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QbD-Based RP-HPLC Method Development and Validation for Quantitation of Rimegepant in Standard and Pharmaceutical Formulations

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ABSTRACT
The pharmaceutical industry relies heavily on advanced analytical techniques to ensure the quality, safety, and efficacy of drugs. Quality by Design (QbD) has emerged as a systematic and scientific approach to analytical method development, emphasizing understanding and control of variability to achieve predefined objectives. This study focuses on the development and validation of a reverse-phase high-performance liquid chromatography (RP-HPLC) method for quantifying Rimegepant, a calcitonin gene-related peptide (CGRP) receptor antagonist, used in treating migraines.
The QbD framework was applied to optimize critical analytical parameters, including mobile phase composition, pH, flow rate, and detection wavelength. Using tools like Failure Mode and Effect Analysis (FMEA) and Design of Experiments (DoE), critical method variables were identified, optimized, and evaluated within a design space. The method was validated as per ICH Q2(R1) guidelines, assessing parameters like specificity, accuracy, precision, linearity, robustness, and sensitivity.
The validated method demonstrated excellent performance, meeting all regulatory requirements, and was successfully applied for routine analysis of Rimegepant in bulk and pharmaceutical formulations. This approach provides a robust, efficient, and regulatory-compliant framework for method development, ensuring reproducibility and reliability.
Keywords: Rimegepant, Reverse-Phase High-Performance Liquid Chromatography, Quality by Design, Analytical Validation, Migraine Therapy

I. INTRODUCTION

- The pharmaceutical industry prioritizes the development of robust analytical methods to ensure the safety and efficacy of therapeutic drugs.
- Analytical techniques like RP-HPLC are widely employed for quality control due to their high sensitivity, accuracy, and reproducibility.
- Traditional method development often relies on trial-and-error approaches, which can lead to inefficiencies and inconsistencies.
- Quality by Design (QbD) offers a structured, risk-based, and scientifically driven approach to analytical method development.
- Rimegepant, a CGRP receptor antagonist, represents a significant advancement in acute migraine therapy. Its precise quantitation is essential for quality control.
- The application of QbD principles ensures that critical method parameters are systematically optimized, resulting in a robust and reliable method for Rimegepant quantitation.

Principle

- RP-HPLC operates on the principle of separating compounds based on their hydrophobic interactions with a nonpolar stationary phase and a polar mobile phase.
- Rimegepant, being hydrophobic, is well-suited for separation using RP-HPLC.
- The QbD framework enhances the traditional RP-HPLC method by identifying and optimizing critical quality attributes (CQAs) and critical process parameters (CPPs) to minimize variability.
- Risk assessment tools like FMEA identify potential sources of variability, and DoE helps determine the optimal conditions within a predefined design space.

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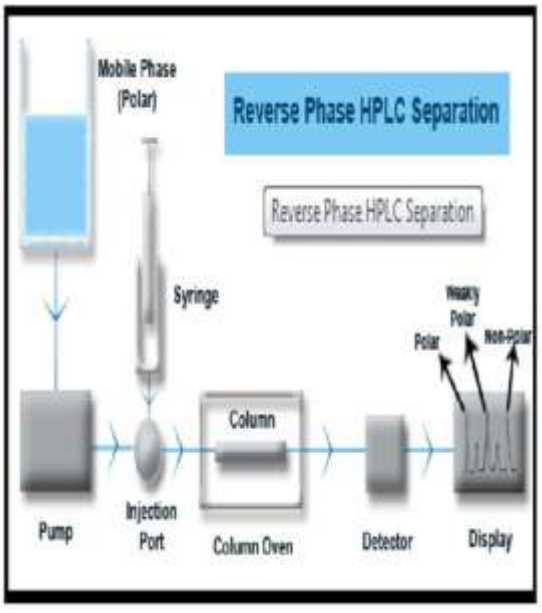
Method

- The development of the RP-HPLC method was guided by QbD principles to achieve a robust and efficient analytical method. Key steps included:

1. **Defining the Analytical Target Profile (ATP):** Establishing method requirements for sensitivity, accuracy, and precision.
2. **Selection of Mobile Phase:** Acetonitrile and phosphate buffer (60:40 v/v) were optimized for separation and peak symmetry.
3. **Stationary Phase:** A C18 column (250 mm × 4.6 mm, 5 µm particle size) was selected for its high resolution and compatibility with Rimegepant.
4. **Detection Wavelength:** UV detection was set at 280 nm for maximum sensitivity.
5. **Risk Assessment:** FMEA was used to identify critical method parameters such as mobile phase composition, pH, and flow rate.
6. **Optimization Using DoE:** Box-Behnken design optimized key variables, ensuring robust performance across a range of conditions.
7. **Validation:** The method was validated following ICH Q2(R1) guidelines.

RP – HPLC method –



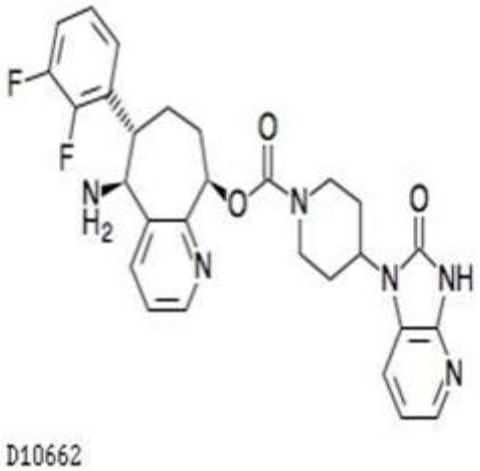
Applications

- Quantitation of Rimegepant in bulk drug samples.
- Quality control analysis of Rimegepant in pharmaceutical dosage forms.
- Stability studies to monitor degradation under thermal, oxidative, and photolytic conditions.
- Routine analysis in pharmaceutical manufacturing and quality assurance laboratories.
- Regulatory submissions for Rimegepant formulations.
- Validation of production processes in pharmaceutical manufacturing.
- Identification of impurities and degradation products during formulation development.
- Batch release testing in compliance with regulatory standards.

Evaluation Methods

- Specificity: The method was tested for its ability to differentiate Rimegepant from impurities and excipients.
- Linearity: A calibration curve was constructed across the concentration range of 10–100 µg/mL, demonstrating a correlation coefficient of 0.999.
- Accuracy: Recovery studies were performed by spiking known amounts of Rimegepant into placebo, with recoveries ranging from 98% to 102%.
- Precision: Both repeatability and intermediate precision showed %RSD values below 2%, indicating high precision.
- Robustness: Variations in flow rate, pH, and mobile phase composition had minimal impact on method performance.
- Sensitivity: The limits of detection (LOD) and quantitation (LOQ) were determined as 2.5 µg/mL and 7.5 µg/mL, respectively.

Chemical Structure –



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Parameters

- Mobile Phase Composition: Acetonitrile: Phosphate buffer (60:40 v/v)
- Stationary Phase: C18 column, 250 mm × 4.6 mm, 5 µm particle size
- Flow Rate: 1.0 mL/min
- Column Temperature: 25°C
- Detection Wavelength: 280 nm
- Injection Volume: 20 µL

II. RESULTS AND CONCLUSION

- The QbD-based RP-HPLC method demonstrated excellent specificity, accuracy, and precision for the quantitation of Rimegepant.
- Linearity was achieved across a broad concentration range, with a correlation coefficient of 0.999.
- Robustness was confirmed by evaluating the method under varying conditions, ensuring consistent performance.
- Sensitivity studies confirmed the method's ability to detect and quantify low concentrations of Rimegepant.
- The developed method is reliable, reproducible, and suitable for routine analysis in quality control laboratories.
- This QbD-based approach offers a systematic framework for method development, ensuring regulatory compliance and minimizing variability.

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