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Implementation of QbD Approach in Analytical Method Development of Acebrophylline and Erdosteine by HPLC

Sahil Prajapati[1], Dr. Deepa Patel[2]
Kalol institute of Pharmacy, India

Abstract: ***The present study focuses on the development and validation of a robust, reliable, and regulatory-compliant analytical method for the simultaneous estimation of Acebrophylline and Erdosteine using High-Performance Liquid Chromatography (HPLC) under a Quality by Design (QbD) framework. The QbD approach ensures systematic understanding of method variables, enhanced robustness, and regulatory flexibility. Design of Experiments (DoE) was applied to evaluate critical analytical parameters (CAPs) such as mobile phase ratio, flow rate, and pH, which influence critical analytical attributes (CAAs) including retention time, tailing factor, and theoretical plates. The optimized method was validated according to ICH Q2(R2) guidelines for parameters such as accuracy, precision, linearity, robustness, and specificity. The results demonstrated that the developed RP-HPLC method is accurate, precise, and suitable for routine analysis of the combination.***
Keywords: Acebrophylline, Erdosteine, Quality by Design (QbD), RP-HPLC, Analytical method validation, DoE, ICH Q2 (R2).

I. INTRODUCTION

Analytical method development is a crucial step in pharmaceutical quality assurance, ensuring that a drug product maintains its identity, strength, quality, and purity. Traditional method development often relies on the One-Factor-At-A-Time (OFAT) approach, which is time-consuming and fails to account for interactions between parameters. The QbD approach represents a paradigm shift—focusing on predefined objectives, product and process understanding, and risk management.

Acebrophylline, a bronchodilator and mucolytic agent, and Erdosteine, an antioxidant mucolytic drug, are co-formulated to manage chronic obstructive pulmonary disease (COPD) and bronchitis. Despite their therapeutic importance, no official pharmacopoeial or validated simultaneous estimation method has been established for this combination. Hence, a QbD-driven RP-HPLC method was developed for their simultaneous quantification.

II. QUALITY BY DESIGN (QBD) APPROACH

Quality by Design (QbD), proposed by J.M. Juran and formalized in ICH Q8 guidelines, builds quality into a product rather than testing for it at the end. In analytical method development, QbD involves the following stages:

1) Defining Analytical Target Profile (ATP): Establishes intended method performance, such as specificity, accuracy, precision, and linearity for Acebrophylline and Erdosteine.
2) Identifying Critical Method Parameters (CMPs): Variables such as mobile phase composition, pH, flow rate, and column temperature that influence method performance.
3) Determining Critical Analytical Attributes (CAAs): Parameters like retention time, resolution, and tailing factor affecting output quality.
4) Design of Experiments (DoE): Applied to understand interactions among CMPs and optimize chromatographic conditions.
5) Method Operable Design Region (MODR): Defines the permissible working range ensuring robustness.

The systematic application of QbD minimizes variability, enhances reproducibility, and reduces the need for post-approval revalidation.

III. ANALYTICAL TECHNIQUES

Among various analytical methods, High-Performance Liquid Chromatography (HPLC) stands as a versatile and precise technique for separating and quantifying pharmaceutical analytes. The RP-HPLC technique uses a non-polar stationary phase and a polar mobile phase for effective separation.

A. Key Components Include

Pump system: Ensures consistent flow rate (0.8–1.0 mL/min).
Injector: Delivers reproducible sample volume (typically 20 µL).
Column: C18 stationary phase for separation.
Detector: UV or PDA detector, commonly at 254–274 nm wavelength.
The optimized mobile phase for this study consisted of methanol and buffer system, adjusted to achieve ideal retention times and resolution for both drugs.

IV. DRUG PROFILE

A. Acebrophylline

Chemical Formula: $C_{22}H_{28}Br_2N_6O_5$
Molecular Weight: 616.3 g/mol
Category: Bronchodilator and mucolytic agent
Mechanism: Relaxes airway muscles and enhances mucus clearance.
Solubility: Slightly soluble in water, soluble in ethanol and methanol.
Uses: Treatment of asthma, COPD, and chronic bronchitis.

B. Erdosteine

Chemical Formula: $C_8H_{11}NO_4S_2$
Molecular Weight: 249.3 g/mol
Category: Mucolytic and antioxidant agent
Mechanism: Converts into active metabolite M1 that breaks disulfide bonds in mucus and enhances mucociliary clearance.
Solubility: Poorly soluble in water; soluble in organic solvents like DMSO.
Uses: Management of productive cough and bronchitis.

V. LITERATURE REVIEW

A review of the existing literature indicates that both Acebrophylline and Erdosteine have been individually analyzed by various analytical methods such as UV spectroscopy, HPTLC, HPLC, and UPLC. However, no validated simultaneous estimation method using RP-HPLC has been reported. Patents such as US9133196B2, EP3087979A1, and KR100554108B1 describe improved synthesis and formulations but lack analytical method optimization for combined dosage forms. Hence, this study bridges that analytical gap through a scientifically designed QbD framework.

VI. REGULATORY PERSPECTIVE

The Central Drugs Standard Control Organization (CDSCO) approved the combination of Acebrophylline 100 mg + Erdosteine 300 mg in 2023 for Phase III clinical trials, indicating regulatory recognition of its therapeutic potential. Analytical method development in compliance with ICH Q8, Q9, and Q10 ensures the method's global acceptability. Furthermore, ICH Q2(R2) guidelines govern validation aspects—accuracy, precision, linearity, and robustness—providing a standardized approach to regulatory submission.

VII. FUTURE SCOPE

The developed QbD-based analytical method lays a strong foundation for:
Routine quality control testing of Acebrophylline–Erdosteine formulations.
Stability studies and degradation profiling under ICH Q1A(R2) conditions.
Extension to bioanalytical method development for pharmacokinetic studies.
Application of Green Analytical Chemistry (GAC) principles to further optimize solvent use and minimize environmental impact.

VIII. CONCLUSION

The implementation of the Quality by Design (QbD) approach in RP-HPLC method development provides a structured, scientific, and risk-managed pathway for analytical research. The developed method for simultaneous estimation of Acebrophylline and Erdosteine demonstrates robustness, precision, and regulatory compliance. This approach not only ensures consistent analytical performance but also aligns with modern quality paradigms in pharmaceutical development.

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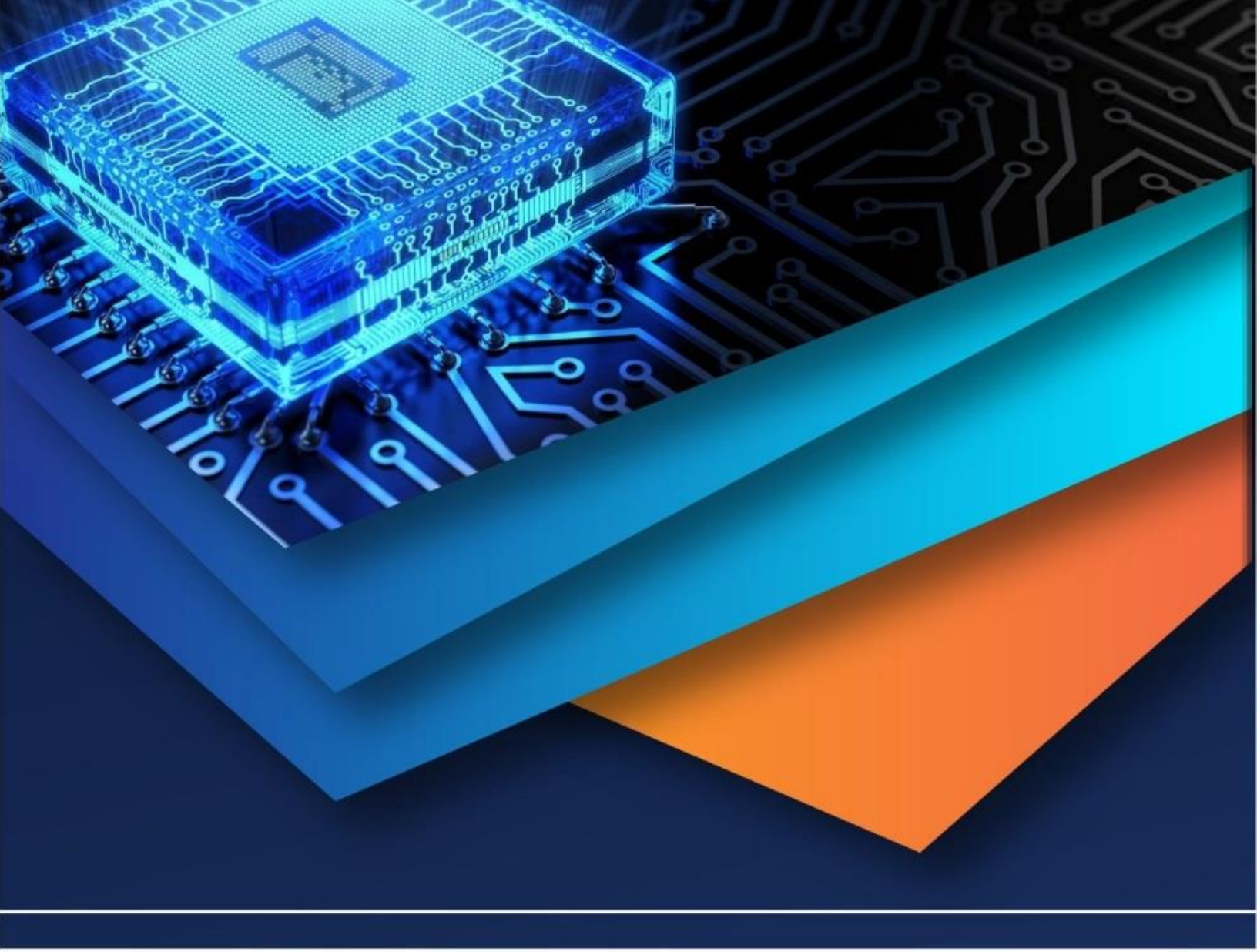

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