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Brief Overview of Analytical Techniques for Rebamipide Estimation

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A B S T R A C T

Rebamipide is an antiulcer medication. The ongoing process of developing and validating analytical methods is crucial for research, development, quality control, and assurance. These methods are essential for evaluating equivalence, managing risks, and establishing product-specific criteria while maintaining consistent results. Validation ensures an analytical procedure's fitness for its intended purpose.

Literature reviews show multiple validated analytical techniques using UV spectrometry, RP-HPLC, and HPTLC to quantify Rebamipide, either alone or combined with other drugs. These methods follow ICH guidelines, validating factors like accuracy, precision, and robustness. The developed techniques are uncomplicated, sensitive, and replicable, suitable for analysing both bulk and tablet forms of Rebamipide.

This comprehensive review evaluates the practicality and limitations of various analytical approaches for Rebamipide analysis, providing valuable insights for researchers studying Rebamipide.

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

1. Introduction

Rebamipide is an anti-ulcer medication used primarily for treating stomach ulcers. Its effectiveness in ulcer management comes from its ability to strengthen the gastric mucosa's protective layer by increasing prostaglandin E2 levels. This process supports the healing of gastric ulcers by enhancing mucosal health and reducing free radical damage. Besides its role in treating ulcers, Rebamipide acts as a mucosal protector by boosting natural prostaglandin production and providing cytoprotective benefits against ulcers. It is also used in ophthalmic solutions for treating dry eye syndrome. [1, 2] As a Class IV drug under the Biopharmaceutical Classification System, Rebamipide's chemical structure is 2-[(4-chlorobenzoyl) amino]-3-(2-oxo-1H-quinolin-4-yl) propanoic acid, with a molecular formula of C19H15ClN2O4 and a molecular weight of 370.786 g/mol. It appears as a white solid powder, soluble in organic solvents such as dimethyl sulfoxide, methanol, and ethanol, but has limited water solubility, and is generally administered at a dose of 100 mg. [3] Figure 1 illustrates the structure of Rebamipide. This review aims to provide a detailed analysis of various analytical methods used for estimating Rebamipide.

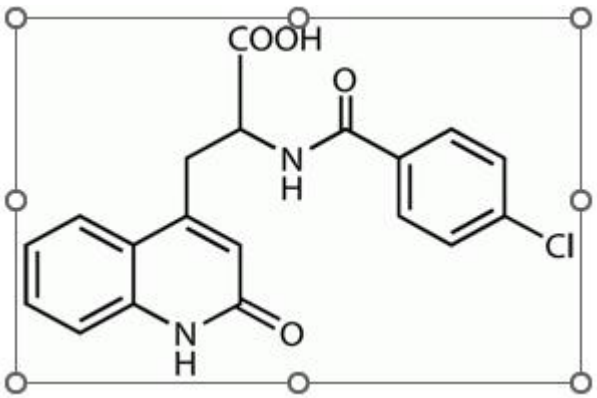

Figure 1. Structure of Rebamipide

1.1 Construction of references:

Analytical Approaches for Determining Rebamipide in Bulk and Formulated Products:

Rebamipide, a gastroprotective agent, has been the subject of various analytical studies aimed at developing effective methods for its quantification in both bulk drug and pharmaceutical formulations. This review highlights key advancements in the spectrophotometric and chromatographic analysis of rebamipide, underscoring the accuracy, precision, and applicability of these methods.

1.1.1 UV Spectrophotometric Methods:

Praveen K. Srivastava et al. (2011) introduced a novel UV spectrophotometric method for quantifying rebamipide, notable for its rapidity, sensitivity, and cost-effectiveness. This method, which measures absorbance at a newly identified wavelength of 227 nm in phosphate buffer (pH 7.4), demonstrates linearity in the range of 2.5 to 12.5 µg/ml. The regression equation established was relative absorbance = 0.1061 × concentration (µg/ml) + 0.0009 with a high correlation coefficient ($r^2 = 0.9997$). The method was validated according to ICH and USP guidelines, yielding limits of detection (LOD) and quantification (LOQ) of 0.73 µg/ml and 2.21 µg/ml, respectively. The low relative standard deviation (RSD < 2.0%) underscores the reliability of the method, making it suitable for routine analysis of various dosage forms, with results closely aligned with label claims.

Similarly, Khaggeswar et al. (2011) developed a UV spectrophotometric method for the simultaneous estimation of rebamipide and tramadol, analgesics, in both pure and solid dosage forms. The method employed wavelengths of 228 nm for rebamipide and 271 nm for tramadol, with detection limits of 0.27 µg/ml and 0.24 µg/ml, respectively. The linear regression analysis for both drugs conformed to ICH guidelines, validating the method's robustness for combined drug analysis.

Advanced Spectrophotometric Techniques: Expanding on traditional UV methods, Mohammed A. Alqarni et al. (2022) developed four distinct spectrophotometric techniques for the quantification of rebamipide and its impurity, the debenzylated isomer (DER). These methods included ratio difference spectrophotometry (Method A), derivative ratio spectrophotometry (Method B), a second derivative approach (Method C), and mean cantering of ratio spectra (Method D). Each technique was designed to effectively differentiate and quantify the REB and DER, offering versatile tools for comprehensive analysis in the presence of impurities and degradation products.

Chromatographic Methods: Chromatographic analysis was performed in the U.R. Manglani et al. (2006) developed a reversed-phase HPLC method tailored for the quantification of rebamipide in plasma. Utilizing a C-18 silica column and a mobile phase of acetonitrile, water, methanol, and acetic acid, excellent chromatographic separation was achieved with UV detection at 280 nm. The retention times for rebamipide and the internal standard were approximately 4.9 ± 0.3 minutes and 7.6 ± 0.3 minutes, respectively. The method demonstrated high recovery rates from human plasma (>91%) and maintained linearity across a concentration range of 10–500 ng/ml ($r^2 = 0.991$). Both intra- and inter-day assessments confirmed the precision and reproducibility of the method, establishing it as a reliable technique for plasma drug analysis.

1.1.2. High-Performance Liquid Chromatography (HPLC) Methods:

Min Kyo Jeoung et al. (2004) developed a straightforward HPLC method for rebamipide quantification in human plasma. The method utilized a single liquid-liquid extraction with ethyl acetate at pH 2–3, followed by reversed-phase chromatography with fluorometric detection (excitation at 320 nm and emission at 380 nm). Separation was performed at 60°C on a reversed-phase column with an acetonitrile–water–acetic acid mobile phase (30:70:5, v/v, pH 2.4) at a flow rate of 1.0 ml/min. The assay demonstrated a linear range of 2–500 ng/ml, with a quantitation limit of 2.0 ng/ml. Both intra-day and inter-day relative standard deviations (RSD) were below 10%, with assay accuracy ranging from 97% to 104%, indicating the method's high precision and reliability [8].

D.C. Son et al. (2005) presented a novel HPLC method with fluorescence detection for rebamipide quantification in the human plasma. The method involved extracting rebamipide and the internal standard (ofloxacin) using ethyl acetate and analyzing the samples on a reversed-phase C18 column. The method achieved clear chromatographic separation, with retention times of 8 min for rebamipide and 11 min for the internal standard. Validated over a concentration range of 0.01–1 µg/ml, the method demonstrated mean intraday precision and accuracy of 5.16% and 3.27%, respectively, and interday precision and accuracy of 3.01% and 3.28%, respectively. Extraction recoveries were 85.5% for rebamipide and 97.8% for the internal standard, with a lower quantitation limit of 0.01 µg/ml [9].

Sandeep Sonawane et al. (2011) developed and validated a stability-indicating RP-HPLC assay method for rebamipide, testing its stability under various degradation conditions such as acid and alkali hydrolysis, thermal stress, oxidation, and photodegradation. The method employed a HiQ sil C-18HS column with a mobile phase of 0.02M potassium phosphate (pH 6.8) and methanol (40:60 v/v), with detection at 230 nm. Validation studies confirmed the specificity, linearity, accuracy, precision, and robustness of the method, with a linear response range of 0.5 5 µg/ml.

1.1.3. Thin-Layer Chromatography (TLC) Methods:

P Patel et al. (2014) developed an HPTLC method for rebamipide quantification in tablet dosage forms. The method involved applying the drug to silica gel F254 TLC plates and separating it using a mobile phase of methanol, ethyl acetate, and glacial acetic acid (3:7:0.5, v/v/v). Detection was performed at 229 nm using a CAMAG TLC scanner, with rebamipide exhibiting an RF value of 0.56. This method provides a cost-effective alternative to quantify rebamipide in tablets.

Atul A. Shirkhedkar et al. (2021) highlighted the advantages of HPTLC for its affordability, high sample throughput, and minimal sample preparation. They developed a stability-indicating densitometric TLC method for Rebamipide analysis in bulk material and tablets, emphasizing its capability for the simultaneous analysis of multiple samples, reduced analysis time, and lower costs compared to HPLC.

1.1.4. Mass Spectrometry (MS) Method:

Kathryn Smith et al. (2023) developed a comprehensive method using Ultivo LC-MS/MS to detect 127 drugs and metabolites in urine and serum/plasma samples. This method features a 10-minute injection-to-injection time and demonstrates high precision and accuracy, with an average total imprecision of <15% CV for 20 extracted controls and an accuracy of 99.9% for 46 unique external controls. The Ultivo system showed excellent run stability, with an internal standard reproducibility of ≤ 6 % %and an overall instrument-to-instrument agreement of 99.8%. The consolidation of a broad spectrum of analytes onto a single platform enhances space efficiency, reduces turnaround times, and improves patient accuracy.

2. Summary of the Reported Analytical Methods

The literature review explores various analytical techniques developed for quantifying rebamipide across different matrices, including human plasma, pharmaceutical formulations, and bulk materials. The methods reviewed encompass high-performance liquid chromatography (HPLC) with either fluorometric or fluorescence detection, UV spectrophotometry, and high-performance thin-layer chromatography (HPTLC).

These studies illustrate the diverse applications and effectiveness of these techniques in accurately measuring rebamipide concentrations, supporting both pharmacokinetic studies and quality control processes in pharmaceuticals. The methods demonstrate strong linearity, sensitivity, and precision, with quantitation limits spanning from nanograms to micrograms per millilitre. Many of the methods are validated according to international standards, such as those set by the International Conference on Harmonisation (ICH), and include assessments of stability-indicating properties to ensure robustness and reliability.

A summary of these analytical methods is presented 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
LC-MS/MS Kathryn Smith et al. (2023)	Rapid, High sensitivity and specificity, Versatility, Quantitative accuracy.	Complexity and cost, High maintenance and calibration.

3.Conclusion

The reviewed methods, ranging from UV spectrophotometry to advanced chromatographic techniques, collectively offer a robust framework for the accurate and precise quantification of rebamipide in various matrices. The adaptability of these methods to different analytical scenarios underscores

their value in both routine quality control and specialized research settings. The advancements in analytical methods for rebamipide quantification, ranging from HPLC to TLC and LC-MS/MS, reflect significant progress in ensuring accurate, reliable, and efficient analysis. Each method offers unique advantages, making them suitable for various analytical needs, from routine quality control to complex stability studies and comprehensive drug screening.

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