World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

Quantitative simultaneous determination of montlukast and bambuterol in combined tablet formulation by RP-HPLC method

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Received: 12-08-2022 / Revised Accepted: 03-09-2022 / Published: 05-09-2022

ABSTRACT

A simple, Accurate, precise method was developed for the simultaneous estimation of the Bambuterol and Montelukast in bulk and Tablet dosage form. Chromatogram was run through Std Discovery 150 x 4.6 mm, 5µ. Mobile phase containing Buffer 0.1%OPA: Acetonitrile taken in the ratio 65:35 was pumped through column at a flow rate of 1.0 ml/min. Temperature was maintained at 30°C. Optimized wavelength selected was 254.0 nm. Retention time of Bambuterol and Montelukast were found to be 2.067min and 3.032 min. %RSD of the Bambuterol and Montelukast were and found to be 0.6% and 0.4% respectively. %Recovery was obtained as 100.12% and 99.96% for Bambuterol and Montelukast respectively. LOD, LOQ values obtained from regression equations of Bambuterol and Montelukast were 0.09, 0.26 and 0.14, 0.42respectively. %Assay was obtained as 99.97% and 100.02% for Bambuterol and Montelukast respectively. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.

Keywords: Bambuterol, Montelukast, RP-HPLC, Method Development, Validation

INTRODUCTION

Montelukast is a leukotriene receptor antagonist (LTRA) used for the treatment of asthma[1,2] and to relieve symptoms of seasonal allergies[3]. Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene, and results in less inflammation. Because of its method of operation, it is not useful for the treatment of acute asthma attacks. The effectiveness of montelukast is typically in addition to or complementary with the use of inhaled corticosteroids[4] or other agents in asthma step therapy. Montelukast, like zafirlukast, is a leukotriene receptor antagonist[5] used as an alternative to anti – inflammatory medications in the management and chronic treatment of asthma and exercise- induced bronchospasm (EIB)[6] Unlike zafirlukast, Montelukast does not inhibit CYP2C9 or CYP3A4 and is therefore, not expected to effect

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How to Cite this Article: C. P. Vaishnavi, Makula Ajitha. Quantitative simultaneous determination of montlukast and bambuterol in combined tablet formulation by RP-HPLC method. World J Pharm Sci 2022; 10(09): 42-51; https://doi.org/10.54037/WJPS.2022.100904

the hepatic clearance of drugs metabolized by these enzymes. Again because of its very specific focus of operation, it does not interact with other allergy medications such as theophylline. The IUPAC name of Montelukast is (3S,7R)-N-[(2,4-difluorophenyl)methyl]-11-hydroxy-7-methyl-9,12-dioxo-4-oxa-1,8-diazatricyclo[8.4.0.0^{3,8}] tetradeca-10,13-diene-13-carboxamide[7]. Montelukast is marketed in United States and many other countries by Merck & Co. with the brand name Singulair®[8]. It is available as oral tablets, chewable tablets, and oral granules. In India and other countries, it is also marketed under the brand name Montair®, produced by Indian company Cipla.

Bambuterol is **a** long acting beta2-adrenoceptor agonist for the management of lung diseases associated with bronchospasm[9]. Bambuterol is bisdimethylcarbamate prodrug of terbutaline[10].It is called as bronchiodilator because it widens (dilates) the airways. It works by opening the air passages in lungs more freely. For people with asthma this helps to relieve symptoms such as coughing, wheezing and feeling breathless, particularly at night[11]. Bambuterol is used for prevention of reversal of bronchospam in patients. It stimulates the beta- adrenergic receptors (beta 2 receptors) of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially mast cells. Generic Name Bambuterol DrugBank Accession Number DB01408 Background. Bambuterol is a long acting beta-adrenoceptor agonist used in the treatment of asthma. Commercially, the Astra Zeneca pharmaceutical company produces and markets Bambuterol as Bambac and Oxeol. The Indian company Cipla produces with the brand name Bambudil. The chemical name of bambuterol is[3-[2-(tert-butylamino)-1-hydroxyethyl]-5-(dimethylcarbamoyloxy) phenyl] N, N-dimethylcarbamate.

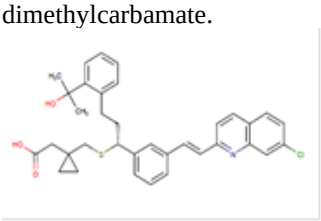


Figure 1: Structure of Montelukast

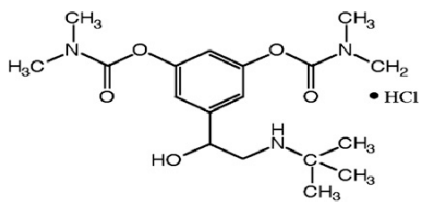


Figure 2: Structure of Bambuterol

According to a literature review, there are some techniques for the simultaneous estimate of these medicines as well as others for assessment of the drugs alone or in combination with other drugs. Utilizing UV-Spectrophotometry [12-16] RP-HPLC [17-22]. There is no established technique for the stability-indicating simultaneous measurement of Montelukast and Bambuterol by RP-HPLC in pharmaceutical dosage form, according to a survey of the literature. The primary goal of this work is to provide an efficient, quick, and accurate RP-HPLC approach for estimating of montelukast and bambuterol in medicinal dose and tablet form. According to ICH recommendations, a proven approach was also used to estimate the amounts of montelukast and bambuterol.

MATERIALS AND REAGENTS

Montelukast and Bambuterol pure drugs were received from Spectrum Pharma research solutions, Hyderabad. The combination tablet Montelukast and Bambuterol (**Telekast Plus**) was purchased from a local pharmacy store. Rankem in India provided all of the chemicals and buffers utilised in this method like Acetonitrile, Phosphate buffer, Methanol, Potassium dihydrogen Ortho phosphate buffer, Ortho-phosphoric acid, Distilled water.

Instrumentation and Chromatographic Conditions

For the development and validation method, an automated sample injector was employed with a WATERS HPLC, model: 2695 SYSTEM with Photo diode array detector. For the separation, a Discovery 150 (C18 250 mm x 4.6 mm, 5µm) column was employed. Acetonitrile is employed as mobile phase B, while 0.1% ortho phosphoric acid is used as mobile phase A. (35:65 Ratio). The analysis was done in isocratic mode with an injection volume of 10 mL and a flow rate of 1 mL/min. The duration was six minutes. The measurements were made at 254 nm.

PREPARATION OF SOLUTIONS

Diluent: Based up on the solubility of the drugs, diluent was selected, Acetonitrile and Water taken in the ratio of 50:50

Preparation of Standard stock solutions: Accurately weighed 10 mg of Montelukast, 10mg of Bambuterol and transferred to 50ml volumetric flasks and 3/4 th of diluents was added to these flask and sonicated for 10 minutes. Flask were made up with diluents and labeled as Standard stock solution. (200µg/ml of Montelukast and 200µg/ml Bambuterol)

Preparation of Standard working solutions (100% solution): 1ml from each stock solution

was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (20µg/ml of Montelukast and 20µg/ml of Bambuterol)

Preparation of Sample stock solutions: 10 Tablets were accurately weighed and average weight equivalent to 1 tablet was transferred into a 100ml volumetric flask, 50ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters (100µg/ml of Montelukast and 100µg/ml of Bambuterol)

Preparation of Sample working solutions (100% solution): 2ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (10µg/ml of Montelukast and 20µg/ml of Bambuterol)

Preparation of buffer:
0.1% OPA Buffer: 1ml of ortho phosphoric acid was diluted to 1000ml with HPLC grade water.

METHOD VALIDATION

To prove that the technique is suggested for routine analysis, the HPLC method's validation was done for the simultaneous estimation of Montelukast and Bambuterol drug material in accordance with the ICH criteria.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Linearity: stock solutions of Montelukast and Bambuterol is taken in to 6 different volumetric flasks and diluted to 10ml with diluents. Linearity solutions are prepared such that 0.25, 0.5, 0.75, 1, 1.25, 1.5ml.

Accuracy:
Preparation of Standard stock solutions: Accurately weighed 10 mg of Montelukast, 10mg of Bambuterol and transferred to 50ml volumetric flasks and $3/4^{th}$ of diluents was added to these flask and sonicated for 10 minutes. Flask were made up with diluents and labeled as Standard stock solution. (200µg/ml of Montelukast and 200µg/ml Bambuterol)

Preparation of 50% Spiked Solution: 0.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.
Preparation of 100% Spiked Solution: 1.0ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 150% Spiked Solution: 1.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.
Acceptance Criteria:
The % Recovery for each level should be between 98.0 to 102.

Robustness: Small deliberate changes in method like Flow rate, mobile phase ratio, and temperature are made but there were no recognized change in the result and are within range as per ICH Guide lines. Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus, mobile phase plus, temperature minus (25°C) and temperature plus(35°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

LOD sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flasks and made up with diluents. From the above solutions 0.1ml each of Montelukast, Bambuterol, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluents

LOQ sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flask and made up with diluent. From the above solutions 0.3ml each of Montelukast, Bambuterol, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluent.

System suitability parameters: The system suitability parameters were determined by preparing standard solutions of Montelukast (20ppm) and Bambuterol(20ppm) and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

Degradation studies:
Oxidation:
To 1 ml of stock solution of Bambuterol and Montelukast, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 60^0c. For HPLC study, the resultant solution was diluted to obtain 20µg/ml & 20µg/ml solution and 10 µl were injected into the

system and the chromatograms were recorded to assess the stability of sample.

Acid Degradation Studies:
To 1 ml of stock solution Bambuterol and Montelukast, 1ml of 2N Hydrochloric acid was added and refluxed for 30mins at 60^0c. The resultant solution was diluted to obtain 20µg/ml & 20µg/ml solution and 10 µl solutions were injected into the system and the chromatograms were recorded to assess the stability of sample.

Alkali Degradation Studies:
To 1 ml of stock solution Bambuterol and Montelukast, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 60^0c. The resultant solution was diluted to obtain 20µg/ml & 20µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Dry Heat Degradation Studies:
The standard drug solution was placed in oven at 105°C for 1hr to study dry heat degradation. For HPLC study, the resultant solution was diluted to 20µg/ml & 20µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample**.**

Photo Stability studies:
The photochemical stability of the drug was also studied by exposing the 200µg/ml & 200µg/ml solution to UV Light by keeping the beaker in UV Chamber for 1days or 200 Watt hours/m^2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 20µg/ml & 20µg/ml solutions and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Neutral Degradation Studies:
Stress testing under neutral conditions was studied by refluxing the drug in water for 1hr at a temperature of 60º. For HPLC study, the resultant solution was diluted to 10µg/ml & 20µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of the sample**.**

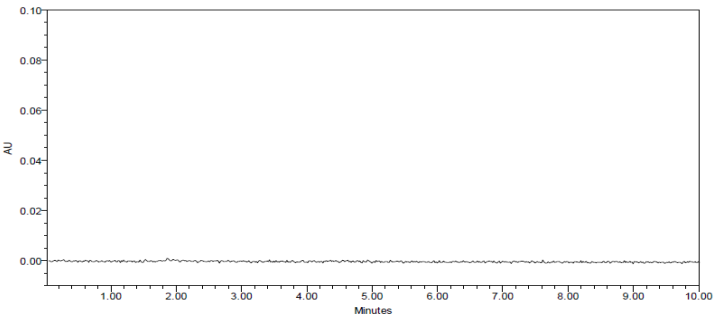
RESULTS AND DISCUSSIONS

Table 1: System suitability table

S.No.	Montelukast			Bambuterol			
Inj	RT (min)	USP Plate Count	Tailing	RT (min)	USP Plate Count	Tailing	RS
1	2.286	8888	1.32	3.033	8752	1.15	6.9
2	2.287	8874	1.33	3.052	8747	1.13	6.8
3	2.287	8893	1.32	3.055	8782	1.15	7.0
4	2.289	8894	1.35	3.055	8760	1.15	7.0
5	2.302	8893	1.33	3.057	8778	1.15	7.1

Table 2: Specificity data

Sample name	retention time(Mins)	Area
Montelukast	2.067	373382
Bambuterol	3.032	517493



Blank Chromatogram

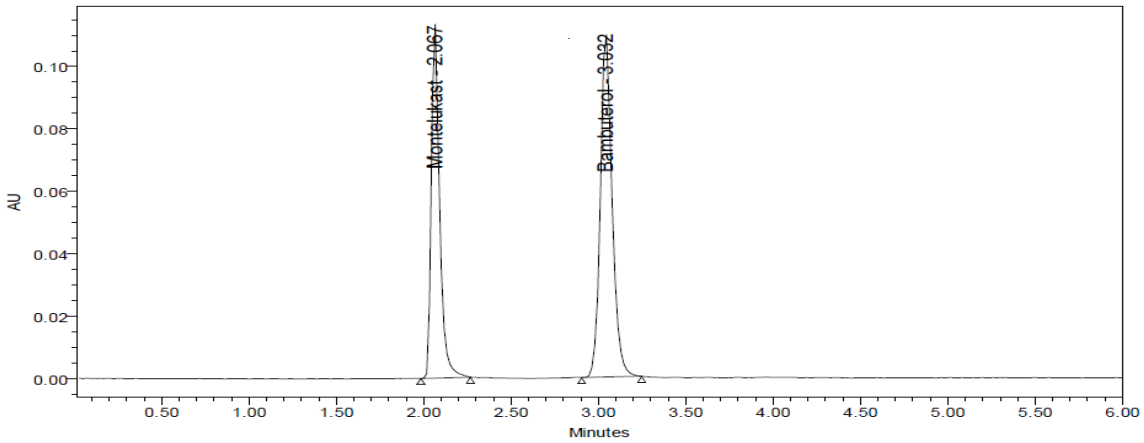


Figure 3: Specificity Chromatograms of Montelukast and Bambuterol.

Table 2: Linearity table for Bambuterol and Montelukast:

Bambuterol		Montelukast	
Conc (µg/mL)	**Peak area**	**Conc (µg/mL)**	**Peak area**
0	0	0	0
5	193729	5	191717
10	388341	10	391217
15	582120	15	594428
20	776057	20	792546
25	960832	25	977071
30	1144272	30	1145391

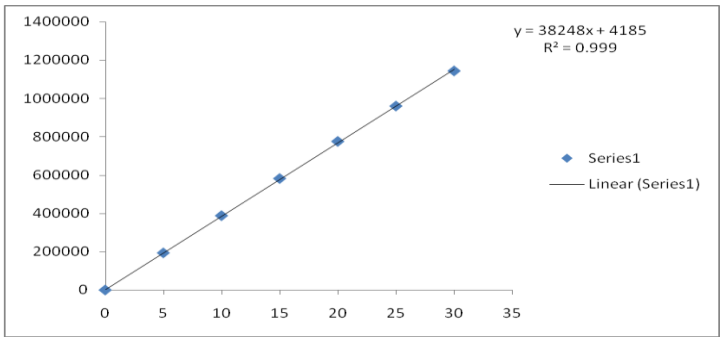


Figure 4: Bambuterol calibration Curve

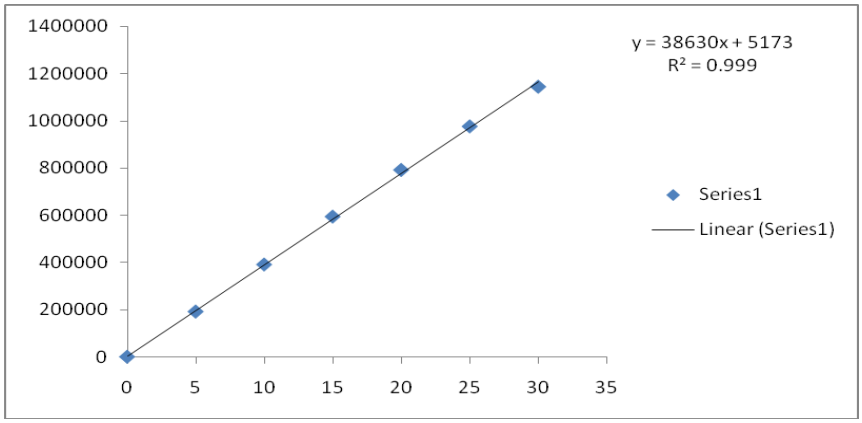


Figure 5: Montelukast calibration Curve

Table 3: Accuracy table of Bambuterol

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	10	10.0	99.5	100.12%
	10	9.9	99.4	
	10	10.0	100.3	
100%	20	20.2	100.9	
	20	20.0	99.8	
	20	20.2	101.0	
150%	25	25.1	100.4	
	25	25.0	99.9	
	25	25.0	99.9	

Table 4: Accuracy table of Montelukast

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	10	10.08	100.77	99.96%
	10	9.98	99.84	
	10	9.97	99.65	
100%	20	9.90	99.02	
	20	10.00	100.01	
	20	9.93	99.25	
150%	25	30.16	100.53	
	25	30.18	100.60	
	25	29.88	99.58	

System Precision: With regard to the working strength of Montelukast and Bambuterol, six duplicate injections of the standard solution at 100% of the prescribed limit were analysed to determine the system accuracy. In Table 5, the results of the peak area are compiled.

Table 5: System precision

S. No	Area of Bambuterol	Area of Montelukast
1.	770285	796836
2.	771229	798798
3.	779926	790084
4.	770712	792136
5.	779033	791625
6.	774701	794912
Mean	774314	794065
S.D	4304.4	3356.2
%RSD	0.6	0.4

The % RSD for the peak areas of Montelukast and Bambuterol obtained from six replicate injections of standard solution was within the limit of (<2%).

Method precision: Analyzing a sample of Montelukast and Bambuterol allowed researchers to gauge the method's accuracy (Six individual sample preparations). Table 6 provides a summary of the data.

Table 6: Method precision

Injection	Montelukast	Bambuterol
1	772242	799045
2	779537	798285
3	776953	791252
4	775504	792363
5	771703	790111
6	773273	799146
Avg	774869	795034
Std dev	3033.4	4224.7
%RSD	0.4	0.5

Results shows, the % RSD of Repeatability study was within the range for Montelukast and Bambuterol is (<2%)

Table 7: Robustness

S.No.	Condition	%RSD of Bambuterol	%RSD of Montelukast.
1	Flow rate (-) 0.9ml/min	0.5	0.5
2	Flow rate (+) 1.1ml/min	0.3	0.3
3	Mobile phase (-) 60B:40A	0.3	0.4
4	Mobile phase (+) 70B:30A	0.6	0.3
5	Temperature (-) 25°C	0.5	0.3
6	Temperature (+) 35°C	0.4	0.3

Table 8: Forced degradation for Montelukast and Bambuterol

Stress condition	Solvent	Temp (^{0}C)	Exposed time
Acid	2N HCL	60^0c	30 mins
Base	2N NAOH	60^0c	30 mins
Oxidation	20% H_2O_2	60^0c	30 mins
Thermal	Diluent	105^0c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^0c	

Degradation Studies: Degradation studies were performed with the formulation and the degraded samples were injected. Assay of the injected samples was calculated and all the samples passed the limits of degradation.

Table 9: Degradation results of Bambuterol and Montelukast

Type of degradation	Montelukast		Bambuterol	
	% Recovered	% Degraded	% Recovered	% Degraded
Acid	94.78	5.22	96.61	3.39
Base	93.61	6.39	93.27	6.73
Peroxide	96.27	3.73	95.45	4.55
Thermal	97.57	2.43	97.96	2.04
Uv	98.57	1.43	98.31	1.69
Water	99.40	0.60	99.16	0.84

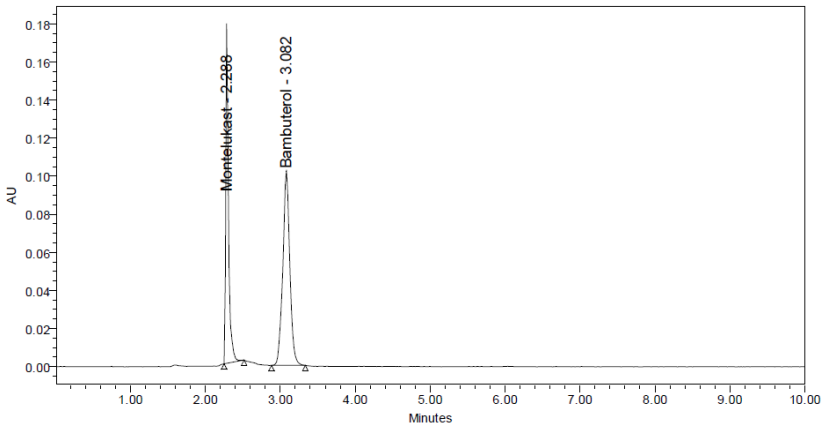


Figure 6: Acid chromatogram of Bambuterol and Montelukast

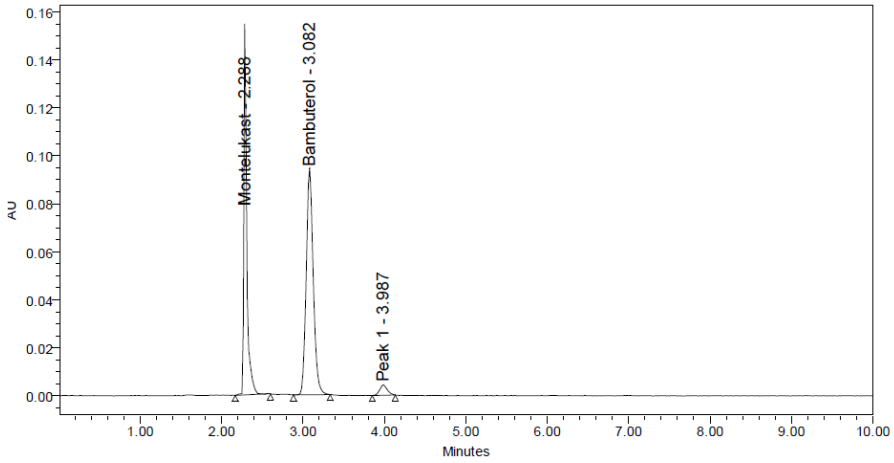


Figure 7: Base chromatogram of Bambuterol and Montelukast

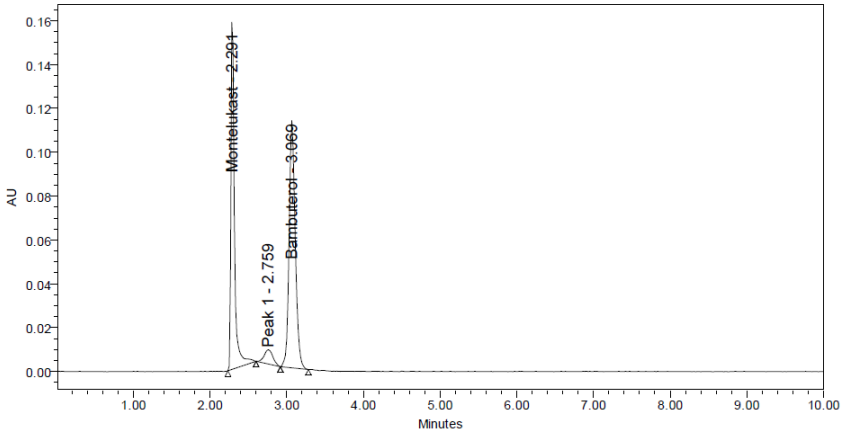


Figure 8: Peroxide chromatogram of Bambuterol and Montelukast

According to the results, samples were degraded when they were subjected to an acid, base, and oxidation interaction. Hydrolysis reaction, heat reaction, and light reaction all showed no deterioration. According to the stress research, none of the degradants co-eluted with the maxima of the active medication.

Assay: (Telecast plus Tablet) bearing label claim, Monteluskast 40mg, Bambuterol 8mg, assay was carried out by injecting sample into HPLC System.

Table 10: Assay data of Bambuterol

S.No.	Standard Area	Sample area	% Assay
1	770285	772242	99.63
2	771229	779537	100.57
3	779926	776953	100.24
4	770712	775504	100.05
5	779033	771703	99.56
6	774701	773273	99.77
Avg	774314	774869	99.97
Stdev	4304.4	3033.4	0.39
% RSD	0.6	0.4	0.4

Table 11: **Assay data of Montelukast**

S.No.	Standard Area	Sample area	% Assay
1	796836	799045	100.53
2	798798	798285	100.43
3	790084	791252	99.55
4	792136	792363	99.69
5	791625	790111	99.40
6	794912	799146	100.54
Avg	794065	795034	100.02
Stdev	3356.2	4224.7	0.53
% RSD	0.4	0.5	0.53

Table 12: Assay outcome for Montelukast and Bambuterol

Drug Name	Label claim dose	%Assay	Brand Name
Montelukast	40mg	100.2	Telekast Plus
Bambuterol	8mg	99.97	

CONCLUSION

The proposed HPLC method was validated as per ICH guidelines and applied for the determination of Montelukast and Bambuterol in tablet dosage form. The method was found to be accurate, precise, robust and specific. Retention time of Bambuterol and Montelukast were found to be 2.067min and 3.032 min. %RSD of the Bambuterol and Montelukast were and found to be 0.6% and 0.4% respectively. %Recovery was obtained as 100.12% and 99.96% for Bambuterol and Montelukast respectively. LOD, LOQ values obtained from regression equations of Bambuterol and Montelukast were 0.09, 0.26 and 0.14, 0.42 respectively. %Assay was obtained as 99.97% and 100.02% for Bambuterol and Montelukast respectively. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.

ACKNOWLEDGEMENT

The authors are thankful to the Department of Pharmaceutical Analysis, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India, and Spectrum Pharma Research Solution, Hyderabad, Telangana, India, for providing Montelukast and Bambuterol as gift samples.

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