Comprehensive Review on Analytical Method Development and Validation of Rosuvastatin Calcium

Muskan Mulla, Dr. Uday A. Deokate, Pratiksha Kamble, Vaishnavi Punase, Lalit Bhoye

Department of Pharmaceutical Chemistry, Government College of Pharmacy, Karad.

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ABSTRACT

Rosuvastatin Calcium is a potent antihyperlipidemic drug belonging to the class of HMG-CoA reductase inhibitors i.e statins. It acts by selectively inhibiting the enzyme 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase, which is responsible for cholesterol synthesis which helps in increasing LDL clearance from blood. The present review focuses on the different Analytical Method Development of Rosuvastatin and QbD based approaches.

Keywords: Rosuvastatin Calcium, Antihyperlipidemic, Analytical Methods, QbD, ICH.

INTRODUCTION

The development and validation of analytical methods are fundamental to pharmaceutical research and development. Selecting an appropriate method involves considering several important factors, such as accuracy, precision, sensitivity, selectivity, robustness, and ruggedness. Practical aspects like the availability of samples, the concentration of the analyte, time constraints, cost, and access to suitable equipment also play a key role in this decision-making process.

Rosuvastatin is a commonly prescribed statin used to treat high cholesterol levels and reduce the risk of cardiovascular diseases. It works by inhibiting HMG-CoA reductase, an enzyme that is essential for cholesterol synthesis, thereby lowering low-density lipoprotein (LDL) cholesterol in the blood.

Various analytical techniques—including High-Performance Liquid Chromatography (HPLC), High-Performance Thin-Layer Chromatography (HPTLC), UV-Visible spectrophotometry, and Liquid Chromatography–Mass Spectrometry (LC-MS)—are widely used for its analysis. When combined with proper method validation, these techniques ensure accurate, precise, and reliable results, making them highly effective for routine quality control in pharmaceutical applications. (Dhamdhere RB, Vijayalakshmi A. 2020).

Quality plays a critical role in the pharmaceutical industry. Rather than focusing only on testing the final product, Quality by Design (QbD) is a modern approach that ensures quality is built into both the product and the process right from the beginning. (Patel B. N., Naik S. N. 2023).

Quality by Design (QbD) is an approach that focuses on gaining a deeper scientific understanding of both the product and the processes involved. It emphasizes designing appropriate controls and testing strategies based on this scientific knowledge during the development stage. Additionally, the insights gained throughout the product's lifecycle are used to support continuous improvement.

QbD does not mean reducing analytical testing; instead, it ensures that testing is performed at the right stage and is guided by scientific reasoning and risk assessment. By implementing QbD, more robust and reliable analytical methods can be developed that align with ICH guidelines. This is why many pharmaceutical industries are increasingly adopting this approach. In a QbD framework, various factors that may influence method robustness are carefully evaluated during analytical method development. (Dhamdhere RB, Vijayalakshmi A. 2020).

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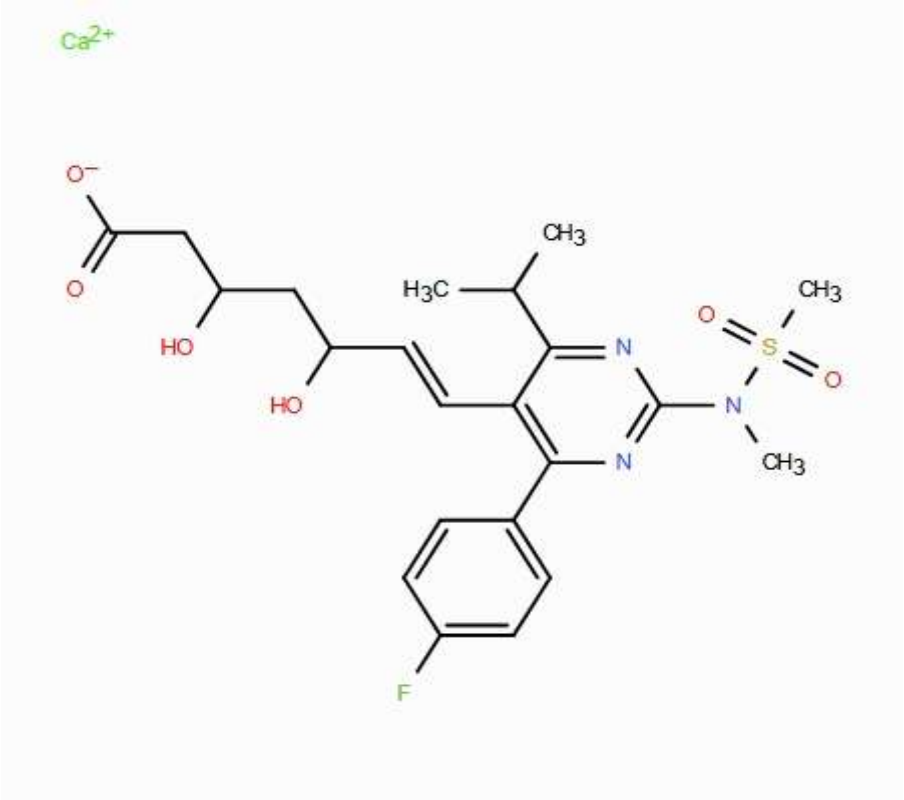
Drug Profile

Drug	**Rosuvastatin Calcium**
IUPAC Name	6-Heptenoic acid, 7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-, calcium salt
Chemical formula	C44H54CaF2N6O12S2
Molecular weight	481.54 g/mol
Dosage Forms	Tablets: 5 mg, 10 mg, 20 mg, 40 mg
Administration Route	Oral

Rosuvastatin Calcium [3]



Different Analytical Method of Rosuvastatin

By UV-Visible Spectroscopy

Sr.no.	**Title**	**Description**	**Reference**
1	Analytical method development & validation for the Estimation of Rosuvastatin Calcium in Raw material and Tablet Formulation by UV Spectrometric method.	**Solvent**- 0.1n NaoH **Wavelength**- 240nm **R^2**- 0.999	Sailaja, B., & Kumari, K. S. (2016)

2	Method Development and validation of Rosuvastatin by using UV Spectroscopy	**Solvent**- 0.1n NaOH **Wavelength**- 247nm **R^2**- 0.999	Anusha, S., Sankar, K. G., Prakash, (2023)
3	Method Development and validation of Rosuvastatin by using UV Spectroscopy	**Solvent**- Ethanol:water 40:60v/v **Wavelength**- 243nm **R^2**- 0.9994	Chinababu, D., Aleesha, S. K., (2022).
4	Method Development and validation of Rosuvastatin by using UV Spectroscopy in Bulk & Pharmaceutical dosage form	**Solvent**- Methanol **Wavelength-** 243nm **R^2**- 0.9981	Maity, S., Majumdar, S., & Senapati, S. (2025)
5	UV Spectrometric Method Validation of Rosuvastatin in bulk drug form and stress Degradation Studies by UV.	**Solvent**- Ammonium acetate buffer & Acetonitrile 30:70 **Wavelength**- 242nm **R^2**- 0.9969	Jadhav, V. (2022).
6.	Development and validation of UV Spectroscopy Technique for Estimation of Rosuvastatin drug in Bulk and Pharmaceutical Dosage Form.	**Solvent**- Sodium Citrate **Wavelength**- 299nm **R^2**- 0.9969	Navale S, Pingale M, Bhosale S, (2023)

HPLC Method

Sr.no.	Title	Description	Reference
1.	High Performance Liquid Chromatographic Method Development & Validation of Rosuvastatin Calcium API	**1. Stationary Phase**- P Cogent RPABX C 18 5µ 100^0 (150×4.6mm) **2. Mobile phase**- 0.1ml Formic acid & Acetonitrile **3. Linearity**- 200 µg/ml **4. Flowrate**- 0.5ml/min	Naveen Kumar, K., Nagesh, (2023)
2.	Stability indicating RP-HPLC method development and validation for simultaneous estimation of Telmisartan &Rosuvastatin in Bulk & in tablet dosage form	**1. Stationary Phase**- Oyster ODS3 (150×4.6mm, 6mm) **2. Mobile phase**- 10mM Phosphate buffer 1.1g Acetone 1-Suphuric acid	Gholve, R., Pekamwar, S., (2021)

		3. Linearity- 23.6841-71.0522 µg/ml **4. Flowrate**- 1.0 ml/min	
3.	Development & Validation of RP-HPLC method for Determination of Rosuvastatin in Bulk & Pharmaceutical Dosage Form	**1. Stationary Phase**-C18 column 100×4.6mm **2. Mobile phase**- Phosphate buffer & Acetonitrile (50:50 v/v) **3. Linearity**- 5-30 µg/ml **4. Flowrate**- 0.5ml/min	Pandya CB, Channabasavaraj KP, (2010)
4.	Development & Validation of 2 Chromatograph Stability indication methods for determination of Rosuvastatin in pure form & Pharmaceutical Preparation	**1. Stationary Phase**-C18 column 250mm **2. Mobile phase-** Acetonitrile:0.5% Formic acid **3. Linearity-** 5-300 µg/ml **4. Flowrate-** 1.0 ml/min	Raj HA, Rajput SJ, Dave JB, Patel CN. (2009)

Analytical Comparison of Uv and Hplc

Sr. No.	**UV Visible**	**Components**	**HPLC**
1.	Limited	**Selectivity**	High, very good separation capabilities
2.	Good for Simple Assays	**Sensitivity**	Superior, detects low level impurities
3.	Low cost and simple setup	**Cost and Equipment**	High cost but Complex Instrumentation
4.	Very Simple	**Sample Preparation**	Need optimized mobile phase, column etc.
5.	Minimal	**Need of Solvent**	Very High
6.	Limited Expertise	**Expertise**	Skilled personnel
7.	Fast	**Analysis Time**	Moderate
8.	Higher (Less Sensitive)	**LOD (Limit of Detection)**	Lower (more sensitive)
9.	Higher	**LOQ (Limit of Detection)**	Lower

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Analytical Method Validation

Validation

Validation is a structured process used to evaluate and provide objective evidence that a method meets the requirements for its intended purpose. It involves assessing the performance of the method and confirming its ability to satisfy defined criteria. In essence, validation ensures a clear understanding of the method's reliability and consistency, particularly when analyzing low concentrations or working under challenging analytical conditions. (Santhosh, G., Nagasowjanya, G., (2014).

Method Validation

Validation of an analytical method is a process established through laboratory studies to assess the performance and reliability of a procedure, ensuring it meets the requirements for its intended purpose. The validation process begins with the planned and systematic collection of data by the applicant to support the suitability and effectiveness of the analytical method. (Nunsavathu SN, Rajaganapathy K. (2024).

For Method validation following parameters recommended by FDA, USP and ICH are as follows.

Sr. No.	Parameter	Description
1	Specificity	No interference from Excipients/Impurities
2	Linearity	Response vs Concentration Relationship
3	Accuracy	% Recovery at 80%, 100%, 120% levels
4	Precision	Repetability (Intra/Inter Day)
5	LOD	Lowest Detectable Concentration
6	LOQ	Lowest Quantifiable Concentration
7	Robustness	Effect of Small Changes (pH, Flow Rate, Wavelength
8	System Suitability	System Performance Check before anlaysis

Quality by Design

Quality by Design (QbD) in analytical method development focuses on creating methods that are reliable, reproducible, and well-suited for their intended purpose. Originally introduced in the pharmaceutical industry, QbD has now been widely adopted across other fields such as biotechnology, chemical manufacturing, and food production due to its structured and science-based approach to ensuring quality

The International Council for Harmonisation (ICH) has established a set of guidelines that support the implementation of Quality by Design (QbD). Key guidelines include

ICH Q8(R2) for pharmaceutical development

ICH Q9 for quality risk management,

ICH Q10 for pharmaceutical quality systems.

The primary objective of these guidelines is to standardize regulatory requirements across different regions, ensuring a consistent and unified approach to maintaining quality in pharmaceutical products.

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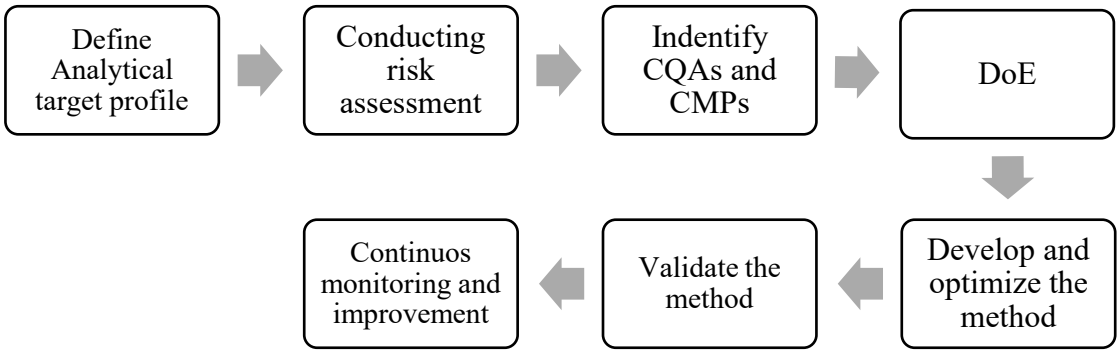
Steps of QbD



Benefits of QbD

Role of QbD in Analytical Development

Quality by Design (QbD) in analytical method development focuses on systematically designing methods that are reliable, reproducible, and fit for their intended purpose. Analytical method development itself involves creating procedures that can accurately measure specific compounds or properties. By applying QbD principles, these methods are developed with a clear understanding of critical factors, ensuring consistent performance and improved quality.

Application of QbD in Analytical Method Development

- Chromatographic Method Development
- Optimizing Separation Condition
- Enhancing Robustness
- Improving Resolution and Sensitivity
- Defining Critical Attributes and variables
- Defining validation parameters

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- Continuious Monitoring

Qualty Risk Management

ICH Q8 focuses on pharmaceutical development, ICH Q9 addresses quality risk management, and ICH Q10 outlines the pharmaceutical quality system. Together, these guidelines form an integrated framework that supports a modern, science-based, and risk-oriented approach to pharmaceutical development and manufacturing.

Tools required for Risk Assesment

1. Failure Mode Effects Analysis (FMEA)

2. Fault Tree Analysis (FTA)

The purpose of conducting risk assessment before development is to identify variables that carry a high level of risk—meaning even small changes in these factors can significantly impact the final outcome.

Advantages

1. It helps in identifying low-risk areas, allowing efforts in those regions to be minimized, postponed, or avoided.

2. It enables early detection of high-risk areas, supporting timely re-development and improving overall understanding of the process.

CMPs (Critical Method Parameters)

These are the input variables in an analytical method that can be controlled during development. They include factors such as mobile phase composition, flow rate, and columns temperature, all of which can influence the method's performance.

CQAs (Critical Quality Attributes)

These are the output responses that indicate the performance and effectiveness of the developed method. They include parameters like peak area, retention time, resolution, and theoretical plates, which reflect the quality and reliability of the analysis.

SR. NO	CMP (INPUT)	CQA (OUTPUT)	RISK LEVEL
1.	pH of Mobile phase	Affect retention time, Peak Shape	High
2.	Flow Rate	Affect retention time and Resolution	High
3.	Column Tempreature	Affect Peak shape	Medium
4.	Injection Tempreature	Affect Peak Area	Medium

Critical factors are identified by evaluating how different method parameters affect quality attributes using quality risk assessment tools such as FMEA and FTA. Based on this assessment, high-risk parameters—like pH, flow rate, and similar variables—are selected for further optimization to ensure better method performance and reliability.

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CONCLUSION

This Review Provides an overview of various analytical methods. Analytical methods utilizing RP-HPLC and QbD are well established and can give more accurate and proper results.

FUTURE ASPECT

Future research of Rosuvastatin calcium in the method development should focus on the Hyphenated techniques like LC-MS/MS and UPLC can significantly improve the detection sensitivity and reduce analysis time also by the bioanalytical development also can be done. Green Chemistry methods can also prove the better option in the future aspect of rosuvastatin

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