may develop with cosolvents, data needs to be reviewed. Acid/base diluting may lessen the severity of conditions if too much degradation is identified, and degradation products do not need to be reported in stability analyses, however SIM could guarantee that these contaminants do not obstruct the analysis of degradation products.[19]

**3) Forced degradation studies (stress studies)-**

Studies on forced deterioration or stress are conducted to purposefully deteriorate the sample. These investigations are performed to assess an analytical technique's capacity to quantify an active substance and its breakdown products without interference can potentially cause degeneration products. In order to improve a drug product, these studies may also be useful in formulation development, manufacturing, and packaging.

The following are some justifications for conducting forced degradation studies: creation and validation of stability-indicating methods, identification of mechanisms for drug and substance degradation Identification of breakdown products in products formulas relating to drug compounds as opposed to hose that are related to substances other than drugs .[20]

**step2.Validate the analytical method-.** Once a suitable analytical method has been selected, it must be validated. Validation is the process of demonstrating that the analytical method is accurate, reliable, and reproducible. The validation process typically involves the following steps:[21]

- Establishing the specificity of the method: This involves demonstrating that the method is only able to detect the drug substance or drug product in question.
- Establishing the accuracy of the method: This involves comparing the results of the method to the results of a reference method.

- Establishing the precision of the method: This involves measuring the variation in the results of the method when it is performed multiple times under the same conditions.
- Establishing the robustness of the method: This involves demonstrating that the method is not affected by changes in the sample preparation, the instrumentation, or the data analysis.

**step3.Conduct stability testing**. Once the analytical method has been validated, it can be used to conduct stability testing. Stability testing is the process of exposing the drug substance or drug product to a variety of environmental conditions, such as heat, light, and humidity, and monitoring its chemical and physical properties over time. The results of the stability testing can be used to determine the shelf life of the drug substance or drug product and to identify any potential stability issues.

**step4.Establish the acceptance criteria for the SIAM**. The acceptance criteria for the SIAM must be established based on the results of the stability testing. The acceptance criteria should be set so that the drug substance or drug product will meet its specifications throughout its shelf life.

**step5.Document the SIAM.** The SIAM must be fully documented, including the method development and validation results, the stability testing results, and the acceptance criteria. The documentation should be clear and concise, and it should be easy to follow.

**case study1**

**Validated stability- indicating HPLC method for simultaneous determination of ampicillin cloxacillin in combination drug products.[22]**

According to ICH, degradation investigations were conducted in acidic, alkaline, neutral, oxidative, light, and thermal environments.

Developed SI HPLC method:

Acetonitrile:Phosphate buffer(PH 5.0) in the ratio of 15:85 (v/v) for 1min, then changed to 30:70 for next 14 min finally equilibrated back to the same ratio of 15:85 (v/v)from 15-20 min.

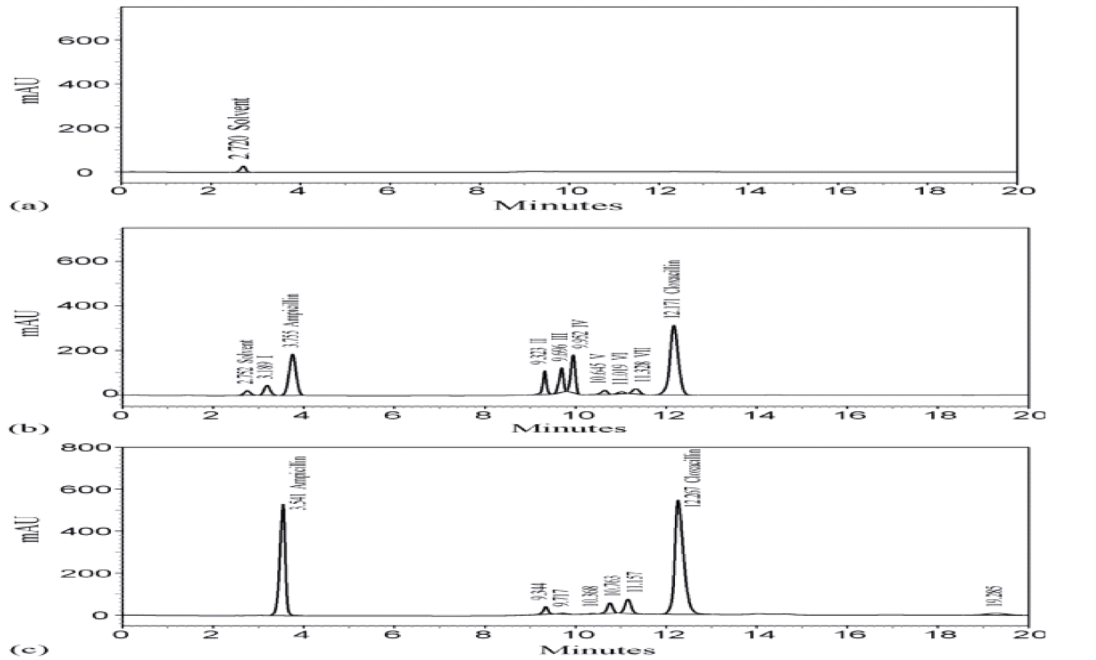


Fig. 8. Chromatograms showing resolution of components in (a) blank (b) mixture of stress samples (c) degraded formulation[6]

**Key**: Acidic condition: II,III & IV alkaline condition: I,III& IV neutral condition: I,III,V& VII, oxidative condition: I, IV&V light and thermal condition: II, V& VI

6) V. kumar, H. Bhutani, S. Singh, Journal of pharmaceutical and biomedical analysis, vol.43(2007) page no.769-773.

**ADDITIONAL ANALYTICAL METHODS FOR SIM-**

Methods that indicate stability will have high biological activity, purity, and potency.[23]

Several techniques, including as electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blotting, isoelectrofoccusing), high-resolution (For instance, reversed phase Gel filtration, SEC, chromatography, and ion affinity chromatography, exchange, and Mapping peptides [24]The chosen analytical technique should be capable of detecting contaminants at a level of 0.05% of the sample. analyte of interest or less) and the peak replies must fall between the linearity of the detector. All impurities created during a formal stability investigation at or should be captured by the analytical approach. lower than the ICH thresholds [25,26].

With the use of these methods, it is possible to gain more understanding about the impurities' structure. A potential structural alerts area is provided for A discussion about genotoxicity and how to manage such impurities restricted more strictly [27,28,29].

When necessary to create stability Indicating method, new analytical technologies that are constantly being developed can also be applied[30] Structural analysis of degradation products is required for contaminants generated during formal shelf-life stability studies and over the qualification threshold limit [26].

Using different chromatographic techniques, such as Reversed Phase High Performance Liquid Chromatography (RP-HPLC), Thin Layer Chromatography (TLC), Gas Chromatography (GC), Capillary Electrophoresis (CE), Capillary Electrophoresis Chromatography (CEC), and Super critical Fluid Chromatography (SCFC), the unknown impurity that is observed during the analysis, pharmaceutical development, stress studies, and formal stability studies of the drug substances and drug product can be anayzed.[31]

**Reversed Phase High Performance Liquid Chromatography (RP-HPLC):** RP-HPLC is the method of choice for protein separation and one of the most essential processes for protein separations. RP-HPLC has been utilised on a large industrial scale along with the nano, micro, and analytical levels for preparative purifications.[32]

**TLC: Thin Layer Chromatography-**

Non-volatile mixtures can be isolated utilizing a technique called thin layer chromatography. The experiment is performed on a piece of glass, plastic, or aluminum foil that has been lightly coated with an adsorbent compound. In general, silica gel, cellulose, or aluminum oxide can be used as the constituent.[33]

**Gas chromatography-**

In analytical chemistry, gas chromatography (GC) is an effective form of chromatography used for separating and analyzing substances that can be evaporated without decomposing. GC is frequently employed to assess a substance's purity or to distinguish between the various ingredients in a mixture.[34]

**(CE) Capillary Electrophoresis-**

With the help of an applied voltage, the analytical approach of capillary electrophoresis separates ions owing to their electrophoretic mobility. The electrical charge of the molecule, viscosity, and atom radius all influence electrophoretic mobility.[35]

**Chromatography via Capillary Electrophoresis (CEC)-**

Capillary electrochromatography (CEC) is a micro-scale separation procedure which combines liquid chromatography (LC) and capillary electrophoresis (CE). In packed, monolithic, and open-tubular columns, CEC can be performed successfully.[36]

**Supercritical Fluid Chromatography (SCFC)-**

A supercritical fluid, such as carbon dioxide, is employed as the mobile phase in supercritical fluid chromatography (SFC), a form of normal phase chromatography. It can be employed for separating chiral

compounds and is used for the analysis and purification of minor to moderate molecular weight, thermally unstable molecules.[37]

Liquid chromatography-mass spectrometry (LC-MS) and HPLC-DAD (High Performance Liquid Chromatography Photodiode Array ultraviolet Detector) are employed to compare the RRT (relative retention time), UV spectra, and mass spectra (MS/MS or MSN).[38]

**Applications of SIAMs-**

Stability studies are used to determine the active ingredient's re-test period, or the amount of time it may be kept and utilized without being examined right away, as well as the shelf life of the final product.[39]

The product's release and shelf life parameters may vary to account for active ingredient degradation or other permissible modifications that may happen during storage.[40,41]

Drug stability test guideline Q1A (R2) from the International Conference on Harmonization (ICH) mandates that stability samples must be analyzed using SIAMs, or proven stability-indicating analytical procedures.[42]

In order to determine the drug substance's intrinsic stability qualities and to support the acceptability of the suggested analytical process, it also advises conducting stress tests on the drug substance.[43,44]

The stability samples of drug substance and drug product will be rigorously tested using the proven SIAMs.

**CONCLUSION-**

Always plan and analyze stress tests for the development of a stability indicating method with common sense and chemical expertise, taking into account the manufacturing process and the makeup of the finished drug product.[45] The FDA has now made stability indicating test methods a requirement because they are connected to the security of medicinal products. The importance of developing and validating analytical methods has increased recently with the advancement of chromatographic techniques due to their high sensitivity, selectivity, and ability to distinguish between the target analyte of interest and its related substances, which is useful for establishing their limits of specifications in finished products.[46] The developed stability indicating assay method was validated in terms of accuracy, linearity, precision, limits of detection (LOD), and quantification (LOQ) in accordance with ICH Q2(R1) guidelines and was found to be simple, accurate, sensitive, specific, and quick for the simultaneous estimation of metformin hydrochloride and canagliflozin.[47]

An analytical technique known as a "stability-indicating method" can distinguish between the main active (intact) pharmaceutical ingredients (API) and any degradation (decomposition) product(s) produced under specific storage conditions over the course of the stability evaluation period. In order to be able to accurately determine the analyte's concentration at any point during storage, modern testing of the selective analyte of interest has replaced conventional testing of the specific analyte of interest.[48] This is done by studying the analyte's associated impurities and related products that are produced during its storage conditions.The automated forced degradation approach streamlines the forced degradation operating procedures and considerably decreases the amount of manual work required to conduct the tests.[49]. In order to create stability-indicating and degradant-monitoring methodologies as part of a validation program, forced degradation experiments are essential. Studies on forced deterioration offer vital insight into the investigation of degradation products since they produce representative samples, which in turn aid in the development of stability-indicating techniques.

Additionally, it entails stress testing to determine the degradation pathway and defining its boundaries of specification existing in the finished product during its shelf life, resulting in a product that is safe and effective to use.[50]

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