iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 13 **Issue:** XI **Month of publication:** November 2025

DOI: https://doi.org/10.22214/ijraset.2025.75604

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue XI Nov 2025- Available at www.ijraset.com

Stability Indicating Method Development and Validation of Metoprolol Succinate and Empagliflozin by RP-HPLC in Synthetic Mixture

Vandit Patel[1], Riddhi Trivedi[2], Munshi Mahammed Tanzil[3], Deepa R. Patel[4]
[1]*Department of Quality Assurance, Kalol Institute of Pharmacy, Ahmedabad, India*
[2]*Department of Quality Assurance, Kalol Institute of Pharmacy, Ahmedabad, India*
[3]*Department of Quality Assurance, Assistant professor at Kalol institute of pharmacy, Ahemdabad*
[4]*Department of Quality Assurance, Principal of Kalol Institute of Pharmacy, Ahmedabad, India*

Abstract: ***This review article focuses on the development and validation of a stability-indicating RP-HPLC method for the simultaneous estimation of Metoprolol Succinate and Empagliflozin in a synthetic mixture. The analytical technique plays a vital role in the pharmaceutical quality control process, ensuring accuracy, precision, and reproducibility of analytical data. The method was developed using a C18 column with a suitable mobile phase composition, flow rate, and detection wavelength optimized for maximum resolution. Forced degradation studies were performed under various stress conditions such as acidic, alkaline, oxidative, thermal, and photolytic to ensure the method's stability-indicating nature. The proposed method was validated according to ICH Q2(R2) guidelines for parameters such as linearity, accuracy, precision, specificity, robustness, limit of detection, and quantitation. The method was found suitable for routine analysis of combined dosage forms of Metoprolol Succinate and Empagliflozin.***

Keywords: RP-HPLC, Metoprolol Succinate, Empagliflozin, Stability Indicating Method, Validation, ICH Q2(R2)

I. INTRODUCTION

Stability indicating analytical methods are essential in ensuring the safety and efficacy of pharmaceutical formulations throughout their shelf life. High-Performance Liquid Chromatography (HPLC) is one of the most powerful and widely used techniques for drug analysis because of its sensitivity, precision, and accuracy. Among the variants, Reverse Phase HPLC (RP-HPLC) is preferred due to its ability to separate compounds of varying polarity using non-polar stationary phases and polar mobile phases.

Metoprolol Succinate is a selective β1-receptor blocker used in the management of hypertension, angina pectoris, and heart failure. Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor used in the treatment of type 2 diabetes mellitus. The combination of Metoprolol Succinate and Empagliflozin is being explored for patients with co-existing cardiovascular and diabetic conditions. Therefore, a validated stability-indicating RP-HPLC method is necessary for simultaneous estimation.

II. LITERATURE REVIEW

Numerous studies have been reported for the estimation of Metoprolol Succinate and Empagliflozin individually by HPLC and UV spectroscopy. However, only limited literature is available for their simultaneous estimation in combination. Previous methods primarily focused on single-analyte determination or biological matrix analysis. The current work aims to develop a simple, accurate, and cost-effective RP-HPLC method applicable for combined formulations.

III. METHOD DEVELOPMENT AND OPTIMIZATION

Method development involves the selection of appropriate chromatographic conditions to achieve maximum separation and resolution. Preliminary trials were carried out using different mobile phase ratios, flow rates, and detection wavelengths. A reverse-phase C18 column (250 mm × 4.6 mm, 5 µm) was selected with a mobile phase consisting of acetonitrile and phosphate buffer (pH 4.0) in the ratio of 60:40 v/v. The flow rate was maintained at 1.0 mL/min, and detection was performed at 225 nm.

IV. FORCED DEGRADATION STUDIES

Forced degradation studies were performed to evaluate the stability-indicating capability of the method. Samples were subjected to acid (0.1N HCl), base (0.1N NaOH), oxidative (3% H_2O_2), thermal (60°C), and photolytic degradation conditions. Each stressed sample was analyzed, and the degradation peaks were well-resolved from the main analyte peaks, confirming the method's specificity.

V. METHOD VALIDATION (AS PER ICH Q2(R2))

The developed RP-HPLC method was validated as per ICH Q2(R2) guidelines for various parameters.

- Linearity: 5–50 µg/mL for Metoprolol Succinate and 2–20 µg/mL for Empagliflozin with correlation coefficients (R^2)>0.999.
- Accuracy: Recovery within 98–102% for both analytes.
- Precision: %RSD less than 2% indicating repeatability.
- Specificity: No interference observed from excipients or degradation products.
- LOD/LOQ: 0.3 µg/mL and 1.0 µg/mL for Metoprolol; 0.1 µg/mL and 0.3 µg/mL for Empagliflozin respectively.
- Robustness: No significant changes observed upon small variations in flow rate and detection wavelength.

VI. RESULTS AND DISCUSSION

Parameter	Metoprolol Succinate	Empagliflozin	Acceptance Criteria
Linearity (µg/mL)	5–50 (R^2=0.9992)	2–20 (R^2=0.9995)	R^2>0.999
Accuracy (%)	99.3–101.2	98.9–101.0	98–102%
Precision (%RSD)	0.87	0.92	<2%
LOD (µg/mL)	0.3	0.1	—
LOQ (µg/mL)	1.0	0.3	—

The results demonstrated that the developed method is linear, accurate, precise, specific, and robust for both analytes. Chromatograms revealed distinct and well-resolved peaks with retention times of approximately 3.2 min for Empagliflozin and 5.8 min for Metoprolol Succinate.

VII. CONCLUSION

The proposed RP-HPLC method provides a reliable, specific, and reproducible approach for the simultaneous estimation of Metoprolol Succinate and Empagliflozin in a synthetic mixture. The method successfully separates both drugs and their degradation products, fulfilling all validation criteria as per ICH Q2(R2). Hence, it can be effectively utilized for routine quality control and stability analysis in pharmaceutical industries.

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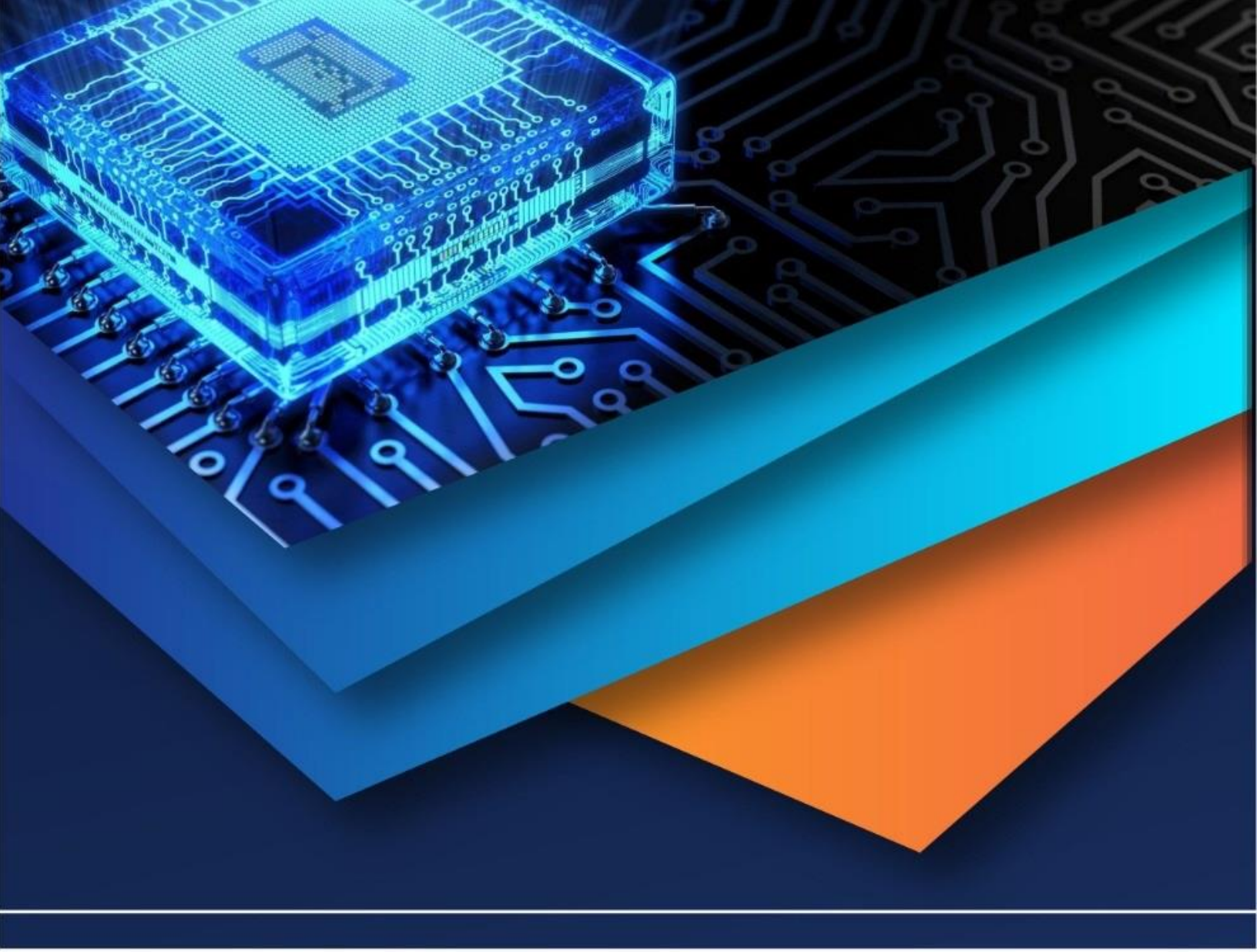

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