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STABILITY-INDICATING UPLC METHOD FOR ESTIMATION OF MONTELUKAST AND FEXOFENADINE SIMULTANEOUSLY IN THE PRESENCE OF STRESS DEGRADATION PRODUCTS

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ABSTRACT

A rapid, sensitive, selective, precise and accurate stability-indicating UPLC method with photodiode array detection for simultaneous determination of montelukast and fexofenadine in bulk drug and in pharmaceutical formulation was developed. The method employed HSS C18 (2.1 mm × 100 mm, 1.8 µm) analytical column as the stationary phase and the mobile phase consisted of 0.1% orthophosphoric acid and acetonitrile (50:50 v/v). The detection and analysis was carried out using photodiode array detector set at 269 nm. The linear regression analysis data for the calibration curves showed good linear relationship in the concentration range of 2.5-15 µg/ml (montelukast) and 30-180 µg/ml (fexofenadine). The method was validated, as per the International Conference on Harmonization guidelines, for selectivity, precision, accuracy, robustness, specificity, limit of detection (LOD) and limit of quantitation (LOQ). Montelukast and fexofenadine was subjected to acid and alkali hydrolysis, oxidation, thermal, water treatment and UV degradation. The method effectively assayed montelukast and fexofenadine in the presence of degradation products. Application of the developed and validated UPLC method to the tablet dosage forms proved that the method is precise and accurate for the estimation of montelukast and fexofenadine in pharmaceutical dosage form.

INTRODUCTION:

Montelukast is an oral leukotriene receptor antagonist utilized for the treatment and maintenance of asthma and to lessen seasonal allergies symptoms. Montelukast exerts its activity by blocking the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in the bronchial tubes and lungs[1-3]. Fexofenadine is a second-generation antihistamine drug used in the management of hay fever and alike allergy symptoms. Fexofenadine acts by blocking H1 receptor for histamine and as a result prevents activation of cells by histamine[4-6]. Fexofenadine along with montelukast is

effective in the control of allergic rhinitis symptoms, and for patients with conventional therapy-resistant pemphigoid nodular is and prurigo nodularis[7,8]. The methods used for fexofenadine and montelukast combined quantification include UV spectrophotometric[9,10], RP-HPLC[11-17], HPTLC[18,19] and LC-MS/MS[20] procedures. All the reported methods[7-19], except LC-MS/MS method[20], are employed in the combined quantification of fexofenadine and montelukast in pure and tablet dosage form. LC-MS/MS method[20] was developed simultaneous quantification of montelukast and fexofenadine in human plasma and applied to oral bioequivalence study in humans. Ultra performance liquid chromatography (UPLC) is an emerging area of analytical separation science. UPLC utilizes the chromatographic principles for separation and analysis using columns packed with smaller particles and/or higher flow rates for increased speed, sensitivity and superior resolution. UPLC reduces analysis times without compromising the quantity and quality of the analytical data. Till date only one UPLC method has been developed for the determination of montelukast and fexofenadine[21]. The method make use of Thermo Scientific UPLC system on Waters (symmetry) column with acetonitrile and 20 mM potassium dihydrogen phosphate in the ratio of 80:30 (*v/v*) as mobile phase. The flow rate was maintained of 1 ml/min and detection at 230 nm. The present study describes the development and validation of a stability-indicating UPLC method for quantitative estimation of montelukast and fexofenadine simultaneously in the presence of their forced degradation products.

MATERIALS AND METHODS:

Instrumentation:

Waters UPLC 2695 System equipped with quaternary pumps, photodiode array detector and auto sampler integrated with Empower 2 Software was used in the current investigation. HSS C18 (2.1 mm × 100 mm, 1.8 µm) analytical column was used for the chromatographic separation and analysis of montelukast and fexofenadine.

Chromatographic conditions:

The column temperature was maintained at 30±1°C. Separations were carried out in isocratic mode using a mobile phase consisted of 0.1% orthophosphoric acid and acetonitrile (50:50, *v/v*). The mobile phase was filtered by a UPLC filters, degassed by ultrasonic bath 15 min prior to its use. The flow rate of the mobile phase was 0.2 ml/min, and the sample injection volume was 1.5 µl. The photodiode array detector was set at 269 nm.

Materials:

Montelukast and fexofenadine reference standards were procured from Dr. Reddy's Laboratories Ltd (Hyderabad, India). Montair-Fx® tablet (Cipla Ltd, India) labeled to contain 10 mg of montelukast and 120 mg of fexofenadine per tablet was obtained from the local market. HPLC grade methanol and acetonitrile,analyticalgrade orthophosphoric acid**,** hydrochloric acid, sodium hydroxide and hydrogen peroxide were from Ramkem (Haryana, India). Milli-Q-water was used throughout the process.

Standard and sample solutions:

An Accurately weighed quantity of montelukast (10 mg) and fexofenadine (120 mg) reference standards was transferred to a 100 ml volumetric flask and dissolved in 100 ml of diluents (acetonitrile and water in the ratio of 50:50, *v/v*). This solution is used as stock standard solution. The working standard solutions were prepared by appropriate dilution of the stock standard solution with diluent at the concentration of 2.5 µg/ml, 5.0 µg/ml, 7.5 µg/ml, 10 µg/ml, 12.5 µg/ml and 15 µg/ml of montelukast, and 30 µg/ml, 60 µg/ml, 90 µg/ml, 120 µg/ml, 150 µg/ml and 180 µg/ml of fexofenadine. Five tablets were weighed and finely powdered. The average weight of one tablet was

calculated, then the tablet powder weight equivalent to 10 mg of montelukast and 120 mg of fexofenadine was transferred into a 100 ml volumetric flask, 50 ml of diluent was added and sonicated for 25 min. The volume was made up with diluent and filtered by UPLC filters. This stock solution was aptly diluted with the diluent for analysis.

Assay method:

Working standard solutions equivalent to 2.5 to 15 µg/ml montelukast and 30 to 180 µg/ml fexofenadine were prepared by suitable dilution of the stock standard solution with the diluent. 1.5 µl of each solution was injected twice onto the column and the peak area responses were determined at 269 nm. The calibration curves were established for montelukast and fexofenadine by plotting the mean peak area response *vs* concentration of drug. The amount of the selected drugs was calculated either from the corresponding calibration curve or regression equation.

Assay of tablets:

1.5 µl of the sample solution (10 µg/ml of montelukast and 120 µg/ml of fexofenadine) was injected into the UPLC system six times. The peak area responses of the drugs were determined at 269 nm. The nominal concentration of montelukast and fexofenadine in the test sample was calculated by either from the corresponding calibration curve or regression equation.

Degradation studies:

ICH guidelines are followed to reveal the inherent stability characteristics of montelukast and fexofenadine[22]. For this purpose, the stress degradation studies were performed on the montelukast and fexofenadine using the developed UPLC method.

Oxidative degradation:

One ml of stock standard solution (fexofenadine-1200 µg/ml and montelukast-100 µg/ml) and 1 ml of 20% H_2O_2 were added in 100 ml volumetric flask. The flask was kept in water bath maintained at a temperature of 60 ^oC for 30 min. Cool the solution to room temperature and dilute to the 100 ml with diluent.

Acid degradation:

One ml of stock standard solution (fexofenadine-1200 µg/ml and montelukast-100 µg/ml) and 1 ml of 2 N HCl were added in 100 ml volumetric flask. The flask was kept at 60 °C reflux condition for 30 min and neutralized with sufficient volume of 2 N NaOH. Cool the solution to room temperature and dilute to 100 ml with diluent.

Alkali degradation:

One ml of stock standard solution (fexofenadine-1200 µg/ml and montelukast-100 µg/ml) was transferred to a 100 ml volumetric flask. The solution was mixed with 1 ml of 2 N sodium hydroxide. The prepared solution was subjected to reflux at 60 °C for 30 min. The sample was cooled to room temperature and neutralized with an amount of acid equivalent to that of the previously added. The resulting solution was diluted to the 100 ml with diluent.

Thermal degradation

100 ml of stock standard solution (fexofenadine-1200 µg/ml and montelukast-100 µg/ml) in a beaker was kept at 105°C in hot air oven for 1 hr. Cool the solution to room temperature after the stress period.

Photo degradation:

100 ml of stock standard solution (fexofenadine-1200 µg/ml and montelukast-100 µg/ml) in a beaker was kept in UV Chamber for 1 hr or 200 Watt hours/m^2 in photo stability chamber. After the specified time period the solution was cooled to room temperature. The resultant solutions in all the degradation conditions were diluted with diluent to obtain 120 µg/ml and 10 µg/ml of fexofenadine and montelukast, respectively. 1.5 µl of each degraded sample was injected into the system and the chromatograms were recorded to assess the stability of fexofenadine and montelukast.

Neutral degradation:

One ml of stock standard solution (fexofenadine-1200 µg/ml and montelukast-100 µg/ml) and 1 ml of water were added in 100 ml volumetric flask. The flask was kept at 60 °C reflux condition for 1 hr. Cool the solution to room temperature and dilute to 100 ml with diluent.

RESULTS AND DISCUSSION:

The present study was aimed at developing a rapid, precise and sensitive stability- indicating UPLC with PDA detection method for the simultaneous estimation of montelukast and fexofenadine. HSS C18 (2.1mm × 100 mm, 1.8 µm) column with temperature set at 30±1°C was used as analytical column as it gave optimum resolution and good symmetric peaks with short run time (2 minutes). Different composition of mobile phases containing water-methanol (*v/v*), water–acetonitrile (*v/v*) and 0.1% orthophosphoric acid-acetonitrile (*v/v*) in different ratios and with different flow rate were tried in order to get suitable composition of mobile phase. This challenge was met by using 0.1% orthophosphoric acid-acetonitrile (50:50, *v/v*) where optimum peak area response, resolution and good peaks without tailing were observed with isocratic mode at a flow rate of 0.2 ml/min. using the optimized conditions, the retention time reported was 0.921 min for montelukast and 1.101 min for fexofenadine (Figure 1).

Method validation:

The method validation was done as per ICH guidelines in terms of system suitability, linearity, LOD, LOQ, accuracy, precision, selectivity, specificity and robustness[23]. System suitability tests were carried out on freshly prepared standard solution of montelukast (10 µg/ml) and fexofenadine (120 µg/ml) to check the various parameters such as retention time, USP plate count, resolution and USP tailing (Table 1). As per USP plate count should be more than 2000, tailing factor should be less than 2 and resolution must be more than 3. All the values of system suitability parameters were passed and were within the limits.

The linearity of the developed UPLC method was demonstrated by analyzing the working standard solution at six different concentrations of montelukast (2.5 µg/ml, 5.0 µg/ml, 7.5 µg/ml, 10 µg/ml, 12.5 µg/ml and 15 µg/ml) and fexofenadine (30 µg/ml, 60 µg/ml, 90 µg/ml, 120 µg/ml, 150 µg/ml and 180 µg/ml). The calibration curve was constructed for montelukast and fexofenadine by plotting the peak area response versus concentration of drug. From the calibration curve regression correlation, intercept and slope were calculated. The results were shown in Table 2. The results displayed a good correlation between the peak area and concentration of analytes in the concentration range of 2.5-15 µg/ml (montelukast) and 30-180 µg/mL (fexofenadine). The sensitivity parameters, limit of detection (LOD) and limit of quantitation (LOQ) for montelukast and fexofenadine was determined using relative standard deviation of the peak area response and slope of the calibration curve. The values (Table 2) indicate the adequate sensitivity of the proposed method. The method selectivity was confirmed by comparison of the chromatograms obtained for mobile phase blank, placebo blank solution and working standard solution (10 µg/ml of montelukast and 120 µg/ml of fexofenadine). Retention times of montelukast and fexofenadine were 0.921 min and 1.101 min respectively (Figure 2). No interfering peaks in mobile phase blank and placebo blank at retention times of montelukast and fexofenadine in this method (Figure 2). As a result, the developed method was said to be specific.

Precision was determined for both system and method at a concentration of 10 µg/ml and 120 µg/ml montelukast and fexofenadine, respectively.

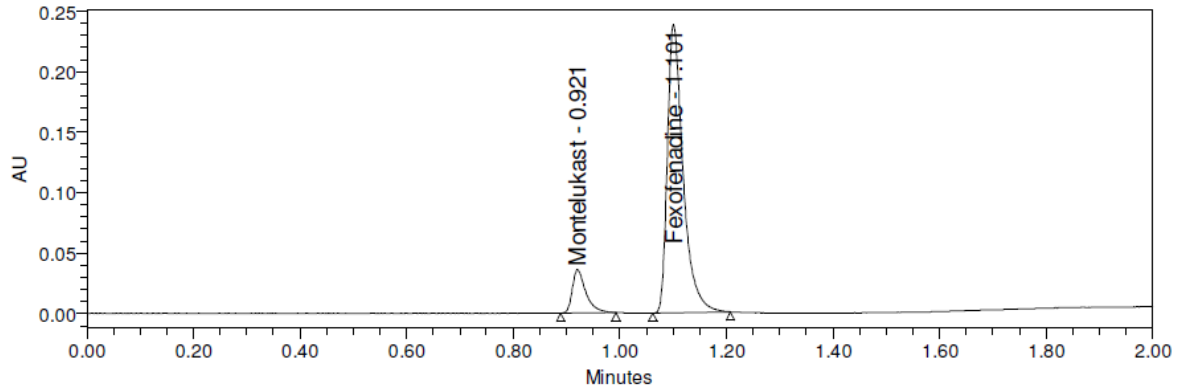

Figure 1: Chromatogram of montelukast and fexofenadine with their retention times

Table 1: System suitability values for montelukast and fexofenadine

Injection No.	Montelukast			Fexofenadine			
	RT (min)	USP Plate Count	Tailing	RT (min)	USP Plate Count	Tailing	Resolution
1	0.92	7001	1.6	1.101	7321	1.5	3.6
2	0.921	6890	1.6	1.101	7228	1.6	3.6
3	0.921	7005	1.7	1.101	7367	1.6	3.7
4	0.921	6902	1.6	1.101	7271	1.6	3.6
5	0.921	6848	1.6	1.102	7237	1.5	3.6
Mean	0.9208	6929.2	1.62	1.1012	7284.8	1.56	3.62
RSD	0.048	1.014	0.760	0.040	0.805	0.511	1.235
Recommended limits	RSD ≤2	> 2000	≤ 2	RSD ≤2	> 2000	≤ 2	> 3

Table 2: Linearity and sensitivity data of the proposed method

Parameter	Montelukast	Fexofenadine
Linearity (µg/mL)	2.5-15	30-180
Regresstion equation ($y^a = m\ x^b + c$)	y = 6333*x* + 755.9	y = 4038*x* + 8964
Slope (m)	6333	4038
Intercept (c)	755.9	8964
Correlation coefficient (R^2)	0.999	0.999
LOD (µg/ml)	0.06	0.80
LOQ (µg/ml)	0.18	2.44

[a]peak area and [b]Concentration of montelukast/fexofenadine in µg/ml

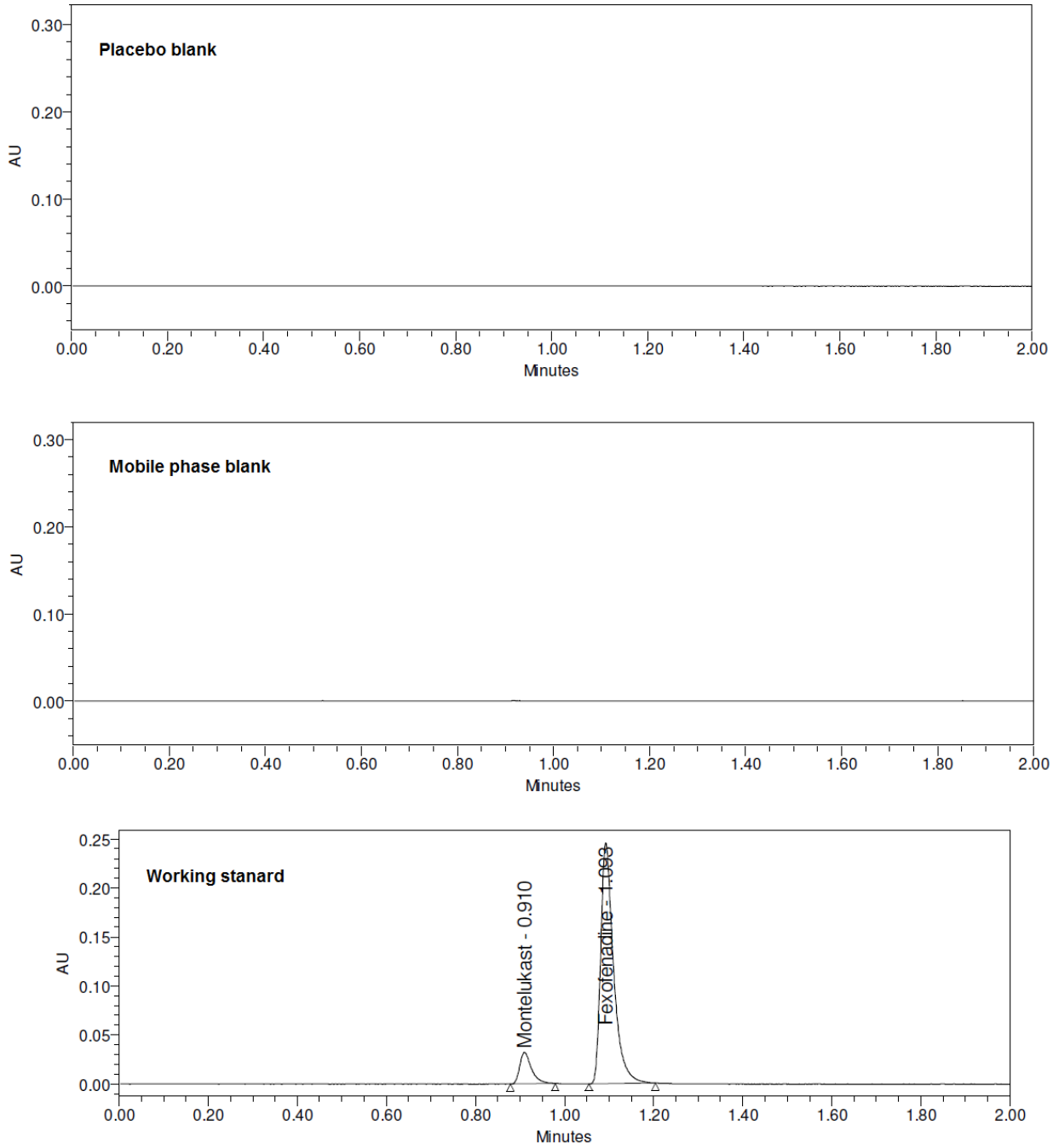

Figure 2: Chromatograms of solutions of mobile phase blank, placebo blank and working standard

Table 3: Results of system, method and inter-day precision

System precision		Method precision		Inter-day precision	
Montelukast					
Injection No.	Peak area	Injection No.	Peak area	Day	Peak area
1	64134	1	63026	1	59884
2	63209	2	62875		
3	63405	3	63727	2	58821
4	62801	4	62539		
5	63006	5	63471	3	59009
6	62394	6	62919		
Mean	63158	Mean	63092	Mean	59238
RSD	0.936	RSD	0.685	RSD	0.957
Fexofenadine					
1	488378	1	492006	1	491409
2	488109	2	491072		
3	488088	3	495089	2	491484
4	484745	4	492730		
5	486898	5	493991	3	494900
6	489540	6	489784		
Mean	487626	Mean	492445	Mean	492597
RSD	0.337	RSD	0.391	RSD	0.404

Table 4: Results of recovery of montelukast and fexofenadine

Spiked level (%)	Amount of drug		% Recovery	Mean
	Added (µg/ml)	Found (µg/ml)		
Montelukast				
50	5	4.91	98.14	99.39
	5	4.95	99.06	
	5	5.05	100.97	
100	10	9.92	99.21	99.04
	10	9.95	99.55	
	10	9.84	98.36	
150	15	15.07	100.44	99.23
	15	14.75	98.33	
	15	14.84	98.92	
Fexofenadine				
50	60	59.94	99.91	100.01
	60	59.96	99.94	
	60	60.10	100.17	
100	120	119.80	99.83	99.54
	120	119.06	99.22	
	120	119.50	99.58	
150	180	177.54	98.64	99.46
	180	180.75	100.41	
	180	178.84	99.35	

Table 5: Results of robustness

Paramater	value	Montelukast		Fexofenadine	
		Peak area*	RSD (%)	Peak area*	RSD (%)
Flow rate (mL/min)	0.15	83481	1.392	650266	0.578
	0.25	48240	0.561	395206	0.345
Temperature (ºC)	25	59697	0.462	492306	0.699
	35	59680	1.132	494599	0.309
Mobile phase ratio (*v/v*)	40:60	60410	1.719	494300	0.369
	50:50	59788	1.093	493371	0.270

*Average of six determinations

Table 6: Montelukast and fexofenadine degradation data

Type of degradation	Montelukast			Fexofenadine		
	Peak area	Recovered (%)	Degraded (%)	Peak area	Recovered (%)	Degraded (%)
Acid	60376	95.40	4.60	464248	95.02	4.98
Base	61443	97.09	2.91	474314	97.08	2.92
Peroxide	62049	98.05	1.95	479726	98.18	1.82
Thermal	62657	99.01	0.99	485381	99.34	0.66
UV light	62858	99.33	0.67	484950	99.25	0.75
Water	62658	99.01	0.99	485114	99.29	0.71

Table 7: Assay of montelukast and fexofenadine in tablets

Injection No.	Montelukast		Fexofenadine	
	Labeled claim (mg)	Assay (%)	Labeled claim (mg)	Assay (%)
1	10	99.59	10	100.7
2	10	99.35	10	100.51
3	10	100.7	10	101.33
4	10	98.82	10	100.84
5	10	100.29	10	101.1
6	10	99.42	10	100.24
Mean	-	**99.695**	-	**100.7867**
RSD	-	**0.685**	-	**0.391**

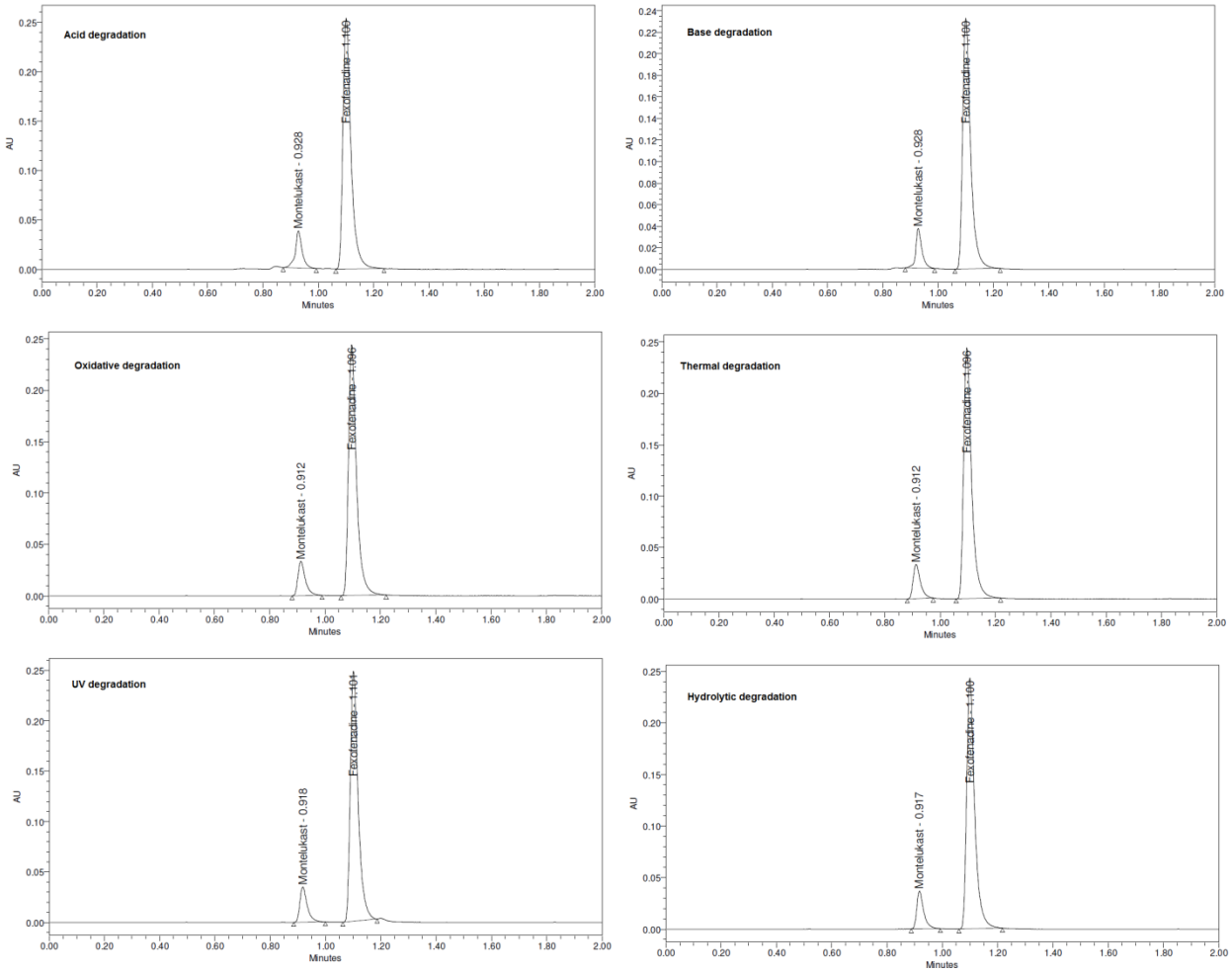

Figure 3: Chromatograms of Montelukast and fexofenadine in applied degradation conditions

System precision and method precision was assessed by six replicate injections of working standard solution and tablet sample preparations into the HPLC system. The relative standard deviation was found to be <1%, indicating the precision of system and method Table 3. The inter-day precision was determined by analyzing the working standard solutions at concentration of 10 µg/ml and 120 µg/ml montelukast and fexofenadine, respectively for 3 consecutive days. The low relative standard deviation (<1%), indicating the inter-day precision of method Table 3. To prove the accuracy of the proposed UPLC method, standard addition technique was applied. Different amounts of pure montelukast and fexofenadine were spiked to tablet sample solution in three different concentration levels (50%, 10% and 150%) and were assayed by the developed UPLC method. The percent recoveries of the added sample solutions were calculated. The average percent recoveries indicate good accuracy of the method (Table 4). The method robustness was demonstrated by studying the effect of slight changes on the peak area response of montelukast and fexofenadine. Three parameters were selected from the proposed method to be examined in the robustness: the mobile phase composition, flow rate and column temperature. Results are shown in Table 5. It was observed that none of these variables had a significant effect (% RSD <1%) on the peak areas of the montelukast and fexofenadine. Therefore, the developed method is considered robust. So as to ascertain whether the developed UPLC method was stability-indicating or not, montelukast and fexofenadine was

exposed to different ICH prescribed stress conditions such as acidic, basic, oxidative, thermal, UV and water degradation conditions. The results of the degradation studies are shown in Table 6. The chromatograms of montelukast and fexofenadine in all degradation conditions are shown in Figure 3. From the percentage of degradation values it was obeserved that montelukast and fexofenadine was less stable in acid degradation condition when compared to all other degradation conditions. The proposed UPLC method effectively analyzed montelukast and fexofenadine in the presence of degradation products. Therefore, the developed UPLC method is to be considered highly specific for intended use and also proved the stability indicating power.

Method application to the analysis of montelukast and fexofenadine in tablets:

The developed and validated method was applied for the simultaneous determination of montelukast and fexofenadine in a commercially available tablet dosage form (Montair-Fx® tablet labeled to contain 10 mg montelukast and 120 mg fexofenadine). Assay results are summarized in Table 7. It was observed that no excipients of tablet dosage form interfered with the assay of montelukast and fexofenadine, indicating the method suitability for routine quality control work.

CONCLUSION:

A new stability indicating UPLC method with PDA detector has been developed for the quantification of montelukast and fexofenadine simultaneously in the presence of stress degradation products. The montelukast and fexofenadine was subjected to different stress conditions such as water, alkaline, acidic, oxidation, thermal and UV degradation. The montelukast and fexofenadine demonstrated degradation under all stress conditions. Further, the UPLC method was validated according to ICH guidelines. The less run time (2 min) enabled the estimation of a number of samples in a short time without any interference from the excipients or degradation products. As a result, it is concluded that the proposed UPLC method could be a useful method for quality control laboratories.

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