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Research Article

Advanced Derivative Spectroscopic Method for Estimation of Montelukast and Bilastine in Their Tablet Dosage Form

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ABSTRACT

The present work aims to develop and validate the advanced derivative spectroscopic method for estimation of Montelukast (MON) and Bilastine (BIL) in their tablet dosage form. This tablet dosage form is used for anti-asthmatic and allergic rhinitis. The developed method can be applied for simultaneous estimation of Montelukast and Bilastine in their combined dosage form. For this advanced derivative method, the absorbance at 226.8 nm (ZCP of Montelukast) and 326.4nm (ZCP of Bilastine) was used to estimate Montelukast and Bilastine, respectively. The developed method is validated by ICH Q_2R_1 guidelines with validation parameters like linearity, LOD, LOQ, accuracy, precision, robustness, ruggedness and assay were performed using this guideline. The method was found to be linear in the concentration range of 2-14 µg/mL for Montelukast (R^2 = 0.999) and 4–28 µg/mL for Bilastine (R^2=0.9997). LOD and LOQ found 0.1216 and 0.3686 for MON, and 0.3406 and 1.0320 for BIL. The precision study wasa carried out by comparing on 3 different concentrations and the result of their %RSD was <2%. Robustness study carried out by the change in scanning speed and change in methanol manufacturer and Ruggedness study carried out by different analyst. Assay study was performed using tablet formulation. The developed method was utilized for simultaneous estimation of Montelukast and Bilastine for its tablet dosage form.

INTRODUCTION

Montelukast (10 mg) and Bilastine (20 mg) combination approved for marketing in India from 11 March, 2020 (CDSCO) combined in a single fixed dose of tablet formulation used for the treatment of allergic rhinitis in adults.[1]

Montelukast is leukotrine receptor antagonist family of medication called as (R,E)-2-(1-((1-(3-(2-(7-Chloroquinolin-2-yl)vinyl)phenyl)-3- (2-(2-hydroxypropan-2-yl) phenyl) propylthio) methyl) cyclopropyl) acetic acid with molecular weight of 586.19 g/mol. The chemical structure of Montelukast is shown in Fig. 1. It is freely soluble in ethanol, methanol, and water and practically insoluble in Acetonitrile. It is used to treat asthma and relieve symptoms of seasonal allergies and it works by blocking the action of leukotrine D4 in the lungs, resulting in decreased inflammation and relaxation of smooth muscle.[2]

Bilastine is a novel selective histamine H_1 receptor antagonist called as 2-[4-(2-{4-[1-(2-Ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl) phenyl] -2-methyl

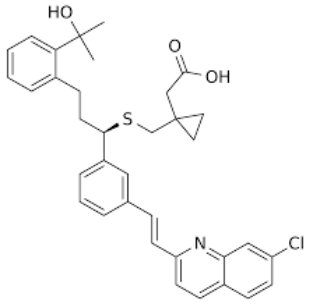

Fig. 1: Structure of Montelukast

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propanoic acid with molecular weight 463.622 g/mol. It is used for the symptomatic treatment of chronic idiopathic urticaria and allergic rhino-conjunctivitis. During allergic response mast, cells undergo degranulation which releases histamine and other substances. The chemical structure of Bilastine is shown in Fig. 2. By binding to and preventing activation of the H_1 receptor, Bilastine reduce the development of allergic symptoms due to the release of histamine from mast cells.[3]

The literature survey reveals that many analytical methods were specified for the determination of Montelukast and Bilastine as individual and combined dosage form with other combinations of drugs. Bilastine is not official in any pharmacopoeia but reported method for determining UV, UPLC, HPLC method.[4-6] Montelukast is official in Indian Pharmacopoeia[7] and also reported method for determination of UV,[8-10] reverse phase high performance liquid chromatography (RP-HPLC),[11,12] High-performance thin-layer chromatography (HPTLC),[13,14] liquid chromatography–mass spectrometry (LC–MS) method.[15] The only one reported UV spectrophotometric method[16] for simultaneous estimation of Bilastine and Montelukast in their combined dosage form. In the available method, wavelength maxima used for measurement of Bilastine was 214 nm, but there will always be chances of interference of methanol around the used wavelength maxima. Therefore present research work attempted has been made to develop and validate advanced derivative spectroscopic methods for simultaneous estimation of Bilastine and Montelukast in their combined dosage form as per ICH Q_2R_1 guideline.[17] Because the developed method facilitates multicomponent analysis and corrects the irrelevant background absorption and advanced derivative spectroscopy method forms the beginning of differentiation or resolution of overlapping bands and the vital characteristics of the derivative process, broadbands are suppressed relative to sharp bands.

Derivative Spectroscopy Method[17-18]

Here absorbance (A) of a sample is differentiated with respect to wavelength λ to generate first, second, or higher-order derivatives.

$$[A] = f(\lambda)\text{: Zero order,}$$
$$[dA/d\lambda] = f'(\lambda)\text{: First order,}$$
$$[d2A/d\lambda 2] = f''(\lambda)\text{: Second order}$$

Derivative spectra often yield a characteristic profile where changes of gradient and curvature in the standard or zero-order spectrums are observed as distinctive bipolar features. Zero-order derivative yields smoothing of spectra. First-order derivative spectra represent the gradient at all spectrum points and can be used to locate hidden peaks, while second and even higher-order derivatives are potentially more useful in analysis. The methods to generate derivative spectra are an optical method and wavelength modulation method.

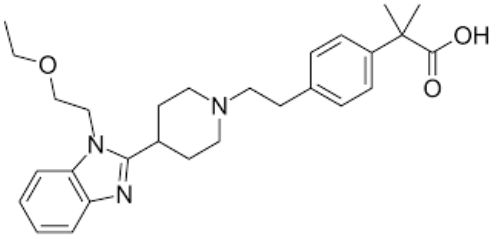

Fig. 2: Structure of Bilastine

If an analysis of binary mixture of X and Y is to be carried out by this method, first or second derivative spectra of individual component is generated, if peaksand valleys of X and Y are dissimilar. At a wavelength of zero crossings of derivative spectra of X, the component Y should show some [dA/dλ] or [d2A/dλ2] and vice versa.

Since the values [dA/dλ] and [d2A/dλ2] also obeys Beer's Lambert's law. First or second derivative spectra of various known concentrations of mixtures of X and Y are analyzed, taking zero-crossing wavelength of X to measure Y and vice versa. A calibration curve of [dA/dλ] or [d2A/dλ2] vs concentration is prepared for each compound.

The advantages of derivative spectroscopy are[19] positions of local maximum are precisely defined even if the absorption spectrum is diffuse. Thus, minor details of a spectrum become enhanced—these details aid in distinguishing between similar spectra of different compounds. Compounds in which absorption spectra overlap and cannot be separated by conventional methods are easily resolved. In quantitative analysis, selectivity and sensitivity are increased. Sensitivity increases are gained from the elimination of errors resulting from overlapping bands.[19,20]

Materials and Methods

Chemical and Reagents

Active pharmaceutical ingredient of Montelukast was obtained as a gift sample from Cadila Pharmaceutical and Bilastine was obtained as a gift sample from Hetero Healthcare.

Instrumentation

Spectroscopic analysis was carried out using UV-1900 UV/Vis-double beam spectrophotometer with spectra Shimadzu software. Spectrophotometer with spectral width 1 nm, wavelength accuracy of 0.3 nm, and pair of 10 mm matching quartz cells were used to measure the resulting solutions' absorbance.

Analytical Method Development

Preparation of Standard Stock Solution

Accurately weigh 10 mg of Montelukast and 20 mg of Bilastine separately in 10 and 20 mL volumetric flask respectively The volume is made up to the mark with methanol and final stock solution containing 1000 µg/mL and overlay spectra of selected drug taken as shown in Fig. 3.

Preparation of a Mixture of Montelukast and Bilastine

From the standard stock solution of Montelukast (take 1-mL) was transferred into a 10 mL volumetric flask, and volume was adjusted up to the mark with methanol (sol. A), and from the standard stock solution of Bilastine (take 1-mL) was transferred into a 10 mL volumetric flask and volume was adjusted up to the mark with methanol (sol. B), then from sol. A take 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4 mL and from sol. B take 0.4, 0.8, 1.2, 1.6, 2, 2.4, 2.8mL were transferred into a series of 10 mL volumetric flask, and volume was adjusted to the mark with methanol. Thus final solution of mixture of Montelukast and Bilastine obtained contain 2+4, 4+8, 6+12, 8+16, 10+20, 12+24, 14+28 µg/mL, all the solution was scanned from 200–400 nm respectively.

Selection of Wavelength for Analytical work

The determination of Bilastine in the presence of Montelukast by conventional UV spectroscopy and with the help of first order was difficult as given in Fig. 4, but the determination of Montelukast at selected wavelength might be possible without the interference from Bilastine. So it was thought of interest to develop the second-order derivative spectrophotometric method for simultaneous estimation of Montelukast and Bilastine from the tablet dosage form by choosing zero-crossing point at 226.8 nm and 326.4 nm. The λ_{max} of Montelukast and Bilastine were found and recorded as given in Fig. 5. The second-order derivative spectra were recorded for both drugs, and zero-crossing points were determined. (Fig. 6). The zero crossing point of Montelukast was 226.8 nm, and Zero crossing point of Bilastine was 326.4 nm.

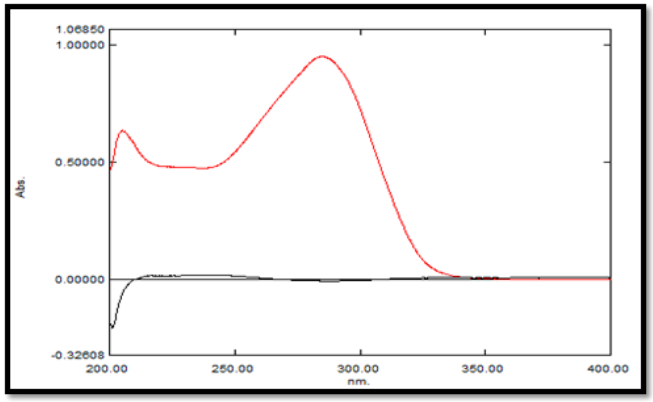

Fig. 3: Overlay spectra of Montelukast and Bilastine

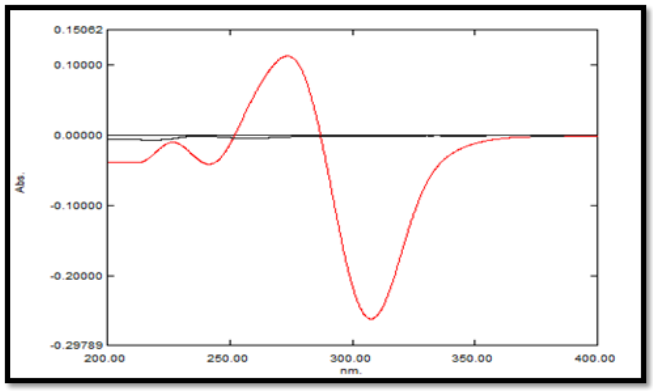

Fig. 4: First order derivative spectra of Montelukast and Bilastine

Stability of the Analytical Solutions of Montelukast and Bilastine

The stability of the Montelukast and Bilastine in solvent (Methanol) was checked by measuring the absorbance of 10 µg/mL and 20 µg/mL solution respectively at specified time intervals. The stability check was done for three hours for both of drugs. It shows that the prepared solution is stable for three hour. The stability study of Montelukast and Bilastine was shown in Figs. 7 and 8 respectively.

Validation of Proposed Method

The proposed method was validated by studying several parameters: linearity, limits of detection (LOD), limits of quantification (LOQ), accuracy, precision, robustness, ruggedness, and assay.

Linearity

The linearity of the measurement was evaluated by analyzing different concentration of the solution of

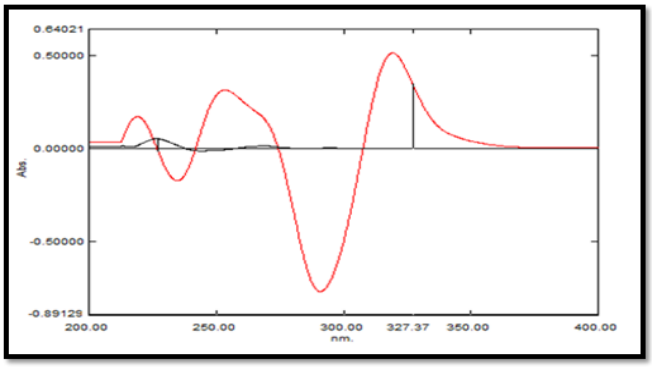

Fig. 5: Second order derivative spectra of Montelukast and Bilastine

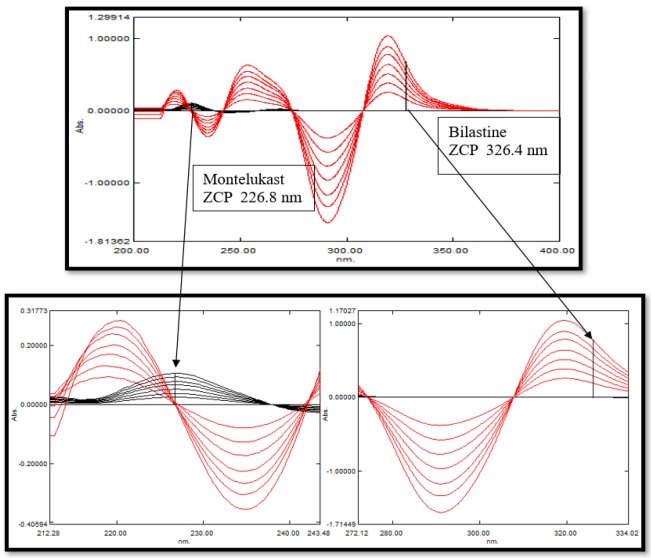

Fig. 6: Overlay of second order derivative spectra of calibration curve

Montelukast and Bilastine. For simultaneous equation method the Beer-Lambert's equation was follow. The calibration table for Montelukast and Bilastine was shown in Tables 1 and 2 respectively The calibration curve of Montelukast and Bilastine was shown in Figs. 9 and 10 respectively.

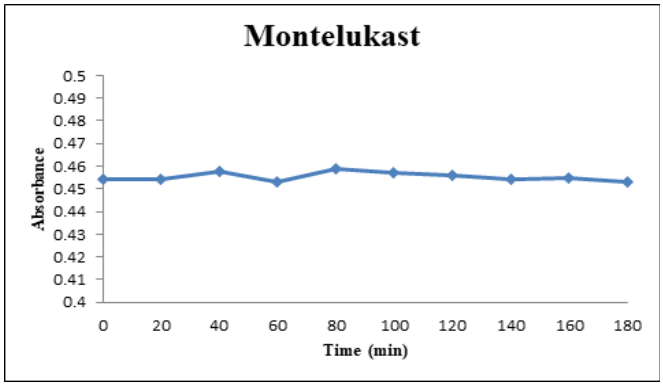

Fig. 7: Stability study of analytical solution of Montelukast

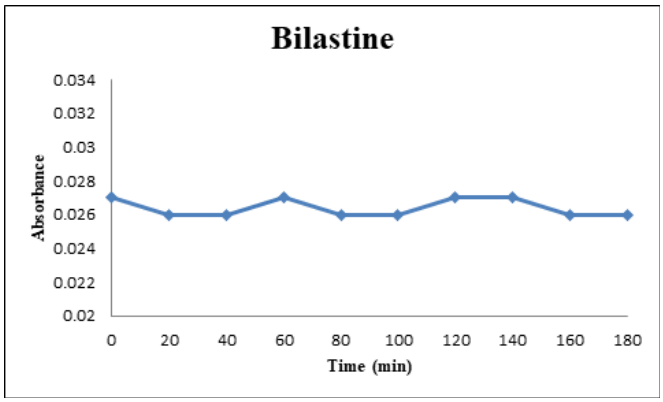

Fig. 8: Stability study of analytical solution of Bilastine

Table 1: Calibration table for Montelukast

Sr. No.	*Concentration (µg/mL)*	*Absorbance*
1	2	0.0928
2	4	0.1788
3	6	0.2836
4	8	0.3630
5	10	0.4548
6	12	0.5472
7	14	0.6366

Table 2: Calibration table for Bilastine

Sr. No.	*Concentration (µg/mL)*	*Absorbance*
1	4	0.0064
2	8	0.0118
3	12	0.0170
4	16	0.0220
5	20	0.0270
6	24	0.0330
7	28	0.0396

Limit of Detection (LoD) and Limit of Quantification (LoQ)

The LoD is the lowest amount of analyte in a sample that can be detected, but not necessarily quantified under the stated experimental conditions. The LoQ is the lowest amount of analyte in the sample that can be determined with acceptable precision and accuracy. The LoD and LoQ values were calculated from linearity data by utilizing the standard deviation and slope of the curve. The results of LoD and LoQ were shown in Table 3.

Accuracy

It was determined by calculating the recovery of Montelukast and Bilastine by application of the developed analytical method to mixtures of the drug product contents to which known amounts of analyte have been added within the range of the method.

To check the proposed method's accuracy, studies were carried out at 80, 100, and 120% of the test concentration as per ICH guidelines. The recovery study was performed three times at each level. Results of the formulation analysis of recovery studies along with statistical validation data were given in Tables 4 and 5.

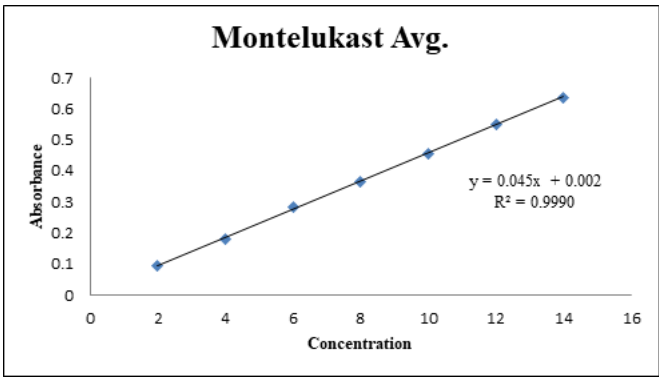

Fig. 9: Calibration curve of Montelukast

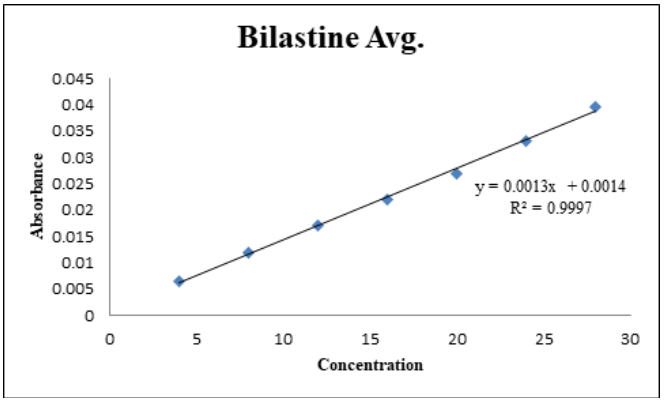

Fig. 10: Calibration curve of Bilastine

Table 3: LoD and LoQ data for montelukast and bilastine

Drug	*LoD (µg/mL)*	*LoQ (µg/mL)*
Montelukast	0.1216	0.3686
Bilastine	0.3406	1.0320

Table 4: Recovery study

Level of % Recovery	Amount Present (mg)		Amount of Standard Added (mg)		Total amount recovered (mg)		% Recovery	
	MON	BIL	MON	BIL	MON	BIL	MON	BIL
80	6	12	4.8	9.6	10.77	21.23	99.73	98.29
80	6	12	4.8	9.6	10.75	22.00	99.53	101.85
80	6	12	4.8	9.6	10.79	21.23	99.93	98.29
100	6	12	6	12	11.98	23.54	99.85	98.07
100	6	12	6	12	11.96	24.31	99.67	101.28
100	6	12	6	12	12.00	23.54	100.03	98.07
120	6	12	7.2	14.4	13.19	26.61	99.95	100.81
120	6	12	7.2	14.4	13.15	26.62	99.62	100.82
120	6	12	7.2	14.4	13.19	25.85	99.95	97.90

Table 5: Statistical validation of recovery study

Level of % Recovery	% Mean Recovery* (*n=3)		Standard Deviation*		Co-efficient of Deviation* (%R.S.D.)	
	MON	BIL	MON	BIL	MON	BIL
80%	99.731	99.478	0.2039	2.0560	0.2045	2.066
100%	99.853	99.145	0.1835	1.8505	0.1838	1.866
120%	99.842	99.844	0.1927	1.6822	0.1929	1.6848

Table 6: Intra-day precision

Sr. No.	Amount Present (µg/mL)		Total amount found (µg/mL)		Average	
	MON	BIL	MON	BIL	MON	BIL
1	2	4	1.98	3.98		
2	2	4	1.99	3.97	1.983	3.977
3	2	4	1.98	3.98		
4	6	12	5.97	11.99		
5	6	12	6.02	11.97	5.993	11.980
6	6	12	5.99	11.98		
7	10	20	9.99	19.99		
8	10	20	9.97	20.01	9.990	19.993
9	10	20	10.01	19.98		

Table 7: Statistical validation of intra-day precision

Drug	Mean* (%) (*n=3)	Standard Deviation*	Co-efficient of Deviation* (%R.S.D.)
Montelukast	1.983	0.00577	0.29110
	5.993	0.02517	0.41990
	9.990	0.02000	0.2002
Bilastine	3.977	0.00577	0.14518
	11.980	0.01000	0.08347
	19.993	0.01527	0.07640

Table 8: Inter-day precision

Sr. No.	Amount Present (µg/mL)		Total amount found (µg/mL)		Average	
	MON	BIL	MON	BIL	MON	BIL
1	2	4	1.97	3.91		
2	2	4	1.91	3.89	1.943	3.870
3	2	4	1.95	3.81		
4	6	12	5.92	11.92		
5	6	12	5.84	11.84	5.923	11.853
6	6	12	6.01	11.80		
7	10	20	9.96	19.94		
8	10	20	9.84	19.89	9.867	19.880
9	10	20	9.80	19.81		

Precision

It is a measure of either the degree of reproducibility or repeatability of the analytical method. Inter and Intra-day precision, which was studied carried out by comparing on 3 different concentrations. Data from 9 determinations over 3 concentration levels covering the specified range. Intra and Inter-day precision were determined in terms of %RSD. Intra-day precision was determined by analyzing Montelukast and Bilastine in combined solution their respective calibration range for three times in the same day. Inter-day precision was determined by analyzing Montelukast and Bilastine in a combined solution for 3 days. Results of Intra-day precision study and statistical validation data are given in Table 6 and 7. Result of Inter-day precision study, along with statistical validation data given in Table 8 and 9.

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in the method parameters and indicates its reliability during normal usage. A robustness study was performed by changing in the scanning speed and changing in the methanol manufacturer. Result of robustness study with statistical validation as shown in Table 10 and 11.

Ruggedness

Ruggedness study was carried out by the degree of reproducibility of test results obtained by analyzing the same sample carried out by different analysts. The results obtained by both the analyst were tabulated, and calculations were done to obtain SD and %RSD. The results are shown in Table 12, and statistical validation of Ruggedness study were shown in Table 13.

Assay

Twenty tablets of Montelukast and Bilastine in combination were weighed and their average weight was determined, and the tablets were crushed to powder sample. From the triturate, weight equivalent to 10 mg of Montelukast and 20 mg of Bilastine was weighed and transferred to 100 mL volumetric flask and dissolved in methanol, and the content was kept in ultra-sonicator for 25 minutes. Finally, the volume was made up to the mark with methanol. The solution was filtered through Whatman filter paper. Then take 1-mL solution from above mixture in 10 mL volumetric flask and volume make up with the help of methanol to the mark and the final solution contains 10 µg/mL for Montelukast and 20µg/mL for Bilastine. The mixed sample solutions were analyzed to obtain spectra and absorbance values were noted. The results of the analysis of tablet formulation are reported in Table 14 and data for statistical validation are given in Table 15.

Table 9: Statistical validation of inter-day precision

Drug	*Mean* (%) (*n=3)*	*Standard Deviation**	*Co-efficient of Deviation* (%R.S.D.)*
	1.943	0.03055	1.57207
Montelukast	5.923	0.08505	1.43583
	9.867	0.08327	0.84392
	3.870	0.05291	1.36731
Bilastine	11.853	0.06110	0.51547
	19.880	0.06557	0.32985

Results and Discussion

The present work described an advanced derivative spectroscopic method for simultaneous estimation of Montelukast and Bilastine in their tablet dosage form. The method is developed by using methanol as a solvent. The solutions were scanned in UV-visible region and second-order derivative spectra were recorded, and zero-crossing points of both drugs were determined. The zero crossing point of Montelukast was 226.8 nm and zero crossing point of Bilastine was 326.4 nm. The method was validated by using ICH guidelines for the following parameters: linearity, LoD, LoQ, accuracy, precision, robustness, ruggedness and assay. Linearity of MON and BIL were found 2-14 µg/mL (R^2=0.9990) and 4-28 µg/mL (R^2=0.9997), respectively. LOD and LOQ found 0.1216 and 0.3686 for MON and 0.3406 and 1.0320 for BIL. Accuracy study was carried out for 80, 100, and 120% concentrations and the percentage recovery for MON and BIL were found within the range. The precision study was carried out by comparing on 3 different concentrations and the result of their %RSD were <2%. Robustness study carried out by change in scanning speed and change in methanol manufacturer and %RSD was found 99.77 ± 0.55 and 99.45 ± 0.36 for MON and 99.82 ± 0.30 and 99.70 ± 0.28 for BIL respectively. Ruggedness study carried out by different analyst and result was found 99.75 ± 0.07 for MON and 99.87 ± 0.11 for BIL. Statistical validation of

Table 10: Robustness study

		Concentration (µg/mL)		*Amount found*		*% Found*		*Average*	
Variation and Level		*MON*	*BIL*	*MON*	*BIL*	*MON*	*BIL*	*MON*	*BIL*
Change in Scanning Speed	Fast	10	20	9.92	19.90	99.20	99.50	99.77	99.82
	Medium	10	20	9.98	19.97	99.80	99.85		
	Slow	10	20	10.03	20.02	100.30	100.10		
Change in Methanol Manufacturer	Finer	10	20	9.97	19.98	99.70	99.90	99.45	99.70
	Merck	10	20	9.92	19.90	99.20	99.50		

Table 11: Statistical validation for robustness study

	Mean (%)		*Standard Deviation*		*Co-efficient of deviation (%R.S.D.)*	
Variation and Level	*MON*	*BIL*	*MON*	*BIL*	*MON*	*BIL*
Change in Scanning Speed* (*n=3)	99.77	99.82	0.5507	0.3013	0.5520	0.3019
Change in Methanol Manufacturer (n=2)	99.45	99.70	0.3535	0.2828	0.3555	0.2837

Table 12: Ruggedness study

		Concentration (µg/mL)		*Amount Found*		*% found*	
Variation and Level		*MON*	*BIL*	*MON*	*BIL*	*MON*	*BIL*
Different Analyst	Analyst 1	10	20	9.98	19.99	99.8	99.95
	Analyst 2	10	20	9.97	19.96	99.7	99.80

Table 13: Statistical validation for ruggedness study

Drug	*Mean* (%) (*n=2)*	*Standard deviation**	*Co-efficient of deviation* (%R.S.D.)*
Montelukast	99.75	0.0707	0.07088
Bilastine	99.87	0.1060	0.10619

Table 14: Analysis of tablet formulation

Sr. No.	*Amount Present (µg/mL)*		*Total amount found (µg/mL)*		*% Label claim*	
	MON	*BIL*	*MON*	*BIL*	*MON*	*BIL*
1	10	20	10.03	19.98	100.3	99.9
2	10	20	9.96	20.02	99.6	100.1
3	10	20	10.00	19.94	100.0	99.7
4	10	20	10.05	20.00	100.5	100.0
5	10	20	10.01	19.96	100.1	99.8
6	10	20	9.99	19.91	99.9	99.55

Table 15: Statistical validation of tablet formulation analysis

Drug	*Mean* (%) (*n=6)*	*Standard Deviation**	*Co-efficient of Deviation* (%R.S.D.)*
Montelukast	100.067	0.314	0.314
Bilastine	99.842	0.201	0.201

tablet formulation analysis was found 100.067 ± 0.31 for MON and 99.842 ± 0.20 for BIL.

Conclusion

A simple, fast, accurate and precise advanced derivative spectroscopic method has been developed and validate for simultaneous estimation of Montelukast and Bilastine in their tablet dosage form. Derivative spectroscopic method, an effective tool for enhancement of resolution, which can be helpful to separate two or more components with overlapping spectra and discrimination in favor of the sharpest features of a spectrum, used to eliminate interferences by broadband constituents. It can be concluded that this developed method will be helpful for further research on both of this drug, and their combination for future analytical studies and research work can be used as a reference for further method development and validation in future.

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