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REVIEW ARTICLE

Concise report on Various Analytical Methods Used for Estimation of Rebamipide

Bindhyashree K M*[1], Naveen Kumar G S[2], Sowmya H G[3]

[1] *Student, Department of Pharmaceutical Analysis, Bharathi College of Pharmacy, Bharathinagara, Karnataka, India*
[2] *Head of department, Department of Pharmaceutical Analysis, Bharathi College of Pharmacy, Bharathinagara, Karnataka, India*
[3] *Assistant professor, Department of Pharmaceutical Analysis, Bharathi College of Pharmacy, Bharathinagara, Karnataka, India*

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Abstract:
Rebamipide falls within the class of medications known as antiulcer agents. The process of developing and validating analytical methods is a continuous and interconnected endeavor essential to research and development, as well as quality control and assurance departments. These analytical procedures are pivotal in assessing equivalence, managing risks, and establishing product-specific acceptance criteria while ensuring result stability. Validation confirms the suitability of an analytical procedure for its intended use. Literature surveys reveal several validated analytical methods utilizing UV spectrometry, RP-HPLC, and HPTLC for the quantification of Rebamipide alone or in combination with other drugs. These methods adhere to ICH guidelines, validating parameters such as accuracy, precision, and robustness. The developed techniques are straightforward, sensitive, and reproducible, applicable for both bulk and tablet forms of Rebamipide. This comprehensive review assesses the practicality and limitations of various analytical approaches for Rebamipide analysis, offering valuable insights for researchers engaged in Rebamipide-related investigations.

Keywords: Rebamipide; UV-Spectroscopy; RP- HPLC; HPTLC; Method Development; Validation

1. Introduction

Rebamipide serves as an anti-ulcer medication, primarily employed in the treatment of stomach ulcers. Its efficacy in combating ulcers stems from its ability to fortify the protective lining of the gastric mucosa, achieved by elevating prostaglandin E2 levels. This enhancement aids in the healing process of gastric ulcers by promoting gastric mucosal health and mitigating free radical generation. Apart from its role in ulcer treatment, Rebamipide functions as a mucosal protective agent, augmenting endogenous prostaglandin production and exhibiting cytoprotective properties against ulcers. Additionally, Rebamipide finds application as an ophthalmic solution for managing dry eye syndrome. [1, 2] Classified under the Biopharmaceutical Classification System as a Class IV drug, Rebamipide's chemical structure is denoted by 2-[(4-chlorobenzoyl)amino]-3-(2-oxo-1H-quinolin-4-yl)propanoic acid, possessing a molecular formula of C19H15ClN2O4 and a molecular weight of 370.786 g/mol. It exists as a white solid powder, soluble in organic solvents like dimethyl sulfoxide, methanol, and ethanol, with limited solubility in water, and is typically administered in doses of 100 mg. [3]. The structure of Rebamipide is shown in Figure 1. This review aims to critically comprehend various analytical methods reported on estimation of Rebamipide.

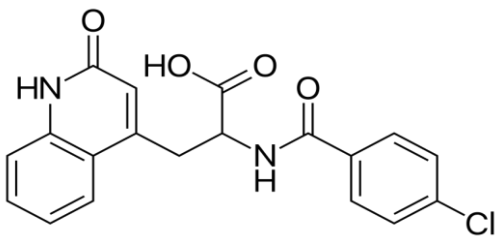

Figure 1. Structure of Rebamipide

* Corresponding author: Bindhyashree K M

2. Analytical methods reported for estimation of Rebamipide in bulk and dosage forms

Praveen K. Srivastava et al. (2011) introduced a novel, rapid, sensitive, simple, and cost-effective UV method for quantifying rebamipide in both bulk and pharmaceutical formulations. The relative absorbance of rebamipide was measured in phosphate buffer (pH 7.4) at the new wavelength (λmax227). The method exhibited a linearity range of 2.5-12.5 μg/ml, with a regression equation: relative absorbance = 0.1061X concentration in μg/ml + 0.0009, and a regression coefficient of 0.9997. It underwent rigorous testing and validation for various parameters according to ICH and USP specifications. The detection and quantification limits were determined to be 0.73 μg/ml and 2.21 μg/ml, respectively. The results demonstrate the accuracy, precision, and reproducibility of the developed procedure, with a low relative standard deviation (<2.0%). This method is suitable for estimating rebamipide in different dosage forms and yields results in good accordance with the label claim. [4]

In the study by Khaggeswar. B et al. (2011), a new UV spectrophotometric method was devised for the quantitative estimation of rebamipide, an effective antiulcer agent, and tramadol, a centrally acting analgesic, in both pure form and solid dosage forms. Linear regression equations for rebamipide and tramadol were established at 228nm and 271nm, respectively. The detection limits for rebamipide and tramadol were found to be 0.27 μg/mL and 0.24 μg/mL, respectively. The analytical results were subjected to statistical treatment as per ICH guidelines for validating analytical procedures and recovery studies. [5]

Mohammed A. Alqarni et al. (2022) developed four spectrophotometric methods for quantifying REB and its impurity and degradation product, the debenzylated isomer of REB (DER). Method A employed ratio difference spectrophotometry, distinguishing between REB and DER at selected wavelengths. Method B utilized derivative ratio spectrophotometry, measuring peak amplitudes of the first derivative of ratio spectra. Method C employed a second derivative approach for quantification, while Method D involved mean centering of ratio spectra, facilitating discrimination between REB and DER. [6]

U R Manglani et al. (2006) presented a simple, rapid, selective, and sensitive reversed-phase HPLC method for determining rebamipide from plasma. The drug was extracted using a mixture of chloroform and isopropyl alcohol, and measured with UV detection at 280nm. Chromatographic separation occurred on a 5μm C-18 silica column, utilizing a mobile phase consisting of acetonitrile, water, methanol, and acetic acid. The method exhibited good resolution and no interference from plasma. The retention times for rebamipide and the internal standard were approximately 4.9±0.3 min and 7.6±0.3 min, respectively, with a mean recovery from human plasma exceeding 91%. The method demonstrated linearity over the concentration range of 10 to 500ng/ml, with a coefficient of correlation (r^2) of 0.991. Both intra-day and inter-day accuracy and precision data showed excellent reproducibility.[7]

Min Kyo Jeoung et al. (2004) devised a straightforward method for quantifying rebamipide in human plasma utilizing high-performance liquid chromatography (HPLC). The procedure involved single liquid-liquid extraction and reversed-phase chromatography with fluorometric detection (excitation at 320nm, emission at 380nm). Analytes were extracted from plasma samples, containing an internal standard (ofloxacin), into ethyl acetate at pH 2–3, yielding a high extraction yield. Separation occurred at 60°C on a reversed-phase column using an acetonitrile–water–acetic acid mobile phase (30:70:5, v/v, pH 2.4) at a flow rate of 1.0ml/min. The assay exhibited a linear range of 2–500ng/ml of the drug in plasma, with a quantitation limit of 2.0ng/ml. Intra- and inter-day relative standard deviations (RSD) were below 10%, and assay accuracy ranged between 97–104%. [8]

D.C. Son et al. (2005) developed a novel high-performance liquid chromatography (HPLC) method with fluorescence detection for quantifying rebamipide in human plasma. Rebamipide and the internal standard (ofloxacin) were extracted with ethyl acetate and quantitated using a reverse-phase C18 column. The chromatograms exhibited no interfering peaks, with retention times of 8 minutes for rebamipide and 11 minutes for the internal standard. The method underwent full validation in human plasma over a range of 0.01–1μg/ml, showing mean intraday precision and accuracy of 5.16% and 3.27%, respectively. Interday precision and accuracy over one week were 3.01% and 3.28%, respectively. Extraction recoveries were 85.5% for the drug and 97.8% for the internal standard, with a lower quantitation limit of 0.01μg/ml. [9]

Sandeep Sonawane et al. (2011) reported the development and validation of a stability-indicating RP-HPLC assay method for quantitatively determining rebamipide in bulk and tablet dosage forms. The method involved subjecting rebamipide solutions to various degradation conditions, including acid and alkali hydrolysis, thermal stress, oxidation by hydrogen peroxide, and photodegradation. Experimental design, including microwave-assisted hydrolysis, was utilized during forced degradation. Chromatography utilized a HiQ sil C-18HS column with a mobile phase of 0.02M potassium phosphate (pH 6.8) and methanol (40:60v/v), with detection at 230nm. The method was validated for specificity, linearity, accuracy, precision, and robustness, exhibiting good accuracy and precision (intra- and inter-day) with a linear response in the range of 0.5 to 5μg/ml. [10]

P Patel et al. (2014) developed and validated a simple high-performance thin-layer chromatographic method for estimating rebamipide from its tablet dosage form. The method involved spotting the drug on silica gel F254 TLC plates under a pure nitrogen stream, followed by separation using a mobile phase consisting of methanol, ethyl acetate, and glacial acetic acid (3:7:0.5v/v/v).

TLC plates were scanned by CAMAG TLC scanner, and detection was carried out at 229nm, with a determined rf value of 0.56 for rebamipide. [11]

Atul A. Shirkhedkar et al. (2021) highlighted the increasing utilization of high-performance thin-layer chromatography (HPTLC) due to its cost-effectiveness, high sample throughput, and minimal sample cleanup requirements. Their study aimed to establish a simple, precise, and accurate stability-indicating densitometric thin-layer chromatography (TLC)-densitometry method for analyzing REB in bulk material and tablets, offering advantages such as simultaneous analysis of multiple samples and reduced analysis time and cost compared to HPLC. [12]

3. Summary of the analytical methods reported so far

The literature review revealed various analytical methods developed for the quantification of rebamipide in different matrices such as human plasma, pharmaceutical formulations, and bulk material. These methods include high-performance liquid chromatography (HPLC) with fluorometric or fluorescence detection, UV spectrophotometric methods, and high-performance thin-layer chromatography (HPTLC). The studies demonstrate the versatility and applicability of these techniques for accurately determining rebamipide concentrations, thus facilitating its pharmacokinetic studies and quality control in pharmaceutical formulations. The methods exhibit good linearity, sensitivity, and precision, with quantitation limits ranging from nanograms to micrograms per milliliter. Moreover, some studies validate their methods according to international guidelines (e.g., ICH) and evaluate stability-indicating properties, ensuring robustness and reliability. However, limitations such as the need for sophisticated equipment, extensive sample preparation, and potential interference from matrix components are noted in some studies. The summary of various analytical methods is shown in Table 1.

Table 1. Key aspects of analytical methods reported on rebamipide

Method	Merits	Limitations
HPLC with fluorometric detection (Jeoung et al., 2004) [8]	Single liquid–liquid extraction, high extraction yield	Requires sophisticated equipment
HPLC with fluorescence detection (Son et al., 2005) [9]	Complete absence of interfering peaks	Extensive sample preparation
UV spectrophotometric method (Sonawane et al., 2011) [10]	Stability-indicating, applicability to tablet dosage forms	Potential interference from matrix components
HPTLC (Patel et al., 2014) [11]	Simple and cost-effective method, rapid analysis	Limited to qualitative analysis
UV method (Jeoung et al., 2004) [8]	Rapid, sensitive, and cost-effective	Limited to qualitative analysis
Spectrophotometric methods (Alqarni et al., 2022) [6]	Discrimination between REB and its impurities	Need for optimization in various conditions

4. Conclusion

In conclusion, the literature review highlights the diverse array of analytical methods developed for quantifying rebamipide in various matrices, including human plasma and pharmaceutical formulations. These methods, ranging from high-performance liquid chromatography (HPLC) to UV spectrophotometry and high-performance thin-layer chromatography (HPTLC), demonstrate robustness, sensitivity, and applicability for pharmacokinetic studies and quality control purposes. While each method possesses its unique advantages, such as simplicity, cost-effectiveness, and stability-indicating properties, limitations such as the need for sophisticated equipment and potential interference from matrix components exist. Overall, these analytical methods contribute significantly to the accurate determination of rebamipide concentrations, thus facilitating its clinical and pharmaceutical applications. Further research focusing on addressing the identified limitations and optimizing the methods for broader applicability would enhance the utility of rebamipide quantification.

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Author's short biography

Bindhyashree K M

Bindhyashree K M is a determined and accomplished individual holding a Bachelor of Pharmacy (B. Pharm) degree and currently pursuing a Master of Pharmacy (M. Pharm). Academic journey reflects a deep-rooted passion for pharmaceutical sciences, marked by her unwavering commitment to the field.

Naveen Kumar G S

Naveen Kumar, an accomplished professional with an PhD, currently serves as an HOD in the Department of Pharmaceutical Analysis at Bharathi College of Pharmacy, Bharathi Nagar, Karnataka. Beyond teaching, Naveen Kumar actively contributes to the academic landscape through the publication of articles, showcasing a dedication to advancing pharmaceutical knowledge. Simultaneously, as a mentor, Naveen Kumar provides guidance to students, fostering their academic and research growth. This tri-fold role, encompassing teaching, publication, and guidance, exemplifies Naveen Kumar's commitment to both imparting knowledge and nurturing the next generation of pharmacists at Bharathi College

Sowmya H G

Sowmya, a dedicated professional, holds an M. Pharm degree and currently serves as an Assistant Professor in the Department of Pharmaceutical Analysis at Bharathi College of Pharmacy, Bharathi Nagar, Karnataka. With a passion for pharmaceutical education, Sowmya contributes to shaping aspiring pharmacists' futures. The role involves imparting theoretical and practical insights, fostering a dynamic learning environment. Sowmya's commitment to continuous learning and research makes a significant impact, positioning them as a valued member of the faculty at Bharathi College