Original Article

Chemo metric assisted Spectrophotometric Method Development through Quality by design Approach for the estimation of Bilastine and Montelukast sodium in combined solid dosage form

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ABSTRACT

Objective: Quality by design (QbD) is a systematic process for pharmaceutical development recommended by regulatory agencies like USFDA. Development of various pharmaceutical processes including analytical methods by applying Quality by design aids in ensuring the robustness of the method. QbD approached chemo metric assisted UV-VIS spectrophotometric analytical method was developed for the estimation of Bilastine (BSE) and Montelukast sodium (MKS) from their combined dosage forms. **Materials and Method:** Simultaneous equation method was selected from the nature of spectra, solvent 50 % alcohol was utilised; and for method 274.5 nm and 351.5 nm was the wavelength for measurement of absorbance of bilastine and montelukast sodium respectively. Effect of input variables on spectrum characteristics were studied for selection of critical parameters and developed method was validated as per ICH Q 2 R1 regulatory guidelines. Linearity of the drugs was ascertained over the conc range 1-32 mcg/ml (microgram/ml) for BSE and 1-20 mcg/ml for MKS. **Results and Discussion:** The percentage purity of assay was found 98.09 % for BSE and 103.62 % for MKS; and the accuracy study data were varied from 0.2523 to 0.5221 for BSE and 0.2512 to 1.2515 for MKS. Precision study was shown acceptable data as SD data varied from 0.1902 to 0.5773 for BSE and from 0.2828 to 0.5458 for MKS. **Conclusion:** The developed method is rigid, robust and efficient for the estimation of BSE and MKS from the composition of dosage form. QbD was applied to build rigid robust method through risk assessment at early stage and defining the design space at the later stage.

Key Words: Bilastine, Montelukast Sodium, Qbd, ICH, Simultaneous Equation Method

Bilastine (BSE) chemically 4-[2-[4-[1-(2-Ethoxy ethyl)-1H-Benzimidazole-2-yl]-1-piperidinyl] ethyl]-α, α-dimethyl benzene acetic acid [1] is an antihistamine, non-sedative histamine H1 receptor antagonist; by binding and preventing activation of H1 receptor bilastine reduces development of allergic symptoms due to release of histamine from mast cell [2]. Literature survey revealed that various analytical methods have been reported for estimation of BSE such as UV spectrophotometric methods lonely [3-6]**,** UV spectrophotometric method with MKS or other drug [7], for estimation of BSE with MKS or other by RP-HPLC [8-14], stability indicating RP-HPLC [15-17], green QbD HPLC [18], LC-MS/MS [19], stability indicating UPLC [20] and RP-UFLC [21] alone or in combination with other drugs.

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Montelukast sodium (MKS) chemically Sodium [1-[[[(1 R)-1-(3-[(E) 2-(7-chloroquinoline-2-yl) ethenyl] phenyl)-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] sulfanyl] methyl] cyclopropyl] acetate [1] is an anti-asthmatic, leukotriene receptor antagonist. It can completely block the binding of CYSLT'S to receptor that they can inhibit the binding of inflammation mediator LTD4 [2]. Literature survey revealed that various analytical methods have been reported for estimation of MKS includes UV spectrophotometric method lonely [22-28]**,** UV spectrophotometric method with BSE or other drug [29-33], for estimation of MKS Qbd technique [34], RP-HPLC methods [35-40], stability indicating HPLC with other [41-43] and HPTLC [44] alone or in combination with other drugs. Montelukast sodium is official in Indian and British Pharmacopoeia [45, 46]**.** Chemical structure of both these drugs is shown in **(Figure 1).**

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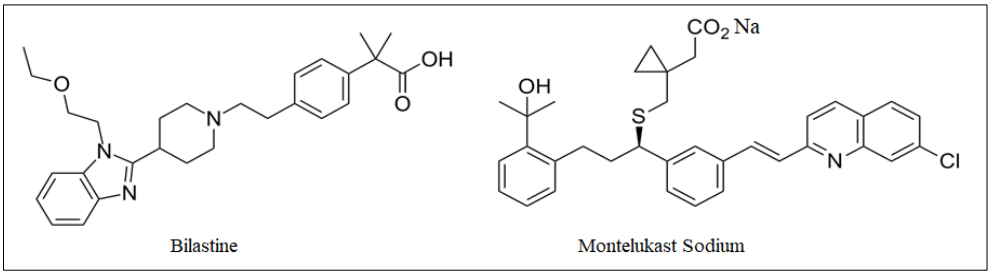

Figure 1: Chemical structure of Drug molecule

Quality by design concept is applied for the development of pharmaceutical processes to assure a predefined product quality. QBD concepts are mentioned in ICH guidelines Q8 (R2) (Pharmaceutical development), Q9 (Quality risk management), and Q10 (Pharmaceutical quality system) [47-49] shown in **(Figure 2).** ICH guidelines Q8 (R2) defines QBD as a "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"[50]. QBD approach in analytical method summarizes a complete understanding of how the analytical technique attributes and operating conditions affect the analytical performance. Factors to study in analytical quality by design (AQbD) approach may include the type of analytical technique chosen, reagents used and instrument parameters.

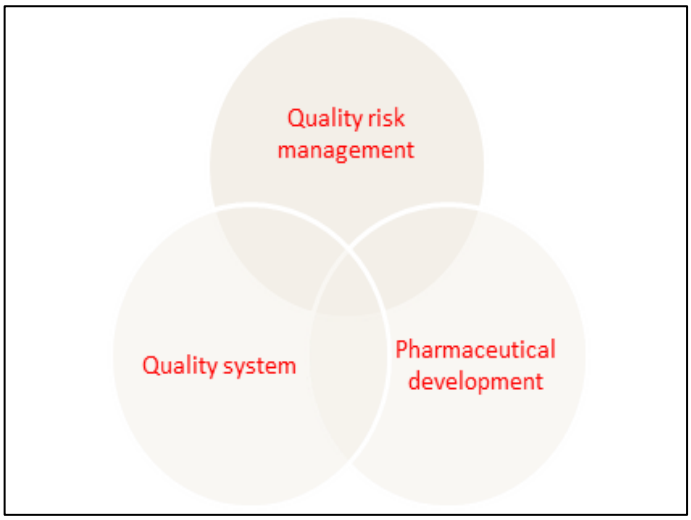

Fig No 2: Analytical QbD approach

There are similar advantages of applying QbD principles to analytical methods as to manufacturing processes and product [51]**.** A QbD approach can be beneficial in the development of suitable, robust, low cost and eco-friendly (eco-friendly solvent, chemicals) method which is applicable at any stage of the lifecycle of the product. Also some regulatory guidelines have mentioned flexibility of changing analytical method without revalidation if the AQbD approach has been implemented during analytical method development. The first stage of AQbD approach is to fix an analytical target profile (ATP) for the method. ATP defines the goal of the analytical method development process and it is the sign of method performance [52, 53]. For analytical method validation ICH Q2 (R1) has given various method performance characteristics for an analytical method. In development of UV-VIS spectrophotometric method, QbD approach was implemented with the study of the effect of method input variables on spectral shape, intensity of absorbance, and absorbance maxima λ_{max} and critical parameters were selected for the proposed method and method was validated as per ICH guidelines Q2 (R1).

MATERIALS AND METHODS

Instrumentation: Analysis was performed with a Shimadzu Double beam UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan) with spectral bandwidth of 2 nm and wavelength accuracy of ± 1 nm with 10 mm matched Quartz cells was used. Electronic balance Afcoset balance (The Bombay Burmah Trading corpo Ltd) with accuracy ±0.1 mg Model No. ER 200A was utilised for weighing and for degassing the solution Digital Ultrasonic cleaner 1.8 Ltr (Labman scientific Instruments Chennai) was used.

Reagents and Chemicals: Pharmaceutically pure samples of BSE and MKS from Glenmark Pharmaceuticals, Nashik, Maharashtra, India were procured as a gift sample and the commercial formulation Bilafav-M Tablet containing bilastine 20 mg and montelukast sodium 10 mg was procured from the local market.

AQbD approach application in method development: AQbD approach was applied to study the influence of input variable parameters on spectrophotometric analytical method performance shown in **(Figure 3).**

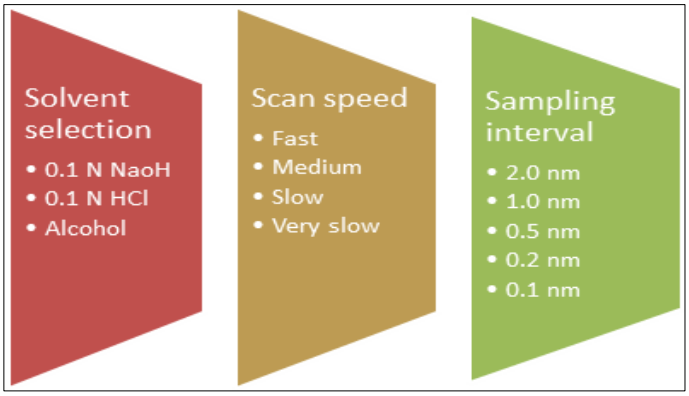

Figure 3: Diagram showing the relationship between input variable parameters and the spectrophotometric method performance characteristics

Solvent selection: BSE is freely soluble in 10% acetic acid glacial, chloroform and in ethanol, slightly soluble in 1 N HCl and soluble in 1N NaOH and sparingly soluble in water; whereas MKS is very soluble in water, methylene chloride and ethanol. Although the solubility of the procured drugs were studied in alcohol 90%, 0.1 N HCl and 0.1 N NaOH separately; and found that BSE is soluble in ethanol, 0.1 N NaOH, slightly soluble in 0.1 HCl however MKS soluble in ethanol and insoluble in NaOH and HCl. Both drugs solubilises in 50% alcohol, hence selected as a common solvent. Each drugs solution with known conc was scanned in UV range of 400 nm to 200 nm. It was found that alcohol 50% is suitable with respect to stable, robust and precise in producing result.

Preparation of stock solutions and standard solutions: 10 mg each of drug BSE and MKS were separately and accurately weighed; and transferred into separate 25 ml volumetric flask. Dissolved into solvent alcohol 50% and volume was made to 25 ml with this solvent. Working standard solution was prepared by diluting 5 ml to 10 ml with 50 % alcohol. Subsequent standard solution of each drug with conc 16µg/ml was prepared by diluting aliquot of stock solution to 10 ml with 50% alcohol into 10 ml capacity volumetric flask.

Selection of wavelength and conc range: From UV spectra it was found that BSE has measurable absorbance at 274.5 nm and 281.5 nm **(Figure 4)** and less interference was observed by MKS; similarly MKS has maximum absorbance at 351.5 nm and negligible interference by BSE was accounted. Chemometric method using simultaneous equation was applied and which was reasonable remedy to overcome interference at each other's absorbance. To study linearity, working conc range 1 to 32µg/ml for BSE and 1 to 20µg/ml for MKS was selected. Also combined drug solution was prepared simulated to marketed formulation. Selected critical parameters based upon above discussion, observations were listed in **(Table 1)** and by using these; method was validated as per ICH guidelines and by analysing marketed preparations.

Experimental Method for estimation: From the overlain spectra simultaneous equation method was applied for estimation of both the analytes from their combined dosage form.

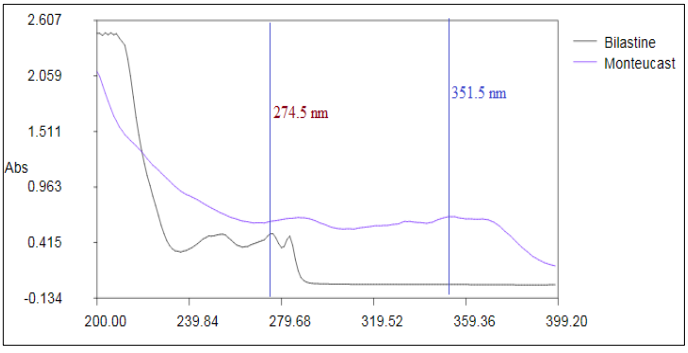

Figure 4: Overlaid spectra of BSE and MKS

Table No 1: Selected critical parameter for UV-VIS analytical method of BSE and MKS

Parameter	Selected variables for simultaneous equation method	
	BSE	MKS
Wavelength	274.5	351.5
Solvent	50% alcohol	50% alcohol
Scan speed	Fast	Fast
Sampling interval	0.2 nm	0.2 nm

Simultaneous Equation Method for estimation of bilastine and montelukast sodium: BSE was shown maximum absorbance i.e. λ_{max} at 274.5 nm where moderate interference by MKS found and MKS has maximum absorbance i.e. λ_{max} at 351.5 nm where negligible interference by BSE observed. At 274.5 nm the λ_{max} of BSE, the MKS was shown consistency in the absorptivity; hence two wavelengths 274.5 and 351.5 nm were considered as 1 and 2 respectively for the said method to estimate BSE and MKS. The equation A= abc was applied for x (BSE) and y (MKS) determination. Working standard solutions of BSE and MKS containing 12µg/ml conc were separately prepared and used for the method.

$$Cx = \frac{A2\ .ay1 - A1.ay2}{ax2.ay1 - ax1.ay2}$$

$$Cy = \frac{A1\ .ax2 - A2.ax1}{ax2.ay1 - ax1.ay2}$$

Where C_X = Conc of BSE in sample solution

A_1 and A_2 = absorbance of sample solution at 1 and 2 wavelength

ay_1 and ay_2 = absorptivity of MKS at 1 and 2 wavelength of standard solution

ax_1 and ax_2 = absorptivity of BSE at 1 and 2 wavelength of standard solution

C_y = Conc of MKS in sample solution

As = Absorbance of Sample solution at 2 wavelength

VALIDATION of the METHOD

Selected critical parameters should meet the performance characteristics of the analytical method so as to attain analytical target profile of the method. An ICH guideline Q2 R1 was applied to study methods performance with critical parameters in order to implement AQbD approach. The method was validated as per ICH guidelines

System suitability: System suitability is studied to demonstrate the suitability of the developed procedure under consideration for the analytical method. Six replicates of working standard solutions with conc 20µg/ml and 16µg/ml of BSE and MKS respectively were prepared separately and absorbance was recorded, calculated SD and % RSD of the response.

Linearity: The linearity of an analytical method is its ability to obtain response i.e. absorbance which is directly proportional to the conc of analyte. Series of working standard solutions were prepared in conc. range of 1-32 µg/ml for BSE and 1-20 µg/ml for MKS and scanned in 400 to 200 nm range in spectrum mode of the spectrophotometer, absorbance of the standard solutions were recorded at their respective wavelength; i.e. 274.5 for BSE and 351.5 nm for MKS in spectrum order. Microsoft office excel software tool was used to obtain the standard regression curve and its analysis as slope, intercept, and correlation coefficient.

Assay of formulation: Assay was carried out by proposed methods and assay was validated by statistical parameters.

Estimation of formulations by simultaneous equation method: Tablet powder equivalent to 10 mg BSE and 5 mg MKS was weighed and transferred into 25 ml volumetric flask. Dissolved into 50% alcohol, mixed well for 10 mins and volume was made to 25 ml with the solvent. Solution was filtered through what man filter paper and aliquots of solution were further diluted with the 50% alcohol to obtain tablet sample solution. Solution was scanned in the range of 400 to 200 nm to obtain absorbance of tablet solution at 274.5 nm and 351.5 nm in spectrum order. Obtained absorbance were utilised to estimate unknown conc of formulation; and results were statistically validated to obtain % of nominal conc, standard deviation and % of RSD.

Accuracy and Precision: The accuracy of an analytical method expresses the closeness of an agreement between test result and true result. Accuracy study was performed by recovery study i.e. standard addition method; diluted standard solutions of BSE and MKS were prepared and standard solutions added in 80,100 and 120% proportionate to the tablet solution. Three replicates at each of these three levels were prepared, measured and % of conc, SD and RSD were calculated. The precision study was carried out by performing assay of tablet six times; also the reproducibility in result was studied by inter day and intraday precision.

Limit of Detection (LOD) and Limit of Quantitation (LOQ): The LOD and LOQ of BSE and MKS by the proposed method were determined using calibration graph method and calculated as 3.3σ/s and 10 σ/s for LOD and LOQ respectively; σ is the standard deviation of calibration curve and s is the slope of regression line.

Robustness and Ruggedness: It is measure of capacity of analytical procedure to remain unaffected by small but deliberate variations in method parameter.

RESULTS AND DISCUSSION

Method development comprises numerous steps, and of which solvent selection, selection of method for measurement are significant one. Uses of aqueous solvents, eco-friendly solvents like hydrotropic have got remarkable weightage due to low cost, readily available and environmentally sound. Drugs underlying analysis must have appreciable solubility in the selected solvent. Chemical structure of the drug and physico-chemical properties available in the literature guides about use of appropriate solvent in the method.

From UV spectra two wavelengths were selected as 274.5 nm (λ_{max} of BSE) and 351.5 nm (λ_{max} of MKS) for calculation of both drugs in combined solution shown in (Fig No 4).

System Suitability: The absorbances of six replicates of standard solutions of respective drugs conc are reported in (Table No 2). The SD and % RSD was found for BSE and MKS and meets the system suitability requirements indicate method was suitable for analysis.

Table No 2: System suitability study of BSE and MKS

Conc in µg /ml	Absorbance of BSE	Conc in µg /ml	Absorbance of MKS
20 µg /ml	0.3124	16 µg /ml	0.5269
20 µg /ml	0.3110	16 µg /ml	0.5443
20 µg /ml	0.3281	16 µg /ml	0.5146
20 µg /ml	0.3115	16 µg /ml	0.5156
20 µg /ml	0.3395	16 µg /ml	0.5332
20 µg /ml	0.3292	16 µg /ml	0.5581
SD	0.006662	SD	0.01281
RSD	0.41972	RSD	0.29142

Linearity: The calibration curve of both drugs was found to be linear shown in **(Figure 5)** in the conc range of 1-32 µg/ml for BSE and 1-20 µg/ml for MKS as shown in **(Figure 6).** The regression equation of line and parameters slope, r^2 value and intercept **(Figure 7)** are tabulated in **(Table 3),** which proved the linear relationship between conc and obtained response.

Assay: The assay was carried out by the proposed method. The spectrum of formulation by method was shown in (Fig No 8). The assay of formulation was carried out by proposed method and calculated % of nominal conc and RSD was found within acceptable limits are summarized in (Table No 4). The results indicated applicability of the method for estimation of formulation.

Accuracy and Precision: The accuracy study was carried out at 3 levels; and the results of accuracy are summarised in **(Table 5),** the obtained results were within acceptable limit; and methods accuracy was justified by calculating % drug content. The precision study was carried out by performing assay of solutions; further the reproducibility in result was studied by interday and intraday precision. The values obtained SD and % RSD was shown methods precision and are summarised in **(Table 5).**

Limit of Detection (LOD) and Limit of Quantitation (LOQ): The LOD and LOQ of BSE and MKS by the proposed method were calculated and shown in **(Table 6).**

Robustness and Ruggedness: Robustness was studied and capacity of analytical procedure to measure analyte was remain unaffected by small but deliberate variations in method parameter. The analytical method was found rugged during development; similarly the result was produced shown in **(Table 6)** by performing the analysis by different analyst.

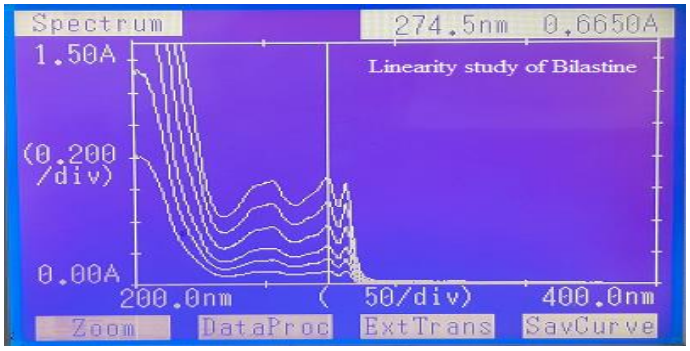

Figure 5: Overlaid spectra of Bilastine obtained in linearity study

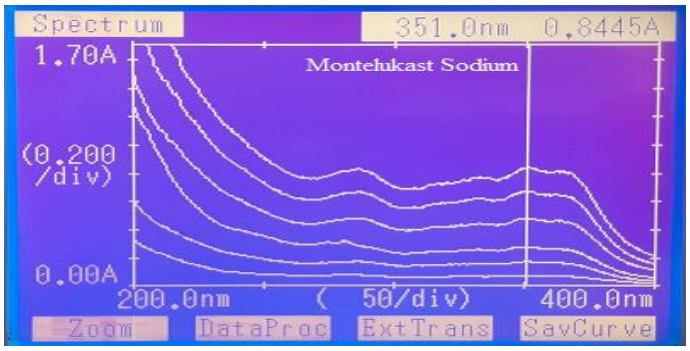

Figure 6: Overlaid spectra of Montelukast obtained in linearity study

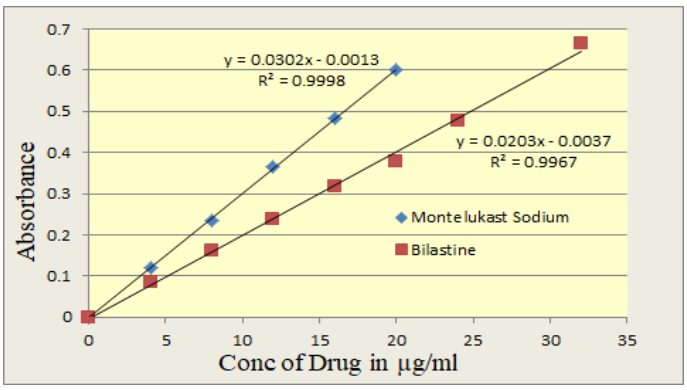

Fig No 7: Calibration curve of BSE and MKS

Table 3: Parameters of regression equation obtained in Microsoft excel

Parameters	BSE	MKS
Detection wavelength	274.5	351.5
Beer's law limit (µg/ml)	1–32 µg/ml	1–20 µg/ml
Correlation coefficient (r^2)	0.9967	0.9998
Regression equation (y = mx + c)	Y = 0.0203X - 0.0037	Y = 0.0302X - 0.0013

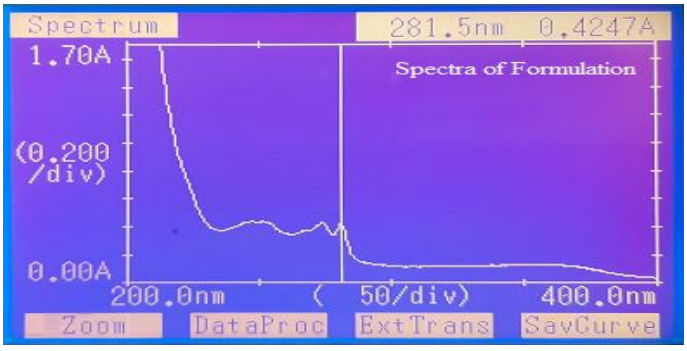

Fig No 8: Spectra of formulation obtained in the assay

Table 4: Results of assay of formulation by proposed method

Name of the Formulation - BILAFAV M (Bilastine 20 mg, Montelukast sodium 10 mg) B No -23S2GTB843, MFG Date- Jul 2023, EXP Date–Jun 2025						
Formulation	**Drug**	**Label Claim (mg/Tablet; n=6)**	**Amount found/mg**	**Drug Content %**	**Std Deviation**	**% RSD**
Method	BSE	20	19.618	98.092	0.15702	0.16092
	MKS	10	10.362	103.62	0.21932	0.24942

Table No 5: Results of accuracy and precision

Parameter	Level of study	Drug Name	S.D.	% RSD
Precision	Intraday Precision	BSE	0.19025	3.9635
		MKS	0.28281	0.2828
	Inter day precision	BSE	0.57732	0.83165
		MKS	0.54582	0.64584
Accuracy study of BSE and MKS	80%	BSE	0.25236	0.21612
	100%		0.28842	0.24982
	120%		0.52218	0.44192
	80%	MKS	0.25123	0.34451

100%	0.68602	0.88492
120%	1.25152	1.81023

Table No.6: Results of LOD and LOQ, robustness

Parameters		BSE	MKS
LOD µg/ml		0.7253	0.6726
LOQ µg/ml		1.1761	0.8458
Robustness	(conc 20 BSE and 16 µg/ml MKS)	0.3724 -to- 0.3973 (± 2 nm)	0.5308 -to- 0.5229 (± 2 nm)
Ruggedness	Analyst 1	SD ± 0.20681 RSD ± 3.53719	SD ± 0.64246 RSD ± 2.9893
	Analyst 2	SD ± 0.20167 RSD ± 5.16971	SD ± 0.062412 RSD ± 2.55771

CONCLUSION

Both the drugs were estimated from their combined formulation by simultaneous equation method. Results were found within acceptable limits, statistical data obtained were shown rigidity of the method. The validated method was employed 50% alcohol as solvent thus become economical. The proposed method is precise, accurate, robust and reproducible hence can be routinely used for simultaneous estimation of bilastine and montelukast sodium from combined dosage form

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