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Research Article

A STABILITY INDICATING RPHPLC METHOD FOR THE ESTIMATION OF MONTELUKAST SODIUM AND FEXOFENADINE HYDROCHLORIDE IN PHARMACEUTICAL PREPARATIONS

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ABSTRACT

A simple, fast and precise reverse phase high performance liquid chromatographic method has been developed for the simultaneous determination of Montelukast Sodium (MON) and Fexofenadine hydrochloride (FEX). Efficient chromatographic separation was achieved on Waters symmetry C_{18} column (150mm x 4.6 mm, 5 µm) as stationary phase with a mobile phase comprising of 0.05 M NaH_2PO_4 in water pH 6.8 **:** Methanol (55:45,v/v) at a flow rate of 1.0mL min^{-1}, column temperature of 30°C and UV detection at 258 nm. The retention time of Montelukast Sodium and Fexofenadine hydrochloride were 11.2 min, and 18.8 min respectively. The proposed method was validated for linearity, accuracy, precision, sensitivity, robustness and solution stability. The test solution was found to be stable for 72 h. It can be conveniently adopted for routine quality control analysis. It can be conveniently adopted for routine quality control analysis.

Keywords: Liquid chromatography, Pharmaceutical preparations, Montelukast Sodium, Fexofenadine hydrochloride

INTRODUCTION

Montelukast Sodium (Molecular Formula $C_{35}H_{35}C_lNNaO_3S$) is a leukotriene receptor antagonist (LTRA) used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies [1]. It is usually administered orally. Montelukast is a $CysLT_1$ antagonist; that is it blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor $CysLT_1$ in the lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene, and results in less inflammation. Fexofenadine hydrochloride (Molecular Formula $C_{32}H_{39}NO_4HCl$) is 4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl] butyl]-α,α-dimethylbenzeneacetic acid of hydrochloride. Fexofenadine is indicated for the relief from physical symptoms associated with seasonal allergic rhinitis and treatment of chronic urticaria [2]. The structure of the drug is shown in Figure 1 and 2. One such combination contains 10 mg of Montelukast Sodium and 120 mg of Fexofenadine hydrochloride.

Several methods were reported for quantitative estimation of Montelukast Sodium such as voltametric [3], capillary electrophoresis [4], spectrophotometry [5-6], and HPLC method using various detectors [7–15].The voltametric, capillary electrophoresis and spectrophotometry is very complicated and lengthy.

A few HPLC[16-18] and spectrophotometry[19-20] methods have been reported for the estimation of Fexofenadine hydrochloride. But there is no method for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride till now.

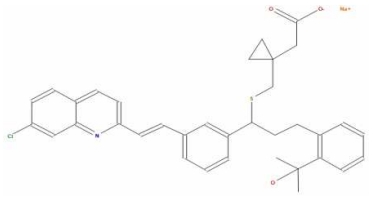

Fig. 1: The chemical structure of Montelukast Sodium (MON)

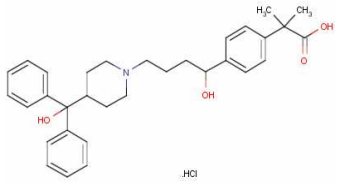

Fig. 2: The chemical structure of Fexofenadine hydrochloride (FEX)

MATERIALS AND METHODS

Chemicals and reagents

Active pharmaceutical ingredient of Montelukast Sodium and Fexofenadine hydrochloride was procured from Sigma Aldrich. Uniair fx tablet dosage form marketed by Somatico Pharmacal Pvt. Ltd, India were procured from the pharmacy. High purity methanol was purchased from S D Fine Chemicals, India.

Instrumentation and chromatographic conditions

The HPLC used is of Waters 2795 module with 2996 PDA detector. Column used was Waters symmetry C_{18} column,150mm x 4.6 mm, 5 µm.

The system was run at a flow rate of 1.0 mL min^{-1}, 20 µL of sample was injected in the chromatographic system and a PDA detector was used for simultaneous determination of Montelukast Sodium and Fexofenadine hydrochloride. Mobile phase comprising of 0.05 M NaH_2PO_4 in water pH 6.8: Methanol (55:45, v/v) at a flow rate of

1.0mL min^{-1} was used. Column temperature was maintained at 30°C and UV detection at 258 nm. Mobile phase was used as a 587iluents.

Preparation of Standard Solutions

The stock solution of Montelukast Sodium (100 µg mL^{-1}) was prepared by dissolving 25.2 mg of Montelukast Sodium (99.6 %) in 587iluents in a 250mL volumetric flask (stock solution A). The stock solution of Fexofenadine hydrochloride (1200 µg mL^{-1}) was prepared by dissolving 30.1 mg of Fexofenadine hydrochloride (99.7 %) in 587iluents in 25mL volumetric flask (stock solution B).

Transferred 5.0 mL of each stock solution A and B to a 50 mL volumetric flask and diluted up to the mark with 587iluents. This is working standard solution containing 10 µg mL^{-1} of Montelukast Sodium and 120 µg mL^{-1} of Fexofenadine hydrochloride.

Preparation of Sample solution:

For analysis of the tablet dosage form, twenty tablets were weighed individually and their average weight was determined. The tablets were crushed to fine homogenous powder and quantity equivalent to one tablet (about 300 mg of homogeneous powder) were transferred in a 100mL volumetric flask. Added about 100 mL of 587iluents to the volumetric flask, shaken for 10 minutes and then sonicated for 15 minutes. The solution was allowed to stand at room temperature for 20-30 minutes and filtered through Whatman no. 41 filter paper.

5.0 mL of filtrate was quantitatively transferred to a 50 mL volumetric flask and solution was diluted up to the mark with

588iluents. The identities of both the compounds were established by comparing retention time of the sample solution with those of standard solution.

RESULTS AND DISCUSSION

Optimization of chromatographic conditions

To develop a suitable RP-LC method for the analysis of Montelukast Sodium and Fexofenadine hydrochloride in their dosage form, different permutation and combinations were tried [21-25].

Several mobile phases using different organic solvents as part of mobile phase were tried. Water and acetonitrile in the ratio of 500:500, v/v was chosen for initial trail with an Agilent Zorbax coulum 25 cm length, 4.6 mm ID and 5 micron particle size C-18 stationary phase. Flow rate was 1.0 mL $min^{-1.}$ When test solution was injected no peaks were detected. Results obtained with 25 cm length, 4.6 mm ID and 5 micron particle size C-8 column also showed no peaks. Water and methanol in the ratio 500:500, v/v was used as a mobile phase using Waters Symmetry C18 column 25 cm x 4.6 mm ID, 5µ.Two peaks due to Montelukast Sodium and Fexofenadine hydrochloride were observed, but the peak tailing was observed for both the components. A peak due to 588iluents was observed at the retention time of Fexofenadine hydrochloride. To further improve the tailing factor of the peaks, a buffer solution consisting of 0.05 M NaH_2PO_4 solution pH 6.8 was used instead of water. A mobile phase consisting of 0.05 M NaH_2PO_4 solution pH 6.8 and methanol in the ratio of 550:450,v/v was used. The peak shape of all the components was found to be good.

Selection of wavelength was done by running the standard solution into the HPLC system using a Photo diode array detector. The scan of both the components is shown in Figure 3 and 4. The PDA scan showed maxima of 258 nm for both the components. Hence the wavelength was selected is 258 nm.

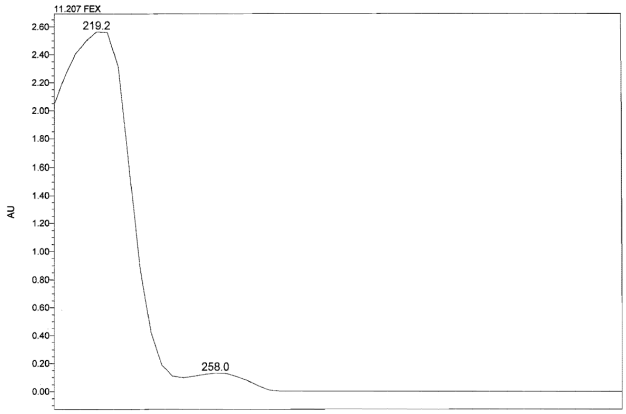

Fig. 3: PDA spectrum scan of Fexofenadine hydrochloride.

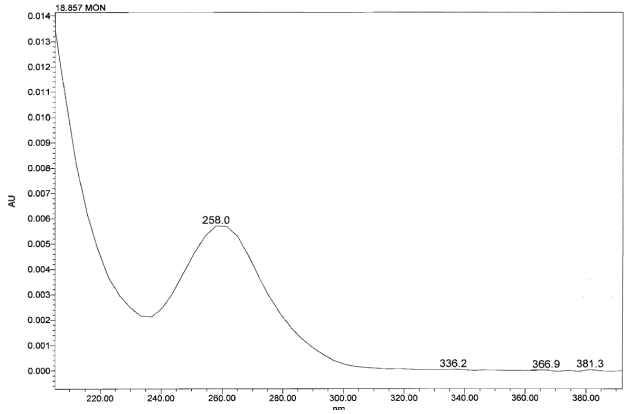

Fig. 4: PDA spectrum scan of Montelukast Sodium

System suitability tests are used to verify that the reproducibility of the equipment is adequate for the analysis to be carried out. System suitability tests were performed as per the general chapter <621> in USP 32 NF 27 to confirm the suitability and reproducibility of the system. The test was carried out by injecting 20-µL standard solutions. Five replicate injections were made. The %RSD values of Montelukast Sodium and Fexofenadine hydrochloride were 0.21 and 0.39 respectively. The %RSD values were found to be satisfactory and meeting the requirements of the general chapter <621> in USP 32 NF 27 (%RSD not more than 2.0 %).

Theoretical plates, resolution, tailing factor were determined and are presented in Table 1. A typical chromatogram of 588iluents, placebo, standard and sample solution is shown in figure 7 thru figure 10.

Table 1: Results of System suitability

Parameters	Fexofenadine hydrochloride	Montelukast Sodium
Resolution	Not applicable	8.5
Tailing factor	1.0	1.1
% RSD	0.21	0.39

Method Validation

The method validation was carried out as per ICH guidelines. Various method validation parameters were performed [26-27].

Specificity

Specificity of the method was evaluated by injecting diluents, placebo, individual Montelukast Sodium and Fexofenadine hydrochloride and sample solution in to the HPLC system to check any interference to the peaks.

No peak was observed at the retention time of Montelukast Sodium and Fexofenadine hydrochloride in diluent and placebo chromatogram. Hence the method was specific.

Linearity

Linearity was evaluated by analysis of working standard solutions of Montelukast Sodium and Fexofenadine hydrochloride of five different concentrations.

Linearity was evaluated by analysis of working standard solutions of Montelukast Sodium and Fexofenadine hydrochloride of five different concentrations. The range of linearity were from 5 µg mL^{-1} to 15 µg mL^{-1} (10 µg/mL is 100% level) for Montelukast Sodium and 60 µg mL^{-1} to 180 µg mL^{-1} (120 µg/mL is 100% level) for Fexofenadine hydrochloride. The peak area and concentration of each drug was subjected to regression analysis to calculate the calibration equations and correlation coefficients. Figure 5 and 6 represents the linearity plots of Montelukast Sodium and Fexofenadine hydrochloride respectively. The regression data obtained for the Montelukast Sodium and Fexofenadine hydrochloride is represented in Table 2. The result shows that within the concentration range mentioned above, there was an excellent correlation between peak area ratio and concentration.

LOD and LOQ / Sensitivity

Sensitivity was determined by establishing the limit of detection (LOD) and limit of quantification (LOQ). The limit of detection (LOD) and limit of quantification (LOQ) were established at signal-to-noise ratio of 3:1 and 10:1 respectively.

The LOD and LOQ of Montelukast Sodium and Fexofenadine hydrochloride was experimentally determined by six injections of each drug. The LOD of Montelukast Sodium and Fexofenadine hydrochloride was found to be 0.9 µg mL^{-1} & 1.9 µg mL^{-1} respectively. The LOQ of Montelukast Sodium and Fexofenadine hydrochloride was found to be 1.3 µg mL^{-1} & 3.1 µg mL^{-1} respectively.

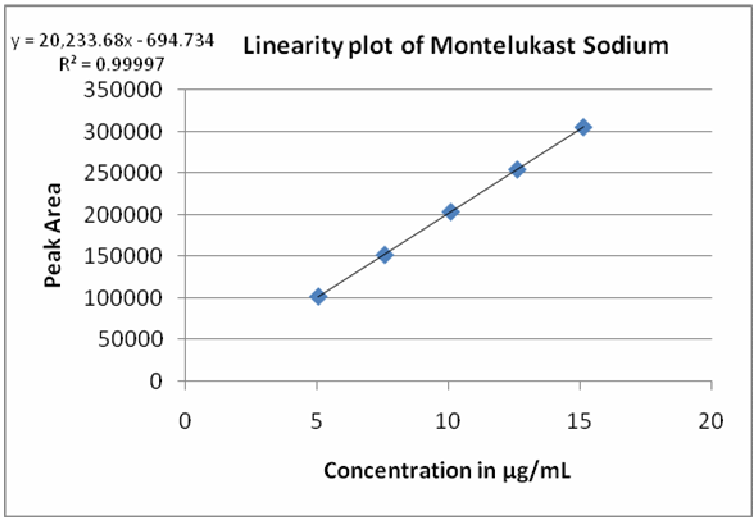

Fig. 5: Linearity plot of Montelukast Sodium

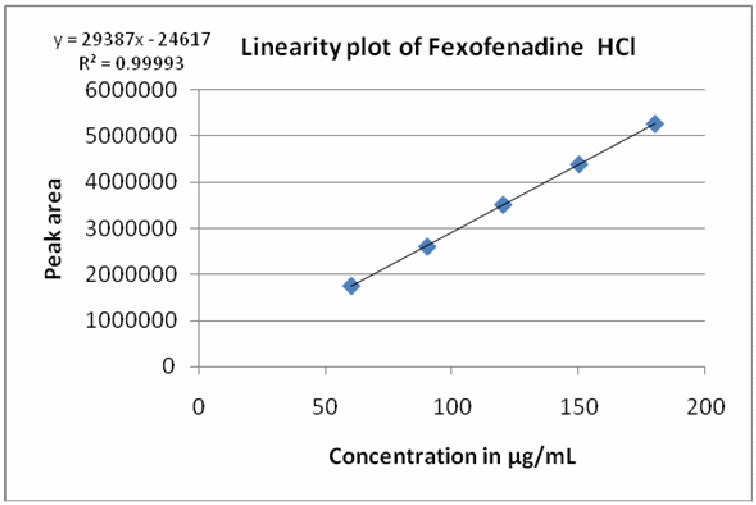

Fig. 6: Linearity plot of Fexofenadine hydrochloride

Table 2: Results of Linearity study

Analyte	Slope	Intercept	Correlation coefficient (r^2) (n=5)
Montelukast Sodium	20233	-964	0.99997
Fexofenadine hydrochloride	29387	-24617	0.99993

Accuracy

Accuracy was determined over the range 50% to 150% of the sample concentration. Calculated amount of Montelukast Sodium and Fexofenadine hydrochloride from standard stock solution was added in placebo to attain 50%, 100% and 150% of sample concentration. Each sample was prepared in triplicate at each level. Blank and standard preparations were injected and chromatograms were recorded.

Accuracy was expressed as the percentage of analytes recovered by the assay. Table 3 lists the recoveries of the drug from a series of spiked concentrations. The results indicate the method is highly accurate for simultaneous determination of Montelukast Sodium and Fexofenadine hydrochloride.

Precision

Repeatability was studied by carrying out system precision. System precision was determined from results for six replicate injections of the mixed standard solutions. The % RSD for five replicate standard injections for Fexofenadine hydrochloride and Montelukast Sodium was found to be 0.21% and 0.39% respectively.

Method precision was determined from results from six independent determinations at 100% of the test concentrations of Montelukast Sodium and Fexofenadine hydrochloride in the product. The results of precision experiment are mentioned in table 4.

Ruggedness (Intermediate Precision)

Ruggedness study was demonstrated by injecting five individual sample preparations at 100% of the test concentrations of Montelukast Sodium and Fexofenadine hydrochloride on different day using another column and system.

Ruggedness study was done by injecting six individual sample preparations at 100% of the test concentrations of Montelukast Sodium and Fexofenadine hydrochloride on different day and different GC system. The mean % Assay obtained was compared with mean % Assay of precision study. The relative standard deviation (RSD) was less than 2%. Refer Table 5.

Table 3: Accuracy of the method

Analyte	Recovery Level (%)	Amount added (µg mL^{-1})	Amount recovered (µg mL^{-1})	RSD (%) n= 3	(%) Recovery
Montelukast Sodium	50	5.05	5.03	0.52	99.6
	100	10.10	10.15	0.43	100.5
	150	15.15	15.11	0.35	99.7
Fexofenadine hydrochloride	50	60.06	60.56	0.28	100.8
	100	120.12	119.89	0.41	99.8
	150	180.18	179.60	0.36	99.7

Table 4: Results of Precision experiment

Results	Montelukast Sodium	Fexofenadine hydrochloride
% Mean Assay	99.7	100.5
% RSD	0.54	0.21

Table 5: Ruggedness of Assay experiment

Results	Montelukast Sodium	Fexofenadine hydrochloride
Drug found in mg/tab (mean)	10.1	120.3
% Mean Assay	101.0	100.3
% RSD	0.46	0.38
% Difference w.r.t. Precision	1.3	0.2

Solution stability

The solution stability of Montelukast Sodium and Fexofenadine hydrochloride was carried out by leaving the test solutions of sample in a tightly capped volumetric flask at room temperature for 72 hours. The same sample solutions were assayed for 24 hours interval up to the study period against freshly prepared standard solution.

The % assay of Montelukast Sodium and Fexofenadine hydrochloride were checked in the test solutions. The % difference of assay of Montelukast Sodium and Fexofenadine hydrochloride with respect to initial assay during solution stability experiment was within 2.0.

No significant changes were observed in the content of Montelukast Sodium and Fexofenadine hydrochloride during solution stability experiment. Sample solutions used during the experiment were stable up to the study period of 120 hours. The results are reported in Table 6.

Table 6: Results of Solution stability

Condition	% Assay of Montelukast Sodium	% Difference w.r.t. initial assay	% Assay of Fexofenadine hydrochloride	% Difference w.r.t. initial assay
Initial	99.9	NA	100.3	NA
24 hours	99.7	0.2	100.5	0.2
48 hours	99.5	0.4	99.8	0.5
72 hours	98.7	1.2	99.9	0.4

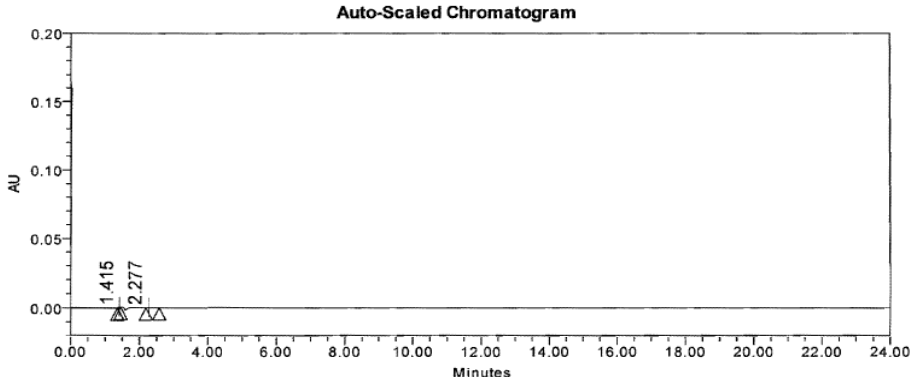

Fig. 7: Chromatogram of diluents

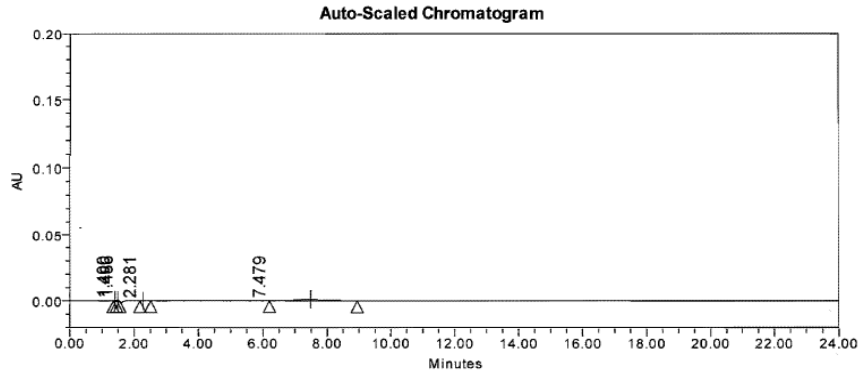

Fig. 8: Chromatogram of Placebo preparation

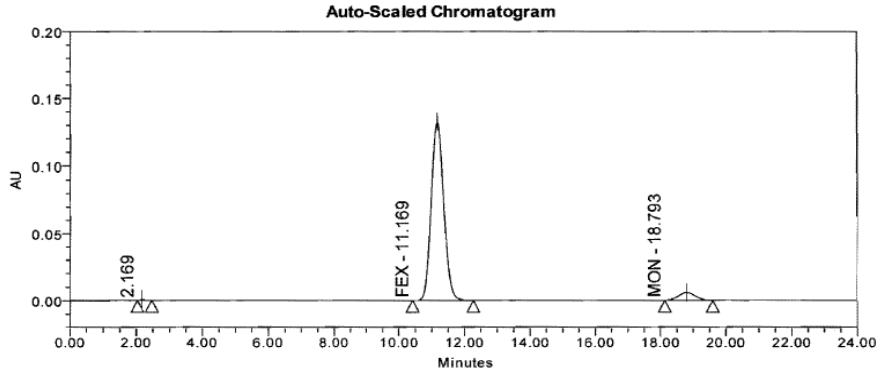

Fig. 9: Chromatogram of Fexofenadine hydrochloride (FEX) and Montelukast Sodium (MON) in standard preparation

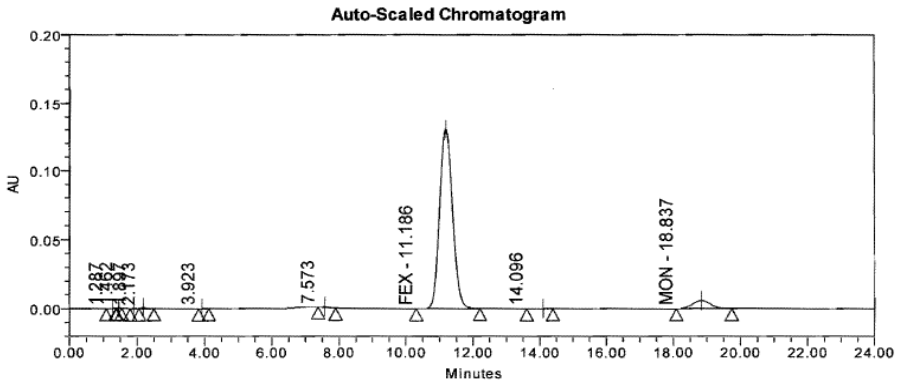

Fig. 10: Chromatogram of Fexofenadine hydrochloride (FEX) and Montelukast Sodium (MON) in sample preparation

Stress Testing (Forced Degradation study)

To further confirm the stability indicating nature of the method, the drug was subjected to stress conditions as per the ICH recommended test conditions [19, 20].

To study the effect of acid, 5 mL of 2 M HCl was added to the sample and the mixture was kept for 48 hours. To study the effect of base, 5 mL of 1 N NaOH solution was added to the sample and the mixture kept for 24 hours. To study the effect of oxidizing conditions, 5 mL of 3% v/v H_2O_2 was added to the sample and the mixture was kept for 48 hours. To study the effect of temperature sample was kept in an oven at 90°C for 5 days.

To study the effect of light sample was and kept in a photo stability chamber for 10 days.

The % degradation of Montelukast Sodium in acid hydrolysis, base hydrolysis, oxidation, thermal and photolytic was 10.6, 20.9, 9.7, 7.3 and 3.3 respectively with respect to the control sample. The % degradation of Fexofenadine hydrochloride in acid hydrolysis, base hydrolysis, oxidation, thermal and photolytic was 0.3, 24.7, 14.0, 4.4 and 1.7 respectively with respect to the control sample. The mass balance was found to be more than 97.0%. The peaks of the degradation products were well resolved from the principle peaks. The results of stress studies are tabulated in Tables 7 and 8.

Table 7: Summary of forced degradation results for Montelukast Sodium

Stress condition	Time	% Assay of MON	Degradation (%) w.r.t. control	Purity angle	Purity threshold	Peak Purity
Control sample	NA	99.8	NA	0.115	0.180	Passes
Acid hydrolysis (2 M HCl)	48 h	89.2	10.6	0.118	0.175	Passes
Base hydrolysis (1 N NaOH)	24 h	78.9	20.9	0.120	0.161	Passes
Oxidation (3% H2O2)	48 h	90.1	9.7	0.115	0.172	Passes
Thermal (90°C)	5 d	92.5	7.3	0.121	0.179	Passes
Light (photolytic degradation)	10 d	96.5	3.3	0.117	0.179	Passes

Table 8: Summary of forced degradation results for Fexofenadine hydrochloride.

Stress condition	Time	% Assay of FEX	Degradation (%) w.r.t. control	Purity angle	Purity threshold	Peak Purity
Control sample	NA	100.3	NA	0.171	0.221	Passes
Acid hydrolysis (2 M HCl)	48 h	100.0	0.3	0.185	0.219	Passes
Base hydrolysis (1 N NaOH)	24 h	75.6	24.7	0.189	0.202	Passes
Oxidation (3% H2O2)	48 h	86.3	14.0	0.190	0.219	Passes
Thermal (90°C)	5 d	95.9	4.4	0.184	0.219	Passes
Light (photolytic degradation)	10 d	98.6	1.7	0.172	0.220	Passes

CONCLUSIONS

The method after being completely validated showed satisfactory data for all the method validation parameters. Method validation study showed that the method is specific, linear, accurate, easily reproducible and can be used for simultaneous determination of Montelukast Sodium and Fexofenadine hydrochloride from pharmaceutical preparations. Stress testing showed that all degradation products were well separated from Montelukast Sodium and Fexofenadine hydrochloride, confirming its stability indicating capability. The method seems to be suitable for quality control in the pharmaceutical industry because of its sensitivity, simplicity and selectivity.

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