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Development of Stability Indicating Method and Study of Validation on the Pharmaceutical Drug Substances by RP –HPLC

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Abstract: High performance liquid chromatography (HPLC) is an integral analytical tool in assessing drug product stability. HPLC method separates, detects, and quantifies the various drug-related degradants that can form on storage or manufacturing of the compounds also detects and quantifies any drug-related impurities that may be introduced during synthesis. Forced degradation studies of new chemical entities and drug products are essential to develop and demonstrate the specific stability- indicating methods. In addition to demonstrating specificity, forced degradation studies can be used to determine the degradation pathways and products that could form during storage and also facilitate the formulation, development of manufacturing and packaging of pharmaceutical drugs. For marketing applications, current Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) guidance recommends inclusion of the results, including chromatograms of stressed samples, demonstration of the stability-indicating nature of the analytical procedures and the degradation pathways of the Active Pharmaceutical Ingredients (API) in solid state, solution, and drug product. A review of literature reveals that a large number of methods reported over the period of last 3 – 4 decades under the nomenclature. An analytical method is developed to test the quality of API is to be validated before its intended use. The objective of validation of an analytical procedure is to demonstrate that it is stable for its intended purpose.

The most of the stability-indicating methods reported fall short in meeting the current regulatory requirements. Hence a systematic approach for the development of validated stability- indicating assay method (SIAM) that can meet the current ICH and regulatory requirements has to be developed. The stability-indicating assay is a method that is employed for the analysis of stability samples in pharmaceutical industry. With the advent of International Conference on Harmonisation (ICH) guidelines, the requirement of establishment of stability- indicating assay method (SIAM) has become more clearly mandated. The guidelines explicitly require conduct of forced decomposition studies under a variety of conditions, like pH, light, oxidation, dry heat, etc. and separation of drug from degradation products. Stability testing of drug substance requires an accurate analytical method that quantities active pharmaceutical ingredients (API) without interference from degradation products.

I. Regulatory Guidelines of ICH

A. Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

B. Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

C. Efficiency Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

D. Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology , the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

II. NEED FOR STABILITY STUDIES

- To determine the shelf life of the drug and drug product.
- To determine the storage conditions of the drug product.
- To assess the inherent stability of a drug and to improve formulations and the manufacturing process.
- To identify reactions which are involved in the degradation of a product.
- To develop and demonstrate the specificity of validated analytical methods.

III. STABILITY INDICATING HPLC METHOD

Step I: Understanding of the physicochemical properties of drug.

Step II: Set up Preliminary HPLC condition

Step III:Preparation of samples required for method development.

Step IV: Developing Separate Stability Indicating Chromatography Conditions.

Step V: Method Optimization: The experimental conditions.

Step VI: Validation of analytical method.

A. Objectives of Research

- To Develop Stability Indicating Related Substances Methods by Using HPLC for Active Pharmaceutical Ingredients (API).
- Validation of Developed Methods w.r.t to Specificity, LOD, LOQ, Precision, Linearity, Accuracy, Ruggedness, Robustness and solution stability, to meet the Regulatory Guidelines.
- Determination of degradation pathways of drug substance and drug products and to generate a degradation profile.
- Discrimination of degradation products in formulations related to drug substances versus those that are related to non-drug substances (eg, excipients).
- Discrimination of degradation products in formulations related to drug substances versus those that are related to non-drug substances (eg, excipients).
- Determination of the intrinsic stability of a drug substance molecule in solution and solid state.
- Reveal the thermolytic, hydrolytic, oxidative and photolytic degradation mechanism of the drug substance and drug product.
- To develop and validate a stability indicating method.
- To identify impurities related to drug substances or excipients.
- To understand the drug molecule chemistry.
- To generate more stable formulations.
- To solve stability related problems.

B. Importance of HPLC

In combination products it is important to know the interaction between the components .During the stability study if there is any interaction happened between the combination drugs it may lead to adverse effect to the patients. Hence study the interaction between the combination drugs and its impurity profile is mandatory. HPLC technique is a well versatile to study the drug content and its impurities within short run time.

IV. VALIDATION PARAMETERS

During the method validation the following Parameters are considered.

A. Analytical Procedure

The analytical procedure refers to the way of of performing the analysis. It should describe in detail the steps necessary to perform each analytical test.

B. Specificity

Specificity is the ability to assess and unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc..

C. Accuracy

The Accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

D. Precision

The Precision of an analytical procedure expressess the closeness of agreement between a series of measurements obtain from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels. i.e., Repeatability intermediate precision and reproducibility. The Precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

E. Linearity

The Linearity of an analytical procedure is its ability to obtain test results which are directly proportional to the concentration of analyte in the sample. A Linear relationship should be evaluated across the range of the analytical procedure.

F. Limit of Detection

The Limit of Detection of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. Signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the limit of detection. Based on the Standard deviation of the response and the slope the limit of detection may be expressed as:

$LOD = 3.3\ \sigma/S$

Where, σ = The standard deviation of the response , S = The slope of the Calibration curve

G. Limit of Quantification

The Limit of Quantization of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determine with suitable precision and accuracy. A typical signal - to - noise ratio is 10:11 is generally considered acceptable for estimating the limit of quantization. Based on the standard deviation of the response and the slope the limit of quantization may be expressed as:

$LOD = 10\ \sigma/S$

Where, σ = The standard deviation of the response , S = The slope of the Calibration curve

H. Range

The Range is normally derived from Linearity studies and depends on the intended application of the procedure. It is established by confirming that the analytical procedure provides an acceptable degree of Linearity, accuracy, and precision when applied to samples containing amounts of analyte within the specified range of the analytical procedres.

I. Robustness

It is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides and indication of its reliability during normal usage.

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