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A Research Article on Analytical Method Development and Validation of Antihistamine Drugs Bilastine and Montelukast Sodium by RP-HPLC and UV Spectrophotometric Method.

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ABSTRACT:
A New,Simple, Precise, Accurate and Specific method was developed by Reverse Phase High Performance Liquid Chromatography and simultaneous Equation Method for Bilastine and Montelukast Sodium in bulk BY RP-HPLC and UV-Visible Spectrophotometer. Literature review clears that there is no single method developed for this combination and RP-HPLC and only one method developed by UV-Visible Spectrophotometer. The wavelength maxima (λmax) for Bilastine were 214nm and
for Montelukast Sodium 284nmin methanol. The linearity for this method was found in the range of 2-60 µg/ml and 2-40 µg/ml for Bilastine and Montelukast Sodium respectively. The wavelength of detection for RP-HPLC method was selected at 254nm. The method has been validated according to ICH guidelines with respect to system suitability, specificity, precision, accuracy, and robustness.

KEYWORDS: Bilastine, Montelukast Sodium, RP-HPLC, Simultaneous equation method, UV spectroscopy.

I. INTRODUCTION

Allergic rhinitis (AR) is defined as symptoms of sneezing, nasal pruritus, airflow obstruction and mostly clear nasal discharge.Allergic rhinitis is a chronic inflammatory disease. AR is an immunoglobulin E−mediated inflammatory reaction occurs in the nasal mucosa caused by inhaled allergens, such as pollen, mold, or animal dander. Allergic Rhinitis is a part of a systemic inflammatory process and is associated with other inflammatory disorders, including asthma, rhinosinusitis, and allergic conjunctivitis.

Asthma is a disease that affects your lungs. It is one of the most common long term disease in children, but adults can have asthma, too. Asthma causes wheezing in children and inconsistent in toddlers. It also shows symptoms like breathlessness, chest tightness, and coughing at night or early in the morning. Allergic rhinitis or asthma can be associated with chronic sinusitis. [32,35]

When AR patients are exposed to allergens, allergic reactions develop in 2 different patterns according to time sequence. One is the early reaction, in which sneezing and rhinorrhea develops with in few minutes and disappears due to release of histamine, prostaglandin D2 and cysteinyl leukotrienes. The other is the late reaction, which shows nasal obstruction approximately 6 hours after exposure to allergens and subsides slowly. The early reaction is the response of mast cells to offending allergens (type I hypersensitivity). In contrast to the early reaction, eosinophils chemotaxis is the main mechanism in the late reaction, which is caused by chemical mediators produced in the early reaction. Several inflammatory cells, eosinophils, mast cells and T cells migrate to nasal mucosa, break up and remodel normal nasal tissue, and these processes result in nasal obstruction which is the main symptom of AR patients.

Symptoms of Allergic Rhinitis:
Sneezing, Runny nose, Itchy nose, Coughing, Itchy & Watery eyes, Sore or Scratchy throat, Frequent headaches, Eczema type symptoms- like having extremely dry itchy skin that can blister, Excessive fatigue. [2, 36]

Combined Dosage Form: Drug Combination Bilastine and Montelukast Sodium was approved by CDSCO on 11th of March, 2020. Drug Combination Bilastine and Montelukast Sodium used for the treatment of allergic rhinitis and mild to moderate asthma. Bilastine is an antiallergenic and acts to reduce allergic symptoms such as nasal congestion and Urticaria. Montelukast Sodium is used to control and prevent symptoms caused by asthma and in allergic rhinitis. [34]

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II. PHYSICOCHEMICAL PROPERTIES OF DRUG:

BILASTINE

Bilastine Fig.1 is a novel new second generation antihistamine drugs that is highly suitable for the H1 receptor antagonist. Chemically it is [2-(4-(2-(4-(1-(2-ethoxyethyl)] benzimidazole-2-yl] piperidin-1-yl] ethyl] phenyl]-2-methylpropanoic acid. It has rapid onset of action for prolonged duration. Bilastine is a white to off white crystalline powder with melting range of 196 to 200°C. It has 4.18 pKa value and 14.5 hrs. of half-life.During the allergic responses mast cell undergo degranulation which releases histamine and other substances. Bilastine binds to H1 receptor and prevent the activation of the H1 receptor and thus Bilastine reduces development of allergic symptoms due to release of histamine from mast cells.[14]

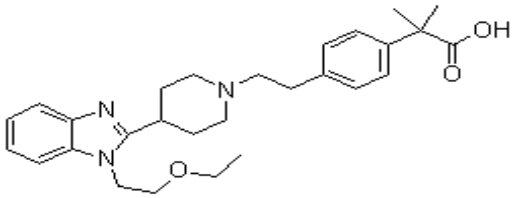

Fig No.01: Structure of Bilastine.

MONTELUKAST SODIUM

Montelukast Sodium (MONT) (FIG.2) is white to almost white hygroscopic powder. Chemically (S, E)-2-((1-(1-(3-(2-(7-chloroquinolin-2-yl) vinyl) phenyl)3-(2-(2-hydroxypropan-2-yl)phenyl)propylthio)methyl) cyclopropyl) acetic acid. Montelukast is a Leukotriene receptor antagonist that demonstrates the marked affinity and selectivity to the cysteinyl Leukotriene receptor Type1 in preference to many other crucial airway receptors like prostanoid, Cholinergic, or beta adrenergic receptors. It is used as an alternative to Anti-inflammatory medication in the management and chronic treatment of asthma, allergic rhinitis and exercise induced bronchospasm (EIB). It is official drug in Indian Pharmacopoeia and British Pharmacopo

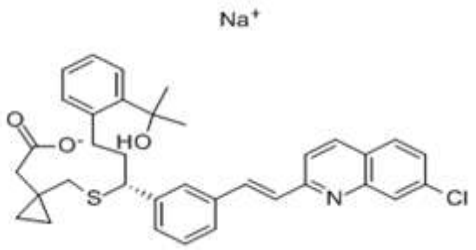

Fig.No.02: Structure of Montelukast Sodium.

Literature survey reveals that montelukast and Bilastine are estimated individually or in combination with other drugs. There is no single method has been developed for this combination by RP-HPLC and HPTLC and only one method has developed by UV-Visible Spectroscopy for simultaneous estimation of Bilastine and Montelukast Sodium. The aim of present investigation was to develop and validate RP-HPLC andUV-Spectroscopic methods which are accurate, sensitive, precise, and cost- effective for Simultaneous estimation of Bilastine and Montelukast sodium in bulk drug.

III. MATERIALS AND METHODS

3.1 Instruments

A double beam UV spectrophotometer (Shimadzu UV-VIS 1800), HPLC System (Shimadzu, prominence-i), Analytical balance(Shimadzu AY20), Sonicator (SIDILU Ultrasonic) were used for experimentation.

3.2 Chemicals and Reagents

Reference standard of Bilastine and Montelukast were obtained as a gift sample from Lee pharma, and Cipla from Mumbai. India. All the chemicals and reagents were of analytical grade. Tablet Biolafav was purchased from local market.

3.3 RP-HPLC METHOD

3.3.1 Chromatographic condition

The HPLC method was performed on a HPLC system (Schimadzu, Prominence-i), The column used was $C_{18,}$ the mobile phase used was Methanol: Water (85:15). Injection volume was 20 µL. The flow rate was set to 1.0 ml/min, temperature was set at 40^0 C and run time was 10 minutes. Detection of both the drugs was carried out at 254 nm by UV detector.

3.3.2 Preparation of Mobile Phase

Mobile phase was prepared by mixing Methanol and water (HPLC grade) in 85:15 (v/v) proportions.

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Mixture was shaken vigorously and sonicated for 30 minutes prior to use.

3.3.3 Preparation of Bilastine stock-working standard solution.

10 mg of Bilastine were weighed accurately and transferred into 10 ml of volumetric flask, dissolved and diluted up to the mark withmethanol: water (80:20) to obtain a final concentration of 1000 µg/ml. Solution was further diluted with methanol to obtain working standard solution of 100 µg/ml of Bilastine.

3.3.4 Preparation of Montelukast stock-working standard solution.

10 mg of Montelukast were weighed accurately and transferred into 10 ml of volumetric flask, dissolved and diluted up to the mark with methanol: water (80:20) to obtain a final concentration of 1000 µg/ml. Solution was further diluted with methanol to obtain working standard solution of 100 µg/ml of Montelukast.

3.3.5 Preparation of sample stock solution:

Correctly weigh 20 tablets, powdered it and calculate the average weight of tablet. Transfer the powder equivalent to 20 mg of Bilastine and 10 mg of montelukast sodium into 100 ml volumetric flask add 80 ml of diluent and sonicate it for 20 minutes and make up the final volume with diluent.

3.4UV- SPECTROPHOTOMETRIC METHOD

3.4.1 Instrumentation

The UV method was performed on SHIMADZU double beam spectrophotometer (Model: UV 1800) using 10 mm quartz cuvettes for spectral measurement. Data acquisition was done by using UV-probe software. The absorption spectra were carried over the range of 200-400 nm.

3.4.2 Determination of wavelength of maximum absorbance (λmax) of BILA and MNOT. Na

Wavelength of maximum absorption was determined by scanning 10µg/ml solution of Bilastine and Montelukast Na using UV-visible double beam spectrophotometer from 200 to 400 nm using methanol as blank.

3.4.3 Preparation of stock solution and test solution

Standard solution (100µg/ml) of Bilastine and Montelukast sodium was prepared by adding 10 mg of Bila and Mont Na in 100 ml of volumetric flask containing 100 ml of methanol, then sonicated for 15 minutes. Series of test solution were prepared in the concentration range of 2-40 1nd 1-30 µg/ml for Bila and Mont Na respectively by diluting appropriate volume of stock solution with methanol.

3.4.4 Preparation of calibration curve

The calibration curve was prepared by scanning test samples ranging from 2-40 and 1-30 µg/ml at 212nm and 284nm for Bilastine and Montelukast Na. Calibration curve was plotted by taking concentration of drug (µg/ml) on X axis and Absorbance on Y axis.

3.5 METHOD VALIDATION

3.5.1 Linearity

The method was validated according to International Conference on Harmonization for validation of analytical procedures in order to determine the linearity, sensitivity, precision and accuracy for each analyte. Calibration curve were generated with appropriate volumes of working standard solution for both UV and HPLC with range of 2-12 µg/ml for UV and 2-12 and 1-6 µg/ml for HPLC for Bilastine and Montelukast respectively.

3.5.2 Precision

Precision was determined by preparing the combination of standard drug solutions. The concentration is prepared in triplicate set for three different concentration level covering the entire linearity range (High, Middle and Low). Precision is the degree of repeatability of an analytical method under normal operational condition. The precision was determined by repeatability, Intra-day and Inter-day study for three different days and result reported as a standard deviation and % RSD.

3.5.3 LOD and LOQ

The limit of detection (LOD) is defined as the lowest concentration of an analyte that an analytical process can reliably differentiate from background levels. The limit of quantification (LOQ) is defined as the lowest concentration of the standard curve that can be measured with acceptable, accuracy, precision and variability. The LOD and LOQ were calculated as,

$LOD = 3.3\sigma / S$

$LOQ = 10\ \sigma / S$

Where σ is the standard deviation of the lowest standard concentration and S is the slope of standard curve.

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3.5.4 Robustness

Robustness of the method was determined by slightly changing the parameters of developed method. For RP-HPLC method changes are made in flow rate and concentration of mobile phase and for UV-Spectrophotometric method slight changes are made in wavelength of the drugs.The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

3.5.5 Accuracy

Accuracy of the method were determined by standard addition method. The sample solutions are prepared in triplicate at different concentration level i.e., at 80%, 100%, and 120% covering the linearity range. Accuracy is the percent of analyte recovered by assay from known added amount. For measurement of accuracy data from nine concentrations over three concentration level covering specified range were determined.

IV. RESULT AND DISCUSSION

4.1 RP-HPLC Method

RP-HPLC and UV- Spectrophotometric method was developed for Bilastine and Montelukast sodium. The method can be employed for routine analysis. The chromatogram of developed method has been showed in fig no.3, shows retention time of Bilastine and Montelukast Sodium at 3.331 and 4.336 respectively. Table no.2 shows the result for linearity of Bilastine and Mont. Na, table no.3 and 4 shows intra-day and inter-day precision results respectively, table no. 4 and 5 shows the robustness result for bilastine and montelukast sodium by slight changing the method parameters

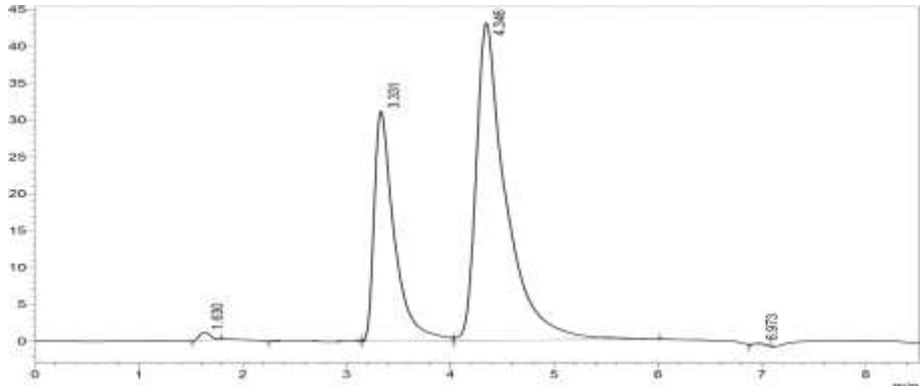

Fig N0.3: Representative chromatogram of optimized method.

Table No.1: Linearity for bilastine and montelukast sodium

Set No.	Bilastine	Montelukast Na
1	21977	40890
2	40185	111094
3	51302	227989
4	68889	340728
5	84519	422345
6	103421	542890
Range	**2-40**	**1-30**
r^2	**0.9962**	**0.9958**

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Equation	**Y = 7968.7x + 5934.6**	**Y = 101614x – 74660**
Y intercept	**5934.6**	**74660**

Table No.2: Result of Intra-day precision.

Sr.No	Bilastine			Montelukast Na		
	Mean	**SD**	**%RSD**	**Mean**	**SD**	**%RSD**
1	21954	76.31	0.34	41255	45.53	0.001
2	51326	47.03	0.09	227974	30.24	0.001
3	103421	23.01	0.04	551059	46.20	0.008

Table No.3: Result of Inter-day precision.

Sr.No	Bilastine			Montelukast Na		
	Mean	**SD**	**%RSD**	**Mean**	**SD**	**%RSD**
1	21954	76.31	0.34	41480	226.69	0.005
2	51326	47.03	0.09	227953	50.98	0.002
3	103421	23.01	0.04	551106	50.01	0.0009

Table no.4: Robustness result for Bilastine

Sr.No	**1.1ml/min**	**0.9ml/min**	**90:10**	**80:20**
1	52880	53798	53952	52846
2	52796	53816	53978	52894
3	52886	53612	53896	52892
4	52879	53728	53916	52878
5	52995	53832	53942	53880
6	52799	53910	53937	51899
Avg. area	**52872**	**53782**	**53936**	**52881**
SD	**72.74**	**102.01**	**28.48**	**19.23**
%RSD	**0.13**	**0.18**	**0.05**	**0.03**

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Table No.5: Robustness result for Montelukast Na.

Sr.No	1.1ml/min	0.9ml/min	90:10	80:20
1	228136	228947	228342	228964
2	228130	228951	228138	228858
3	227142	229742	228446	229154
4	225329	229967	228734	228762
5	226435	229998	228930	229059
6	224116	228891	228640	229351
Avg. area	**226548**	**229399**	**228538**	**229024**
SD	**1599**	**558.88**	**286.0**	**4.89**
%RSD	**0.70**	**0.24**	**0.12**	**0.02**

Table N0 6.: Result of recovery analysis for bilastine

Level	Sr.No	Area	Theoretical Wt.	Practical Wt.	% Recovery	Mean	SD	RSD
80%	**1**	63186	7.2	7.19	99.78	100.09	0.76	0.8
	2	63560	7.2	7.21	100.4			
	3	63394	7.2	7.23	100.1			
100%	**1**	69146	8.0	7.93	99.15	99.34	0.31	0.3
	2	69234	8.0	7.94	99.25			
	3	69342	8.0	7.97	99.62			
120%	**1**	76529	8.8	8.85	100.6	100.8	0.48	0.4
	2	76787	8.8	8.89	101.0			
	3	76395	8.8	8.84	100.4			

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Table N0 6.: Result of recovery analysis for Montelukast Sodium

Level	Sr.No	Area	Theoretical Wt.	Practical Wt.	% Recovery	Mean	SD	RSD
80%	1	285683	3.6	3.53	98.05	98.70	0.52	0.53
	2	285989	3.6	3.54	98.33			
	3	291065	3.6	3.59	99.72			
100%	1	330745	4	3.98	99.74	99.83	0.65	0.65
	2	331967	4	4.0	100			
	3	331523	4	3.99	99.75			
120%	1	381125	4.4	4.48	101.8	101.0	1.28	1.27
	2	380923	4.4	4.48	101.8			
	3	371090	4.4	4.38	99.54			

4.2UV-SPECTROPHOTOMETRIC METHOD.

Fig no.4 shows the overlay spectrum of Bilastine and montelukast sodium, Fig no.4 and 5 shows the calibration curve of bilastine and Montelukast Na at 212 nm and 284 nm respectively. Table no 8 shows the linearity, LOD, LOQ results for UV method, table no 9 and 10 shows intra-day and inter-day precision results for Bilastine and Montelukast Na respectively, table no 10 and 11 shows accuracy result by UV-Spectrophotometric method.

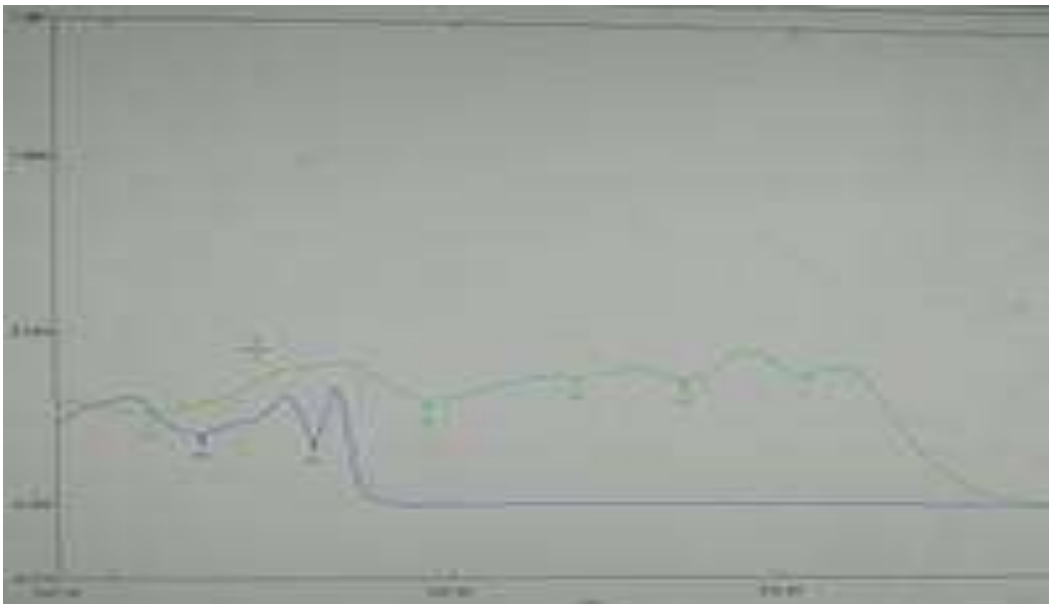

Fig no.4: overlay spectra of bilastine and montelukast sodium.

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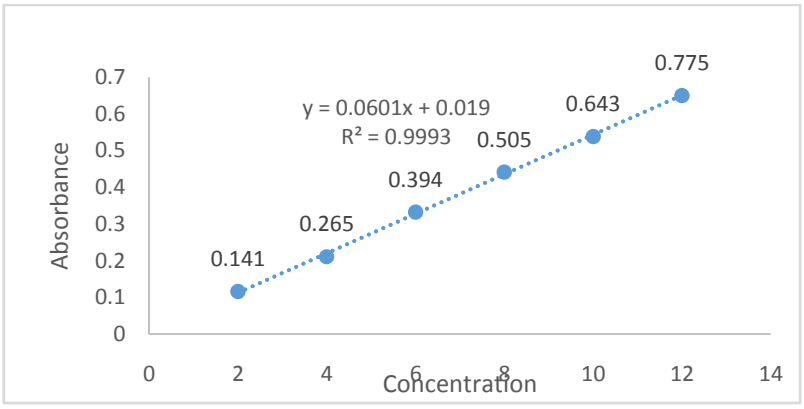

Fig no.5: calibration curve of bilastine at 212 nm.

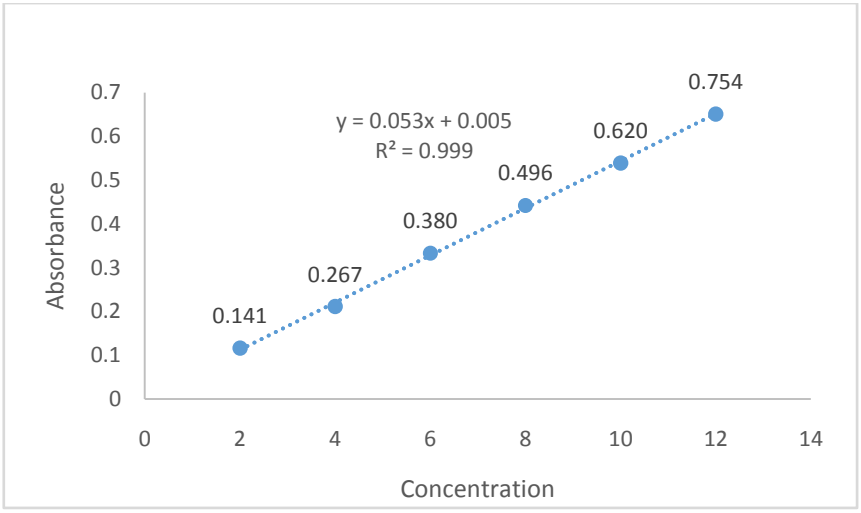

Fig No.6: Calibration curve of Mont. Na at 284 nm.

Table No.8 : Result for Linearity, range, LOD and LOQ.

Parameter		**Bilastine**	**Montelukast Na**
Linearity	**Range**	2-40	1-30
	Equation	Y = 0.0601x + 0.019	Y = 0.060x + 0.018
	R^2	R^2 = 0.9993	R^2 = 0.9993
	% RSD	0.68	0.64
LOD		0.12 µg/ml	0.11 µg/ml

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LOQ	0.36 µg/ml	0.35 µg/ml

Table No.9: Intra-day and inter-day precision result for bilastine.

Title	**Sample No**	**Absorbance**			**Mean**	**SD**	**%RSD**
		I	**II**	**III**			
Intra -day	1	0.139	0.137	0.135	0.137	0.002	1.4
	2	0.507	0.505	0.509	0.507	0.0021	0.39
	3	0.752	0.758	0.756	0.755	0.003	0.40
Inter -day	1	0.142	0.144	0.147	0.144	0.002	1.7
	2	0.508	0.505	0.506	0.506	0.002	1.5
	3	0.750	0.748	0.754	0.750	0.003	0.42

Table No.10 : Intra-day and inter-day precision result for montelukast Na.

Title	**Sample No**	**Absorbance**			**Mean**	**SD**	**%RSD**
		I	**II**	**III**			
Intra -day	1	0.141	0.139	0.140	0.140	0.001	0.71
	2	0.491	0.493	0.496	0.493	0.0025	0.51
	3	0.739	0.735	0.737	0.737	0.0025	0.33
Inter -day	1	0.141	0.142	0.142	0.141	0.001	0.70
	2	0.498	0.501	0.503	0.500	0.003	0.66
	3	0.740	0.738	0.742	0.740	0.002	0.27

Table No.11: Result of robustness study at ± 2nm.

Sr.No	**Bilastine**		**Montelukast Na**	
	210nm	**214nm**	**282nm**	**286nm**
1	0.0048	0.0027	0.0048	0.0027
2	0.79	0.45	0.79	0.45

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Table No.13: recovery analysis for Bilastine

Level	Sr.No	Absorbance	Added	Recovered	% Recovery	Mean	SD	RSD
80%	1	0.456	7.2	7.27	100.9	100.5	0.75	0.75
	2	0.457	7.2	7.28	100.1			
	3	0.451	7.2	7.18	99.72			
100%	1	0.507	8.0	8.1	101.2	100.93	0.679	0.68
	2	0.503	8.0	8.05	100.6			
	3	0.505	8.0	8.08	101.0			
120%	1	0.548	8.8	8.8	100.0	99.76	0.281	0.28
	2	0.545	8.8	8.75	99.45			
	3	0.547	8.8	8.78	99.83			

Table No.14: recovery analysis for Montelukast Na.

Level	Sr.No	Absorbance	Recovered	Added	% Recovery	Mean	SD	RSD
80%	1	0.241	3.7	3.7	100.4	99.83	0.672	0.67
	2	0.238	3.7	3.6	99.09			
	3	0.240	3.7	3.7	100.0			
100%	1	0.261	4.0	4.05	101.2	100.4	0.667	0.66
	2	0.258	4.0	4.0	100.0			
	3	0.260	4.0	4.03	100.7			
120%	1	0.284	4.4	4.43	100.7	100.1	0.547	0.54
	2	0.281	4.4	4.38	99.62			
	3	0.282	4.4	4.4	100.0			

V. CONCLUSION:

Simple, rapid, accurate, robust and precise RP-HPLC as well as UV-Spectrometric methods have been developed and validated for routine analysis of Bilastine and Montelukast sodium in API. Both method are suitable for simultaneous estimation of Bilastine and Montelukast sodium in combination dosage form without interference of each other. The developed methods are recommended for routine and quality control analysis. The value of standard deviation and relative standard deviation are satisfactorily low which indicates the suitability of proposed method. The developed method can be suitably adaptable for their Combination Formulations.

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