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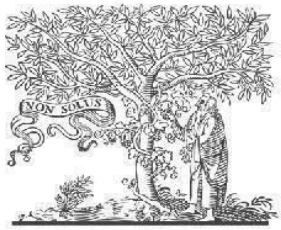

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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION: A REVIEW WITH CASE STUDY

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ABSTRACT
Analytical technique development, validation, and transfer are essential components of pharmaceutical development. Effective method development optimizes laboratory resources and ensures techniques meet drug development objectives at all stages. High-performance liquid chromatography (HPLC) is a reliable technology for both qualitative and quantitative analysis of medicinal products. Developing and validating analytical methods are crucial for drug discovery, development, and manufacturing. This process involves determining the purity and toxicity of a pharmacological substance. Method development includes identifying the interested component in finished products or in-process tests, and preparing drug product samples. It provides practical approaches for determining selectivity, specificity, limit of detection, limit of quantitation, linearity, range, accuracy, precision, recovery, solution stability, ruggedness, and robustness of liquid chromatographic methods. These methods support routine, in-process, and stability analysis.

KEYWORDS – Analytical Method Development. Method Validation, Accuracy, Precision, LOD, LOQ, System Suitability, case Study on Climbazole and Montelukast.

INTRODUCTION
Any product or service requires analysis, but this necessity is even more critical for drugs, as they directly impact human health. Analytical chemistry, the study of separation, measurement, and identification of chemical additives, plays a vital role in this process.
Materials, whether made from herbs or synthetics, often contain multiple substances or ingredients. Analytical chemistry is divided into two main branches: qualitative evaluation, which identifies the chemical additives present in a sample, and quantitative evaluation, which determines the amount of specific compounds in the sample.
Pharmaceutical analysis is crucial for assessing the quality control and assurance of pharmaceutical formulations and bulk drugs. Advances in analytical tools and techniques have significantly improved both the scientific and practical aspects of analysis, leading to reduced time and cost, and increased precision and accuracy.
Regulatory organizations require the development and validation of analytical techniques for active pharmaceutical ingredients, excipients, related substances, drug products, degradation products, residual solvents, and more. The development of these analytical methods results in

official test methods used by quality control laboratories to verify the efficacy, identity, purity, safety, and performance of drug products. Regulatory bodies highly value the significance of analytical procedures in production. To gain drug approval, applicants must demonstrate control over the entire drug development process using validated analytical methods.

Definition of Validation

The FDA (Food and Drug Administration) defines validation as a production and process control procedure that ensures the identity, strength, quality, and purity of drug products. According to FDA guidelines from May 1987, the validation package must include all data and test procedures needed to demonstrate that the system and process meet the required standards.

Analytical Method Development

In the analysis of new products, novel methods are developed when established methods are not available. These new techniques are designed to analyze both pharmacopoeial and non-pharmacopoeial products efficiently, aiming to reduce costs while enhancing robustness and precision.

These methods undergo optimization and validation through trial runs. Alternative approaches are explored and implemented based on their advantages and disadvantages, aiming to replace existing strategies with more effective laboratory data comparisons.

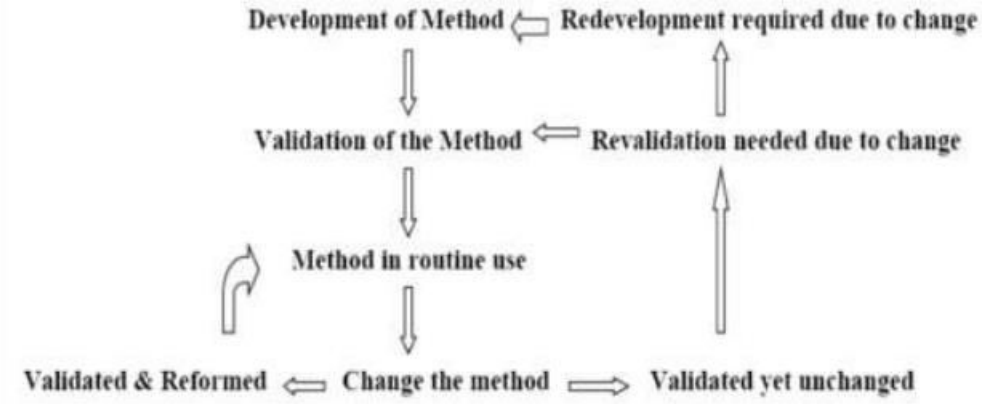

Fig. 1: Life cycle of the analytical method

Purpose of Analytical Method Development

Drug analysis involves the identification, characterization, and quantification of pharmaceuticals in mixtures such as dosage forms and biological fluids. Analytical methods are crucial in the manufacturing process and drug development to provide information on potency (related to dosing accuracy), impurity levels (impacting drug safety), bioavailability (including factors like crystal form, uniformity, and release profile), stability (indicating degradation products), and the influence of manufacturing parameters to ensure consistent drug product quality.

Quality control aims to verify and authenticate products through procedures designed to prevent and rectify errors at various production stages. Decisions regarding product release or disposal rely on these control measures. Developing straightforward and robust analytical procedures for diverse formulations is of utmost importance. The demand for new analytical techniques in the pharmaceutical industry has grown rapidly due to global industry expansion

and continuous drug production, making analytical method development a fundamental task in quality control laboratories.

Need for Analytical Method Development and Validation

- **Cost and Efficiency**: Existing methods may be costly, time-consuming, or resource-intensive, or may lack automation capabilities.
- **Reliability**: Current methods may be prone to errors, susceptible to contamination, or unreliable.
- **Sensitivity**: Some methods may not offer adequate sensitivity to detect low levels of substances.
- **Regulatory Compliance**: New methods may be necessary to meet regulatory requirements.
- **Specificity**: Criteria for drug selection may not be met by existing analytical methods.
- **Formulation Challenges**: Interference from excipients in formulations may render existing methods inadequate.
- **Biological Fluids**: Existing methods may not be available for quantifying drugs in biological fluids.
- **Combination Products**: Analytical methods may not exist for drugs when combined with other medications.

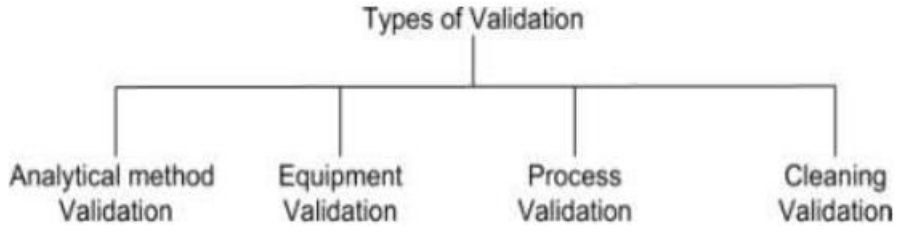

Fig 2: Validation Type

Analytical Method Validation

Method validation, as defined by ICH Q2 (R1), involves providing documented evidence that a process consistently produces results within predetermined parameters and quality characteristics.

Analytical methods must be suitable for their intended use and must confirm the identity, quality, purity, and potency of pharmaceutical substances and products. Validation of methods is essential for both new and established methods used across various laboratories and by different analysts.

Performance Characteristics and Guidelines

Various guidelines outline the performance characteristics that must be validated for analytical methods:

1. **USP Guidelines**:
   - Accuracy
   - Precision
   - Specificity
   - Limit of detection
   - Limit of quantitation

- Linearity
- Range
- Ruggedness
- Robustness

2. **ICH Guidelines**:
- Accuracy
- Precision
- Specificity
- Limit of detection
- Limit of quantitation
- Linearity
- Range
- System suitability
- Robustness

3. **FDA Guidelines**:
- Accuracy
- Precision
- Specificity/selectivity
- Limit of detection
- Limit of quantitation
- Linearity
- Range
- System suitability
- Reproducibility
- Sample solution stability
- Robustness

4. **European Guidelines**:
- Accuracy
- Precision
- Specificity
- Limit of detection
- Limit of quantitation
- Linearity
- Range

Instances Requiring Validation, Verification, or Revalidation

Analytical methods need validation, verification, or revalidation in the following circumstances:

- Before initial use in routine testing
- When transferred to another laboratory
- Whenever conditions or method parameters change (e.g., different instrument characteristics or sample matrices).

Types of Analytical Procedures to Validate

Analytical procedures that typically require validation include:

- Identification tests: Ensuring the identity of an analyte in a sample.
- Quantitative tests for impurities content: Quantifying impurities present in a sample.
- Limit tests for impurity control: Testing to ensure impurities are within acceptable limits.
- Quantitative tests of the active moiety in drug substances or products: Measuring the concentration of the main component(s) in a drug substance.

Analytical method validation ensures that analytical procedures reliably and consistently provide accurate results for their intended applications in pharmaceutical analysis.

RESULT AND DISCUSSION

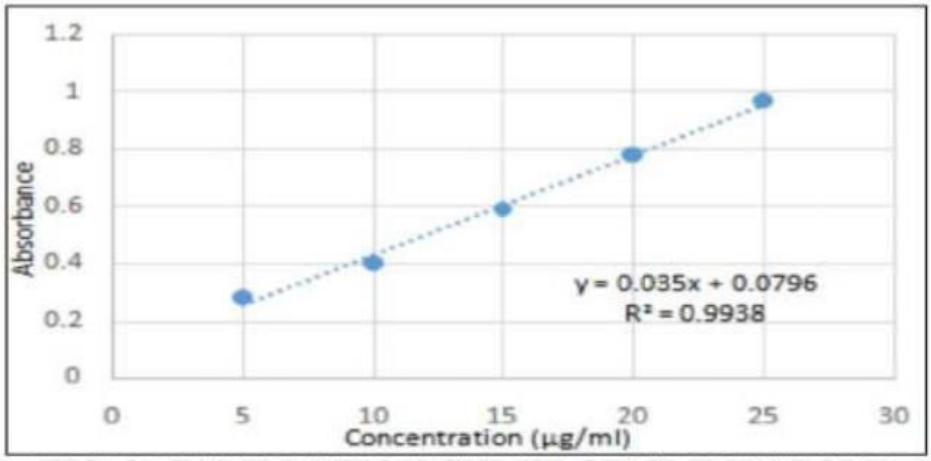

FIG. 3: CALIBRATION CURVE OF CLIMBAZOLE

Concentration(µg/ml)	Absorbance value
5	0.282
10	0.401
15	0.591
20	0.779
25	0.967
Regression equation	Y=0.035x +0.0796
R^2	0.9938

TABLE 2: ESTIMATION OF ACCURACY BY % RECOVERY METHOD

Sr.no	Concentration(%)	Sample conc. (µg/ml)	Amount added (µg/ml)	% Recovery	Statistical analysis
1	80	5	4	98.08	
2	80	5	4	98.40	
3	80	5	4	98.15	%RSD= 99.89
4	100	5	5	99.50	
5	100	5	5	101.04	
6	100	5	5	98.60	%RSD= 1.66
7	120	5	6	99	
8	120	5	6	99.80	
9	120	5	6	98.01	%RSD= 1.05

CONCLUSION

This review article provides an overview of validation, its types, purposes, and the necessity of these processes. It covers essential validation parameters such as linearity, accuracy, precision, range, limit of detection (LOD), limit of quantitation (LOQ), and specificity.

Validation is a critical technique in the pharmaceutical industry, ensuring that quality is built into procedures to support drug development and production. The main objective of this review article is to enhance the quality of analytical method development and validation. As per section Q2 (R1) of the ICH guidelines, UV spectroscopic analysis has been established and validated for the determination of Climbazole. The validation parameters for both approaches showed a %RSD of less than 2%. Accuracy was assessed using accuracy parameters, confirming results within the acceptable range. Precision of current procedures was verified through intraday and interday precision tests, demonstrating that UV spectroscopy is highly effective for quantifying Climbazole. A newly developed method for Montelukast has been validated for linearity, precision, accuracy, and reproducibility. This spectroscopic method is now suitable for routine estimation of Montelukast in tablet dosage forms.

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