RESEARCH ARTICLE

An Innovative RP-HPLC Method for Simultaneous Estimation of Montelukast and Ebastine in Tablet Formulations: Development, Validation, and Stability Assessment

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ABSTRACT

This study aimed to develop and validate an innovative reverse-phase high-performance liquid chromatography (RP-HPLC) method for the simultaneous estimation of montelukast sodium (MNK) and ebastine (EBA) in tablet formulations. Utilizing a Shimadzu LC2010CHT system with a Phenomenex Luna C18 column, the mobile phase consisted of ammonium acetate buffer, acetonitrile, and methanol in a 12:55:33 ratio, with a flow rate of 1.0 mL/min and detection at 250 nm. Validation followed ICH guidelines, assessing linearity, accuracy, precision, robustness, and stability under various stress conditions. Both MNK and EBA showed excellent linearity within 16 to 24 µg/mL with correlation coefficients of 0.999. Accuracy was confirmed through recovery studies showing 98 to 102% mean recoveries. Precision was demonstrated with %RSD values below 2%. The method remained robust under slight variations in conditions, and stability studies indicated minimal degradation of both drugs. The developed RP-HPLC method proved rapid, precise, and robust for the simultaneous quantification of montelukast and ebastine in tablet formulations, demonstrating practicality and reliability for pharmaceutical quality control.

Keywords: Montelukast sodium, Ebastine, RP-HPLC, Method development, Validation, Tablet formulations, Stability studies, Pharmaceutical analysis.

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Conflict of interest: None

INTRODUCTION

The cysteinyl leukotriene receptor antagonist montelukast sodium (MNK), also known as (S, E) -2-((13-(1-cyclopropan-2-yl phenyl)methyl)glycine), works by blocking the action of this receptor.[1,2] It finds application in the upkeep of asthma treatment and alleviation of symptoms related to seasonal allergies.[3-5] According to existing literature, the Indian Pharmacopeia of 2010 recognizes both the bulk and tablet dosage forms of MNK as official analyses.[6]

The non-sedating H1 antihistamine ebastine (EBA), also known as 4-(4-benzhydryloxy-1-piperidyl)-1-(4-tert-butylphenyl)-butan-1-one, can be found in the form of monohydrate or crystalline powder. The British Pharmacopoeia[7] provides official documentation on the quantification of ebastine in its bulk form. A thorough examination of the literature reveals diverse analytical methods for assessing Montelukast in pharmaceutical dosage forms. These approaches include UV spectrophotometry and HPLC techniques. UV spectrophotometry has been reported for assessing MNK and EBA on their own, as well as in combination with other drugs,[8-11] HPLC.[12-14] There are three common methods for conducting HPLC with photodiode array detection: A comparison of high-performance thin-layer chromatography (HPTLC),[17,18] liquid chromatography-mass spectrometry (LC-MS),[16] and high-performance LC-MS (HPLC/PDA)[15] have been carried out.[15,16]

To date, there has been no documentation of a method capable of simultaneously determining both MNK and EBA in combination. In addition to its speed, simplicity, precision, and consistency, the presented approach is well suited to analyzing these two substances simultaneously within tablet formulations. International Council for Harmonisation (ICH) guidelines have been followed in fine-tuning and validating the method.[20] The structure of montelukast sodium and the structure of ebastine are described in Figures 1 and 2.

MATERIALS AND METHODS

Materials

Wellous Pharma Private Limited supplied pharmaceutical-grade Montelukast, while ebastine was obtained from Vasudha Pharma Chem Ltd. All HPLC-grade chemicals and reagents

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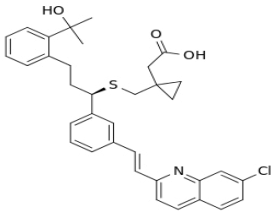

Figure 1: Structure of montelukast sodium

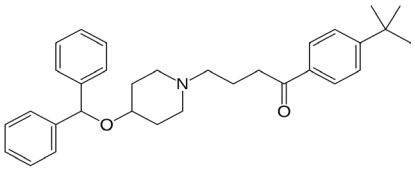

Figure 2: Structure of ebastine

were purchased from Welchem Scientific Traders in Chennai, India. The analytical method adhered to the validation guidelines set by the International Council for Harmonisation (ICH).

Instrumentation

The HPLC analysis was performed using a Shimadzu LC2010CHT system equipped with Lab Solutions software and a Phenomenex Luna C18 column (250 × 4.6 mm, 5 µm particle size). The column's internal diameter was 4.6 mm, and it maintained a constant temperature of 25°C throughout the analysis. Sample components were effectively eluted using a flow rate of 1.0 mL/min, with detection performed at a wavelength of 250 nm. A 20 µL injection volume was used, and the sample cooler operated at ambient temperature. The chromatographic analysis spanned 15 minutes, allowing for the separation and identification of sample components based on their interactions with the C18 stationary phase (Table 1).

Preparation of Standard and Sample Solutions

To prepare the ebastine standard stock solution, 50 mg of ebastine IP WRS was accurately weighed and transferred into a 50 mL volumetric flask. A diluent of 30 mL was added to facilitate dissolution, and the solution was diluted to volume with the diluent. Montelukast and ebastine stock solutions were similarly prepared and diluted to volume in a 50 mL volumetric flask by adding 1-mL of each. For sample preparation, 10 mg of ebastine tablet powder was placed into a 50 mL volumetric flask. After adding 30 mL of the specified diluent, the solution was sonicated for 15 minutes to ensure complete dissolution. The solution was then filtered through Whatman filter paper no. 1 and diluted to 50 mL with the same diluent to remove any particulate matter.

Wavelength Selection

The preparation of standard and sample stock solutions involved using solvents compatible with the mobile phase. UV scanning was performed across the spectral range of 200 to 400 nm to determine the absorption maxima for montelukast and ebastine. The absorption maxima were found to be at 250 nm, establishing this as the optimal wavelength for subsequent HPLC UV detector analyses, ensuring reliable and precise quantification.

Table 1: Chromatographic conditions optimized for the sample

Mobile phase	Buffer (12), acetonitrile (55), and methanol (33)
Column	Phenomenex Luna C18, 250 × 4.6 mm × 5 µ
Flow rate	1.0 mL/min.
Wavelength	250 nm
Sampling system	Automatic
Temp. of autosampler	Ambient
Volume of injection	20 µL
Run time	15 minutes
Mode of separation	Isocratic

Method Development

Ammonium acetate buffer preparation (pH 5.5)

Dissolve 3.85 g of ammonium acetate in 1000 mL of water. Adjust the pH to 5.5 using glacial acetic acid.

Mobile phase preparation

The mobile phase consisted of 12% ammonium acetate buffer, 55% acetonitrile, and 33% methanol. This specific composition was chosen to optimize the separation of compounds during analysis. Methanol served as the diluent for both sample and standard preparations, ensuring compatibility and accurate dilution, thereby enhancing the reliability and precision of the chromatographic process.

Method Validation: Linearity and Range

By diluting and mixing five different standards of stock solutions, calibration standards were created. Consequently, montelukast's concentration ranged from 16 to 24 µg/mL, while ebastine ranged from 16 to 24 µg/mL. For each of these prepared concentrations, individual injections were made to create samples. Linearity graphs were generated by plotting the peak areas against their respective concentrations. Chromatograms were recorded for each solution. The percentage recovery values were subsequently determined using the linear equation y = 19995x - 8208.5 for montelukast and y = 5007.5x + 20940 for ebastine (Table 2 and 3).

Accuracy

Montelukast recovery study

To analyse the proposed approach for accuracy, a series of recovery experiments were conducted by introducing varying quantities (50, 100, and 150%) of pure montelukast drug into the sample, and each concentration level was injected into the HPLC system with three times for replication (Table 4).

Recovery study for ebastine

In order to assess the precision of the suggested approach, a series of recovery experiments were conducted. These involved the addition of various quantities (50, 100, and 150%) of pure ebastine drug into the sample, and each concentration level was injected into the HPLC system three times for replication (Table 5).

Robustness

The robustness of the developed RP-HPLC method for montelukast and EBastine (API) analysis was assessed by exploring the impact of minor variations in the optimized chromatographic conditions. In addition to modifying the flow rate (0.1 mL/min), the mobile phase ratio was adjusted by 2%, the wavelength of detection by 2 nm, and the acetonitrile concentration in the mobile phase by 2%, we also adjusted the mobile phase concentration by 2%. Based on Table 6, the results unequivocally demonstrate the method's robustness, with relative standard deviations below 2% consistently exhibited.

Precision

Repeatability

A constant quantity of montelukast and ebastine (API) was analyzed six times to determine the precision of each method. Table 7 describes montelukast and ebastine's relative standard deviations as percentages of relative standard deviation.

Intermediate precision

To evaluate the method's variation within the same day and across different days, we conducted assessments. There were minimal standard deviations (RSDs) associated with montelukast and ebastine, which are expected. This results in 2% or less relative standard deviations (RSD). These results underscore the exceptional precision inherent in the proposed methodology, as delineated in Table 7.

Limit of Detection and Limit of Quantitation

Limits of detection and quantitation (LoD and LoQ) can be calculated using a formula. A calibration curve is a plot of the slope of the calibration curve with respect to the response standard deviation.

Assessment of System Suitability

There are a number of analytical procedures that evaluate the suitability of a system. This testing results in the characterization of equipment, electronics, analytical procedures, and sample samples as interconnected systems that can be evaluated collectively.

Dosage Estimation of Montelukast and Ebastine as Tablets

In the process of estimating montelukast and ebastine in tablet dosage form, a systematic approach was followed. First, the average weight of 20 tablets was determined in accordance with the Indian Pharmacopoeia (I.P.) method. In a mortar and pestle, the tablets were ground into fine powder. To measure and transfer 100 mg of the active drugs, 100 mg of powdered material was carefully measured into a clean 100 mL volumetric flask. A 15 minutes sonication process was conducted using an ultrasonicator with 70 mL of mobile phase added to the flask. In the next step, the mobile phase was added to the solution to bring it up to standard. In order to ensure the clarity of the resulting solution, a 0.45 m membrane filter was used to remove any gas content. There were five 10 mL volumetric flasks filled with one ml of the stock solution for each of the solvents (mobile phase). Furthermore, the chromatograms and peak areas of a blank solution were meticulously recorded and analyzed using the HPLC system. This procedure is described in more detail and the results are presented in the relevant chapter.

Stability Studies

Stability studies were conducted on the active pharmaceutical ingredients (API) montelukast and ebastine. Studies were conducted to investigate whether the tablet degraded during storage or after administration to humans under various stress conditions. Other degradation pathways were also examined, including acid hydrolysis, basic hydrolysis, thermal degradation, photolytic degradation, and oxidative degradation.

RESULTS AND DISCUSSION

A 1.0 mL/min flow rate was used, with the stationary phase being Phenomenex Luna C18 columns and the mobile phase being methanol, acetonitrile, and an acetate buffer. An injection volume of 20 µL and a run time of 15 minutes was used for detection at a wavelength of 250 nm. These conditions produced pure, well-defined, and symmetrical peaks, along with a high number of theoretical plates. Montelukast has been validated on the basis of linearity and range, exhibiting a correlation coefficient of 0.999, a slope of 10380, and an intercept of 9304. A similar range of linearity was found for ebastine with a correlation coefficient of 0.999, a slope of 10350, and an intercept of 5484 (Tables 2 and 3, Figures 3 and 4).

Table 2: Linearity results for montelukast

S. No	*Concentration (µg/mL)*	*Mean peak area*
1.	16.08	313966
2.	18.24	356165
3.	20	390972
4.	22	431720
5.	24.72	486477

Table 3: Linearity results for ebastine

S. No	*Concentration (µg/mL)*	*Mean peak area*
1.	16.64	228593
2.	18.76	257140
3.	19.76	267024
4.	22.52	305288
5.	23.8	317053

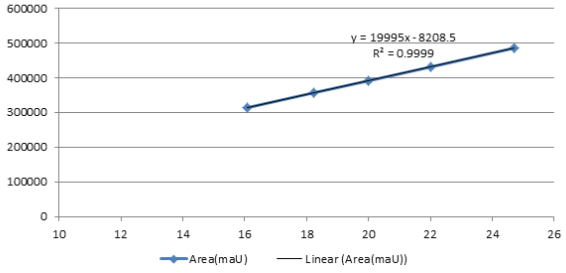

Figure: 3 Linearity graph for montelukast

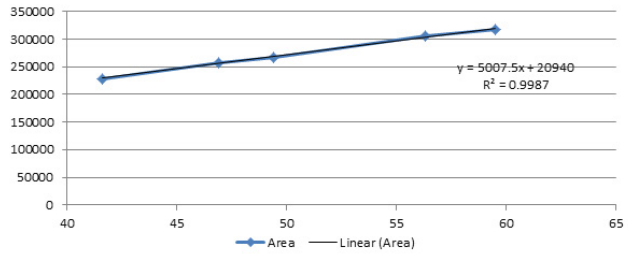

Figure 4: Linearity graph for ebastine

Accuracy

During the accuracy assessment, montelukast fell within the acceptable range of 98 to 102% for recovery, with mean recoveries of 100.26, 99.42, and 100.37%. The %RSD was also within the acceptable limit, at 0.766, 0.204, and 0.765%. For ebastine, the mean %recovery was 100.1207, 101.44, and 101.44%, all within the 98 to 102% range, and the %RSD was 1.250093, 0.325763, and 0.280774%, all of which were less than 2%. RSD values of 1.03029% for montelukast and 1.50256% for ebastine were determined by using solutions containing 10 µg/mL of each drug (n = 6), indicating good repeatability (Tables 4 and 5). It was found that montelukast and ebastine have LoD and LoQ of 0.607 and 1.821 µg/mL, respectively, indicating that the method is highly sensitive. A study determined that the assay of the montelukast and ebastine 10 mg tablets contained 99.6 and 99.20%, respectively, of the active ingredients. Under oxidative stress and photolytic stress conditions, montelukast and ebastine were found to remain stable, confirming the method's specificity.

To our knowledge, no prior studies had been conducted on montelukast and ebastine simultaneously in tablet formulations using RP-HPLC, which we used for this study. The development and validation have made an important contribution to the field of pharmaceutical analysis of this method. Neither ebastine nor montelukast exhibited excellent linearity at concentrations between 16 to 24 µg /mL, as evidenced by high correlation coefficients of 0.999 and 0.9987. This extended range enhances the method's versatility for precise drug quantification.

Method Validation (Accuracy) and Robustness

In our present study, an accuracy assessment was conducted for ebastine, with three concentration levels (50, 100, and 150%) of pure drug. The mean recovery values were found to be 100.04

Table 4: %Recovery for montelukast

Sample	*Concentration (µg/mL)*					
	Concentration present	*Concentration added*	*Concentration estimated*	*Concentration recovered*	*%Recovered*	*Statistical analysis*
S1	9.94	5.2	15.16	5.22	98.99	%Mean-100.26 %RSD-0.766
S2	9.94	5.10	15.22	5.28	100.39	
S3	9.94	4.95	14.96	5.02	100.41	
S4	9.94	9.94	19.81	9.87	99.29	%Mean-99.42 %RSD-0.204
S5	9.94	9.86	19.78	9.84	99.79	
S6	9.94	9.9	19.76	9.82	99.19	
S7	9.94	14.6	24.45	14. 51	99.38	%Mean-100.37 %RSD-0.765
S8	9.94	14.8	24.66	14. 72	99.45	
S9	9.94	14.5	24.66	14.72	101.51	

Table 5: %Recovery for ebastine

Sample	*Concentration (µg/mL)*					
	Concentration present	*Concentration added*	*Concentration estimated*	*Concentration recovered*	*%Recovered*	*Statistical analysis*
S1	10.31	5.1	15.37	5.06	99.21	%Mean-100.04 %RSD-0.817
S2	10.31	5.2	15.59	5.28	101.53	
S3	10.31	4.9	15.18	4.87	99.38	
S4	10.31	9.95	20.36	10.05	101.0	%Mean-100.66 %RSD-0.186
S5	10.31	10.2	20.56	10.25	100.49	
S6	10.31	10.2	20.56	10.25	100.49	
S7	10.31	14.3	24.47	14.16	99.02	%Mean-100.37 %RSD-0.765
S8	10.31	17.4	27.95	17.64	101.37	
S9	10.31	17.6	28.04	17.73	100.73	

Table 6: Robustness testing of the developed RP-HPLC method for montelukast and ebastine

S. No.	*Mobile phase Flow rate changes (1.2 mL)*		*Wavelength changed to 240 nm*		*Column temperature changes to 30ºC*	
	Area of ebastine	*Area of montelukast*	*Area of ebastine*	*Area of montelukast*	*Area of ebastine*	*Area of montelukast*
1.	395232	281025	303581	387719	479196	328247
2.	393285	280861	301430	387846	479025	328161
3.	393152	281950	303678	389327	479964	328336
Average	393889.67	281278.67	302896.33	388297.33	479395	328248
%RSD	0.18	0.132	0.26	0.14	0.065	0.016

Table 7: A. Precision and assay of formulations

HPLC injection replicates	*Area of ebastine*	*mg/tab*	*%/TAB*	*Area of montelukast*	*mg/TAB*	*%/TAB*
Replicate-1	475045	10.59	105.9	340421	9.99	99.9
Replicate-2	471353	10.47	104.7	340991	9.78	97.8
Replicate-3	472368	10.42	104.2	344615	10.07	100.7
Replicate-4	471218	10.46	104.6	341059	10.05	100.5
Replicate-5	475968	10.53	105.3	341741	10.07	100.7
Replicate-6	482058	10.59	105.9	343905	10.06	100.6

± 0.817%, 100.66 ± 0.186%, and 100.37 ± 0.765%, respectively. Similarly, for montelukast, the accuracy assessment was performed with concentrations of 50, 100, and 150% of pure drug. The corresponding mean recovery values were 100.26 ± 0.766%, 99.42 ± 0.204%, and 100.37 ± 0.765% (Table 6). This approach is consistent with the methodology employed, providing robust validation for the method's accuracy across a range of drug concentrations.

Precision and Sensitivity

As part of the repeatability study, montelukast and ebastine solutions were analyzed at 10 µg/mL concentrations to evaluate the precision of the developed method. The resulting low %RSD values confirmed excellent repeatability, establishing the method's reliability for routine analytical applications. A maximum detection limit (LoD) and a maximum quantitation limit (LoQ) were determined without using specific formulas. Based on the calculations, montelukast's LoD and LoQ were 0.607 and 1.821 µg mL, respectively. In the same way, ebastine's LoD and LoQ were measured at 0.451 and 1.353 µg/mL, respectively (Table 7a and b). These outcomes emphasize the method's remarkable sensitivity, essential for accurate analytical assessments in the detection and quantification of these compounds.

Assay of Commercial Formulations

The described method has been successfully used to estimate the content of montelukast and ebastine in a commercial tablet formulation, Ebast-M tablet. In our study, the assay of the marketed formulation revealed a robust accuracy, with ebastine demonstrating an assay value of 105.1% (±0.166), and montelukast at 100.03% (±1.134). These results closely align with those reported by Prashad *et al*., further validating the method's accuracy for drug quantification in commercial formulations.

Stability Studies

The stability of montelukast and ebastine was evaluated under a wide variety of stress conditions, including oxidative, acidic

Table 7: B. Intermediate precision

S.No.	*Intermediate precision*		*Assay results in mg and%*			
	Area of ebastine	*Area of montelukast*	*Ebastine mg/tab*	*%/tab*	*Montelukast mg/tab*	*%/tab*
1.	418093	356511	10.26	10.26	10.34	103.4
2.	418381	356412	10.25	10.25	10.36	103.6
3.	419163	356663	10.37	10.37	10.35	103.5
4.	419609	357707	10.31	10.31	10.33	103.3
5.	419848	357949	10.34	10.34	10.34	103.4
6.	419609	358034	10.33	10.33	10.34	103.4
Ebastine: Average: 10.31 mg/tab (103.1%)					SD:0.471	RSD: 0.472%
Montelukast: Average: 10.34 mg/tab (103.40%)					SD:0.103	RSD:0.0998%

Table 8: Stress studies of ebastine and montelukast

Stress condition	*Time (hours)*	*Ebastine*	*Montelukast*	*Ebastine %degraded*	*Montelukast %degraded*
RT	48	100.5	102.9	0.2	0.3
105°C	2	99.4	99.2	1.3	4.0
UV 254 nm	7	99.6	101.1	1.1	2.1
UV 365 nm	7	99.6	86.3	1.1	16.9
Acid stability	2	99.5	90	1.2	13.2
Base stability	2	99.7	84	1.0	19.2
Oxidation immediate		86	88.5	14.7	14.7
				Assay ebastine = 100.7% Montelukast = 103.2%	

hydrolysis, photolytic, thermal, and photolytic degradation. The results revealed that both compounds remained stable under most conditions, demonstrating the specificity of the developed method. In our present study, the stability of ebastine and montelukast was comprehensively assessed under various stress conditions to evaluate their robustness and degradation profiles. At room temperature (RT) for 48 hours, both compounds exhibited minimal degradation, with ebastine and montelukast showing only 0.2 and 0.3% degradation, respectively. Elevated temperature (105°C) for 2 hours resulted in slightly higher degradation, with ebastine and montelukast degrading by 1.3 and 4.0%, respectively. Under UV irradiation at 254 nm for 7 hours, ebastine and montelukast experienced 1.1 and 2.1% degradation, while UV irradiation at 365 nm for the same duration led to more significant degradation, with ebastine and montelukast degrading by 1.1 and 16.9%, respectively. The compounds also underwent stability testing in acid and base conditions for 2 hours, with ebastine and montelukast showing 1.2 and 13.2% degradation in the acid stability test and 1.0 and 19.2% degradation in the base stability test, respectively. Immediate oxidation conditions resulted in notable degradation, particularly for montelukast, with both compounds degrading by 14.7%. However, despite these stress conditions, the assay values for ebastine and montelukast remained relatively high, with ebastine at 100.7% and montelukast at 103.2%. These findings provide valuable insights into the compound's stability and degradation patterns, emphasizing the need for appropriate storage and handling to maintain their integrity for pharmaceutical use. A study found a decrease in active substance assay for ebastine API under several stress conditions, such as acid hydrolysis and basic hydrolysis. These findings offer valuable information on ebastine's stability and degradation behavior, essential for its pharmaceutical development and formulation (Table 8, Figures 5-14). For montelukast API, the results of the force degradation studies mirrored those of ebastine, further highlighting the importance of understanding the stability of these compounds under different stress conditions to ensure their quality and efficacy in pharmaceutical applications.

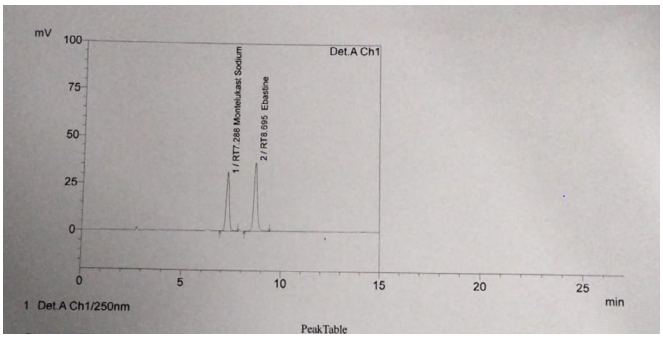

Figure: 5 Standard ebastine and montelukast

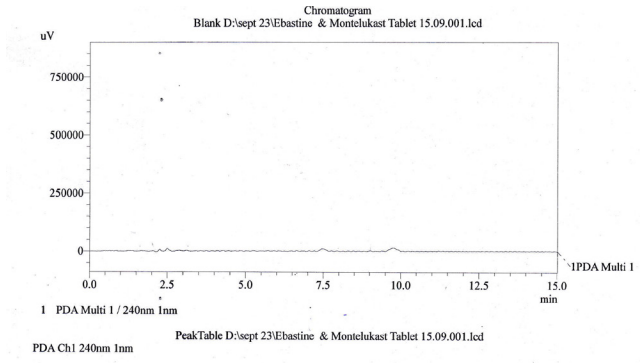

Figure: 6 Ebastine and montelukast as blank chromatogram

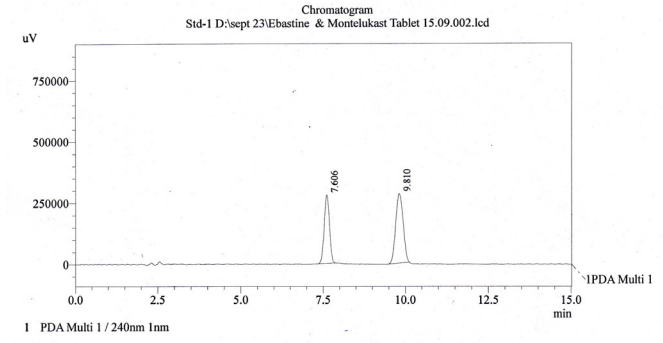

Figure 7: Standard ebastine and montelukast

Comparison with Existing Methods

Montelukast and ebastine can be determined simultaneously using the RP-HPLC method presented here. While previous

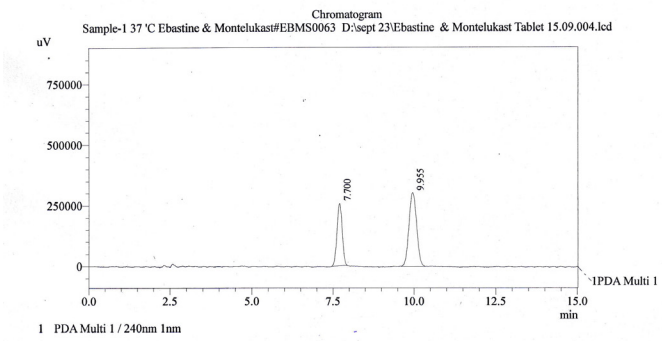

Figure 8: Sample ebastine and montelukast

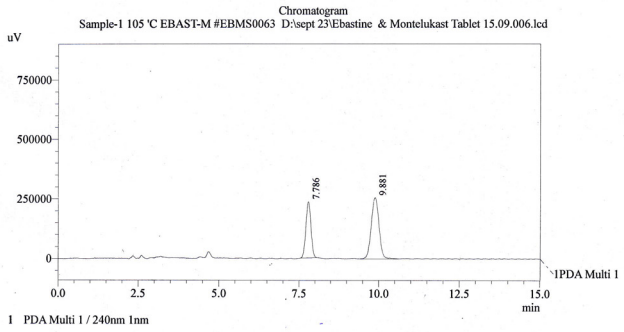

Figure 9: 105°C

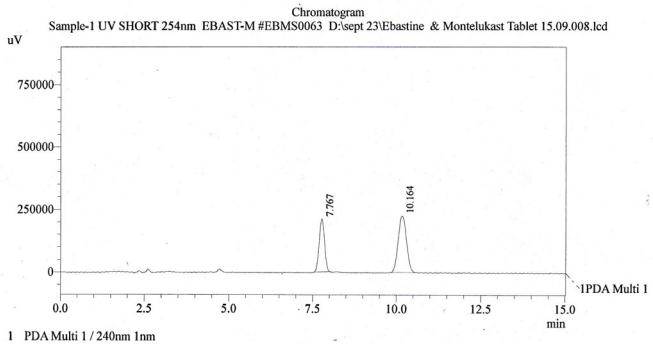

Figure 10: UV short 250 nm (EBAST-M)

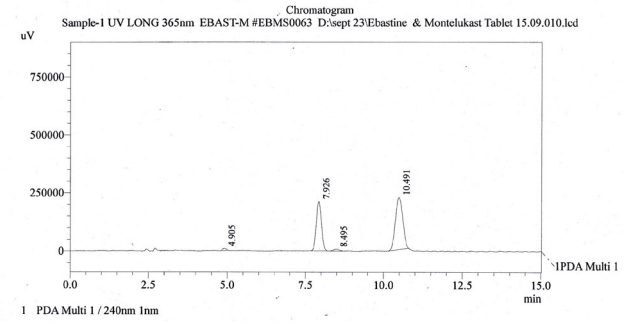

Figure 11: UV long 365 nm

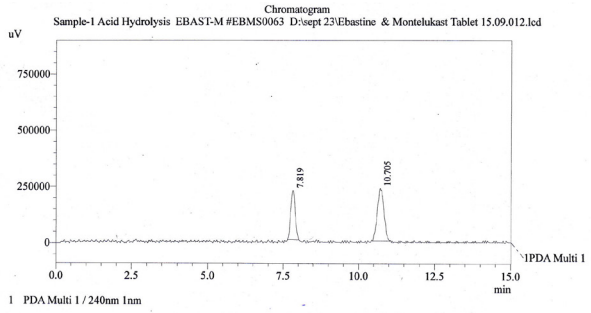

Figure 12: Acid hydrolysis

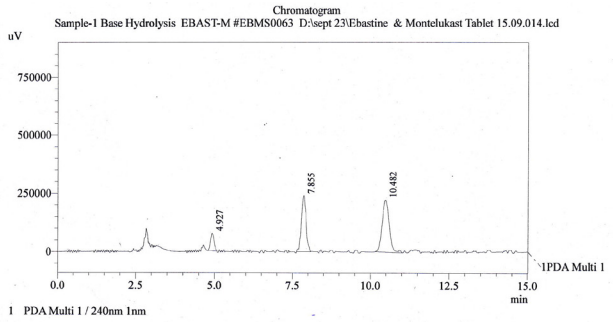

Figure 13: Basic hydrolysis

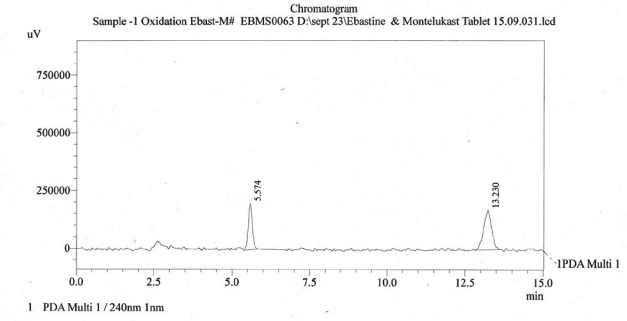

Figure 14: Oxidation hydrolysis

methods mainly focused on individual drug quantification, our method provides a streamlined and efficient approach to simultaneous analysis. This reduces analysis time and resources, making it a valuable tool for quality control in pharmaceutical industries.

CONCLUSION

RP-HPLC's robustness, accuracy, precision, and sensitivity have been demonstrated in the validation method for montelukast and ebastine in tablet formulations. Representing a practical solution for concurrent drug analysis, the method serves as a valuable tool for pharmaceutical industry quality control and research. Its successful application in analyzing a commercial tablet formulation reinforces its practicality and

reliability. The stability studies that have been conducted with montelukast and ebastine have shown that they are appropriate for routine analysis and quality control in pharmaceutical products. It is hoped that this innovative method will contribute to advances in pharmaceutical analysis and further ensure accurate drug quantification in tablet formulations by providing an effective solution to the simultaneous measurement of ebastine and montelukast.

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