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A New Validated Stability indicating RP-HPLC Method for Simultaneous Determination of Montelukast and Rupatadine Fumerate in Bulk and its Pharmaceutical Formulations

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ABSTRACT

A new RP – HPLC method was developed for the simultaneous determination of Montelukast and Rupatadine fumerate in combined dosage form. An Inertsil C18 column(100 x 4.6, 5µm) was used with mobile phase of composition Methanol : Buffer(0.1% triethyl amine in water with pH adjusted to 3.0 (70:30v/v at pH 4.6) at a flow rate of 1.0 mL/min and injection volume of 20µL with UV detection at 266 nm for separating Montelukast and Rupatadine fumerate. The retention time of Rupatadine fumerate and Montelukast were 5.76 min and 2.86 min respectively. The runtime of the analysis was 6 minutes. The specificity, linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), ruggedness and robustness of the developed method were studied to validate as per ICH guidelines. The Linearity range for Montelukast and Rupatadine fumerate were 5.0 – 30.0 µg/ml and 5.0 – 30.0 µg/ml, respectively. The percentage recoveries were in the range for Montelukast and Rupatadine fumerate98.80-100.11 % and 99.06-99.44 %, respectively. The developed method could be used for routine analysis of Montelukast and Rupatadine fumeratein their combined dosage forms.

Keywords: Liquid Chromatography; Montelukast, Rupatadine fumerate, Simultaneous estimation, Validation

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INTRODUCTION

Montelukast((R,E)-2-(1-((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propylthio)methyl)cyclopropyl)aceticacid) is used to prevent difficulty breathing, wheezing, coughing and chest tightness caused by asthma. Montelukast is also used to prevent breathing difficulties during exercise[1,2]. Montelukast is also used to treat the symptoms of seasonal (occurs only at certain times of the year), and perennial (occurs all year round) allergic rhinitis (a condition associated with sneezing and stuffy, runny or itchy nose)[3]. Montelukast is in a class of medications called leukotriene receptor antagonists (LTRAs). It works by blocking the action of substances in the body that cause the symptoms of asthma and allergic rhinitis. This medication does not work immediately and should not be used to treat sudden asthma attacks or other breathing problems. This drug works by blocking certain natural substances (leukotrienes) that may cause or worsen asthma and allergies. It helps make breathing easier by reducing swelling (inflammation) in the airways.

Rupafin tablets contain the active ingredient rupatadine, which is a type of medicine called a non-sedating antihistamine[4,5]. Its chemical designation is 8-chloro-11-[1-[(5-methyl-3-pyridinyl)methyl]piperidin-4-ylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridine fumarate. The empirical formula is $C_{26}H_{26}ClN_3.C_4H_4O_4$ and molecular weight is 532.04. Rupatadine works by preventing the actions of histamine. Histamine is a substance produced by the body as part of its defence mechanisms. It is stored in cells called mast cells, in almost all tissues of the body. When the body reacts to a foreign substance (known as an allergen, eg flower pollen), the mast cells stimulated by the allergen release their stores of histamine. The released histamine then binds to its receptors (H1 receptors), causing a chain reaction that results in allergic symptoms. It causes an increase in blood flow to the area of the allergy, and the release of other chemicals that add to the allergic response.

A number of HPLC, HPTLC, UPLC, LC/MS, and UV-Vis methods were reported for the quantification of Montelukast and Rupatadine fumerate alone, in combination and in combination with other drugs[6-24]. All these have resulted in simple and sensitive methods for separation and determination of these drugs alone and in combination with other drugs and no method was reported for the determination of Montelukast and Rupatadine fumerate in combination. In all these methods reported till now, no degradation studies were carried out to prove that the method is stability indicating method. The present work describes the development of a validated stability indicating analytical RP-HPLC method, which can quantify these

Components simultaneously from a combined dosage form.

Aim of present work was to develop simple, economical, rapid, accurate and precise RP-HPLC methods for determination of these drugs in fixed dose combination. The proposed method was optimized and validated as per the International Conference on Harmonization (ICH) guidelines [25,26].

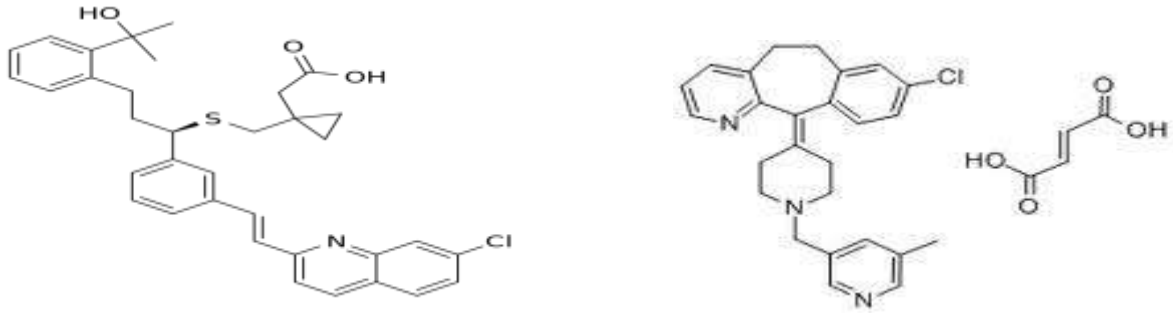

Figure 1 A. Structure of Montelukast **B. Structure of Rupatadine fumerate**

MATERIALS AND METHODS

Materials

HPLC grade methanol and acetonitrile were procured from Merck India. All dilutions were performed in standard class-A, volumetric glassware. For the estimation of commercial formulation, Rupanex-M having Montelukast 10mg and 10mg Rupatadine fumerate were procured from the local market.

Instrumentation

Waters 2695 compact LC chromatographic system, with UV-Vis detector 2996 and a fixed injector equipped with 20µL loop was used for the chromatographic separation. The chromatogram was recorded at ambient temperature and peaks quantified by means of Empower software. Chromatographic separation was carried out on a C18 column [Inertsil, 100mm x4.6mm 5µm]. Sartorius electronic balance was used for weighing the samples. Ultra-sonic bath sonicator was used for degassing and mixing of the mobile phase.

Chromatographic conditions

Chromatographic separation of Montelukast and Rupatadine fumerate was carried on a C18 column. The mobile phase was composed of methanol and 0.1% triethyl amine buffer (pH 3.0) in the ratio of 70:30 v/v. It was filtered through a 0.45 µ membrane filter and degassed for 15 minutes. The flow rate of the mobile phase was maintained at 1.0 ml/min. Detection was carried out at 266 nm at ambient temperature.

Method development

Preparation of Standard Stock Solutions

Weighed accurately about 100 mg of Rupatadine fumerate and 100 mg of Montelukast working standards transfer to the 100 mL of clean and dry volumetric flask, to these add the 60 mL of diluents to sonicate for few minutes to dissolve and then make up the volume with diluents. Filter the solution through 0.45µm

Standard preparation

Transfer 1 mL of stock solution into the 100 mL of clean and dry volumetric flask and make up the volume with diluents.

Preparation of Sample solutions

100 mg Montelukast and 100 mg of Rupatadine fumerate into100 mL volumetric flask add 60 mL of diluents, sonicate to dissolve for 10 minutes and dilute to volume with diluents. Further filter the solution through 0.45µ filter paper. Dilute 1 mL of filtrate to 100 mL with diluent.

Method validation

simultaneous determination of Montelukast and Rupatadine fumerate by RP- HPLC method was validated as per the ICH guidelines.

System suitability and System Precision

System suitability for chromatographic separation was checked on each day of validation to evaluate the components of the analytical system in order to show that the performance of the system meet the standards required by the method. System suitability parameters established for the developed method include number of theoretical plates (efficiency), Resolution, Tailing factor. The HPLC system was equilibrated using the initial mobile phase composition, followed by 6 injections of the standard solution of 100% concentration containing 10µg/mL Montelukast and 10 µg/ml Rupatadine fumerate. These 6 consecutive injections were used to evaluate the system suitability on each day of method validation. The result was given in the Table 1.

Specificity

Blank interference

A study to establish the interference of blank was conducted. Diluent was injected into the chromatograph in the above defined chromatographic conditions and the blank chromatograms were recorded. Chromatogram of Blank solution (Figure 2) showed no peaks at the retention time of Montelukast and Rupatadine fumerate peak. This indicates that the diluent solution used in sample preparation do not interfere in estimation of Montelukast and Rupatadine fumerate in rupanex-M tablets. Similarly typical representative chromatogram of standard is also shown (Figure 3)

Forced Degradation:

In case of forced degradation studies a sample was prepared equivalent to 1.0 mL of Montelukast and Rupatadine fumerate. Then they are transferred into a 10 mL volumetric flask into which 6 mL of diluent was added and then sonicated for 15 minutes with intermittent shaking at controlled temperature. The solution was then filtered through 0.45 µ filter paper. Control sample was prepared by transferring 1 mL of the above solution into a 10 mL of volumetric flask and diluted to volume with diluent. Acid and Base degradation studies were performed by adding acid and base before making up the volume to 10 mL before filtering through 0.45 µ filter paper. From this controlled sample was prepared latter.

Thermal degradation was studied by preparing sample using common procedure as mentioned above. Similarly Sunlight exposure stress sample was prepared and checked for their purity by proposed method. The figures 4A, 4B, 4C and 4D represent the typical chromatograms of control sample, acid, base, thermal, photolytic degradation. The results of degradation studies were given in table 2.

Linearity and range

Linearity and range of Montelukast and Rupatadine fumerate were determined by weighing accurately about 100gm of Rupatadine fumerate and 100 mg of Montelukast in to a 100 mL of clean and dry volumetric flask, add 60 mL of diluents, shake and sonicate to dissolve the content, make up the volume with diluents. Filter the solution through 0.45µm. 0.25 mL 0.5 mL, 0.75 mL, 1.0 mL, 1.25mL and 1.5 mL of above solution were diluted in 100 mL volumetric flask with diluent separately to get 25%, 50%, 75%, 100%, 125% and 150%concentration solutions.

Standard curves for Montelukast and Rupatadine fumerate were obtained in the range of 5.0 – 30.0 µg/ml and 5.0 – 30.0 µg/ml respectively. A statistical method known as linear regression analysis was used to evaluate the linearity of the curve. To assess the linearity of the proposed method slope, intercept and correlation coefficient [r^2] of standard curve were calculated and were given in Figure-5A(For Montelukast) and Figure-5B(For Rupatadine fumerate). The results of linearity were given in Table 3 and 4. From the data obtained (For MNT and RPT) the method was found to be linear within the proposed range.

Accuracy

Accuracy is defined as the closeness of results obtained by that method to the true value for the sample. In general Accuracy is expressed in terms of percentage recovery. Recovery % was assessed by standard addition method. In the present investigation to understand the accuracy the recovery studies were carried out at 50%, 100% and 150% spiked levels. The results of Recovery

% were given in Table 5. The chromatograms of accuracy study of 50%, 100%, 150% and including that of sample were given in figures 6A, 6B, 6C and 6D respectively.

Precision

The closeness of agreement (degree of scatter) between a series of measurements obtained from multiple samplings of the same homogeneous sample. The precision of the method was assessed by six replicate injections of 100% test concentration. The precision was expressed in terms of standard deviation and %RSD. The results were given in Table 6&7 and the corresponding chromatogram was given in figure 7..

Ruggedness

Degree of reproducibility of test results obtained by analyzing the same sample under variety of normal test conditions such as different analysts, instruments, days, reagents, column etc. The Ruggedness of the method was verified by analyzing the six samples of same batch for method precision as per test method by different analysts using different instrument, different days. The analyst's prepared six sample of the same batch on two different day's .Calculated %RSD for two different days in six samples for ruggedness results with the method precision. The results of ruggedness were given in table 8 and the chromatograms corresponding to ruggedness studies of day 1 and day 2 were given in figures 8.

LOD and LOQ

The formulae 3.3 σ/S and 10 σ/S were used to calculate LOD and LOQ respectively. σ is the mean of standard deviation of y intercepts of the three calibration curves and S is the mean of slopes of the calibration curves. The results were given in Table 9 and 10.

Robustness

The ability of the developed method to remain unaffected by the small changes in the parameters is known as Robustness. Robustness was assessed by varying the parameters such as percent organic content, pH of the mobile phase, buffer concentration, temperature, injection volume and flow rate. In the present investigation, a variation ± 0.1 mL/min in the flow rate, a variation in buffer composition were carried out and the results were tabulated in Table 11 and the corresponding chromatograms were given in figures 9A, 9B, 9C & 9D.

RESULTS AND DISCUSSION

In present study a new analytical method reversed phase HPLC method for the simultaneous determination of Montelukast and Rupatadine fumerate tablets in combined dosage form. The column used in this method is Inertsil ODS C18, 100 X 4.6, 5µm with a flow rate of 1.0ml/min

at a wavelength 266 nm and Column temperature is 30°C. The mobile phase preparation done by using buffer 0.10% Triethylamine in water by PH adjusted to 3.0. The mobile phase combination was Buffer: Methanol (30:70). The diluent is a mixture of water and Acetonitrile. The run time was set for 6 minutes. The retention time of Montelukast and Rupatidine is 2.86 and 5.76. The new HPLC method developed and validated for simultaneous determination of Montelukast and Rupatadine fumerate in pharmaceutical dosage forms and assured the satisfactory precision and accuracy and also determining lower concentration of each drug in its solid combined dosage form by RP-HPLC method. The linearity range for Montelukast and Rupatadine fumerate is 0-30 µg/ml the co-relation co-efficient was found to be 0.999. The percentage RSD obtained for system precision of Montelukast and Rupatadine fumerate are 0.77 and 0.48 respectively. The percentage RSD obtained for method precision of Montelukast and Rupatadine fumerate are 0.39 and 0.20.

The LOD values for Montelukast and Rupatadine fumerate are 5.2518 and 0.3293 for system precision respectively. The LOD values for Montelukast and Rupatadine fumerate for method precision are 2.63098 and 0.13898 respectively. The LOQ values for Montelukast and Rupatadine fumerate respectively for system precision are 15.9146 and 0.9981 and for method precision are 7.97268 and 0.42114 respectively. The result of assay of Montelukast and Rupatadine fumerate was found to be 99.43% and 99.47%respectively.

Table 1: System suitability parameters for Montelukast and Rupatadine fumerate by proposed method

Name of the Compound	Retention Time	Tailing factor	Theoretical plates	USP Resolution
Fumaric Acid	1.983	1.11	1878	------
Montelukast	2.864	1.08	4381	4.99
Rupatidine	5.761	0.99	9378	14.16

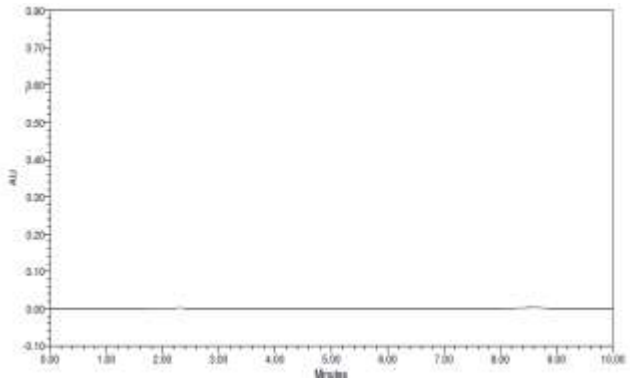

Figure 2: A typical HPLC Chromatogram showing the no interference of diluent for Montelukast and Rupatadine fumerate

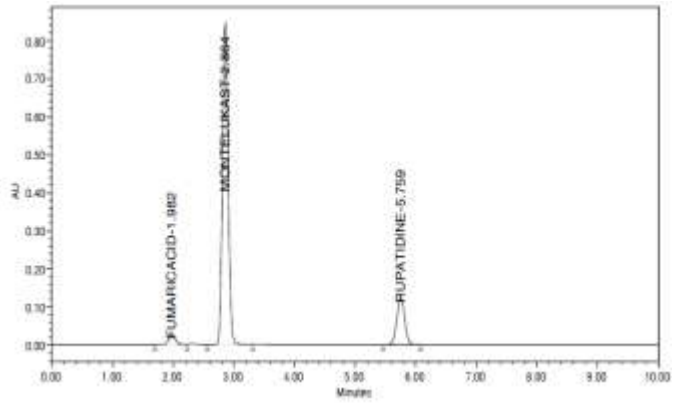

Figure 3: A typical HPLC Chromatogram showing the peak of Montelukast and Rupatadine fumerate

Table 2 Forced degradation specificity data for Montelukast and Rupatadine fumerate

Condition	Time (hours)	Retention time (min)	Area	Retention time of additional degradation peak (min)	% degradation	% of Active drug present after Degradation
Acid Degradation	12	2.8	4628114	1.97	2.07	97.93
				2.318	0.09	99.91
		5.7	948409	3.26	28.53	71.47
				5.75	11.38	88.62
Alkaline Degradation	12	2.8	4132072	1.97	5.84	94.16
				2.29	1.66	98.34
		5.7	1394794	2.66	1.13	98.87
				3.04	4.86	95.14
				3.28	1.43	98.57
				3.85	1.72	98.28
				1.19	1.88	98.12
Thermal Degradation	24	2.85	4342837	1.96	5.72	94.28
				2.30	0.22	99.78
		5.56	896237	3.406	0.46	99.54
				3.995	0.50	99.50
				4.369	0.30	99.70

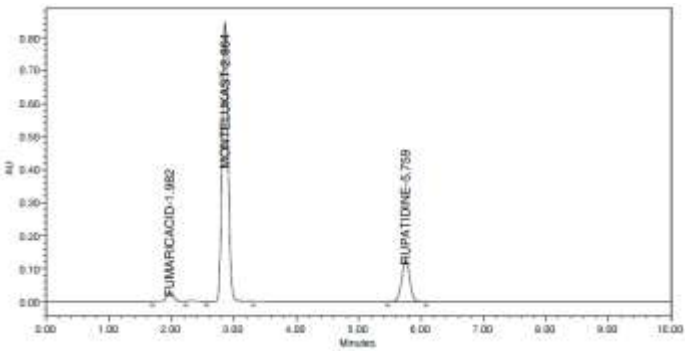

Figure 4A: A typical HPLC Chromatogram showing the Control Sample profile of Montelukast and Rupatadine fumerate by proposed method.

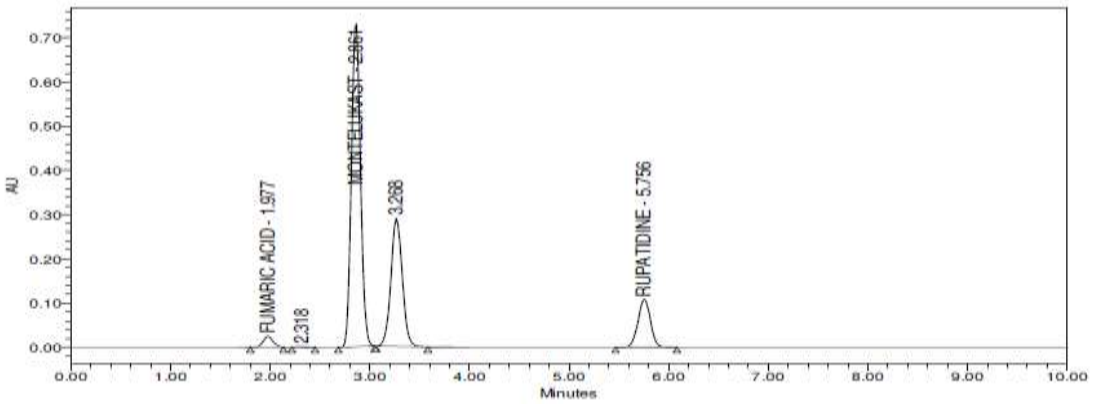

Figure : 4B Chromatogram of Montelukast and Rupatidine Forced Degradation specificity-Acid

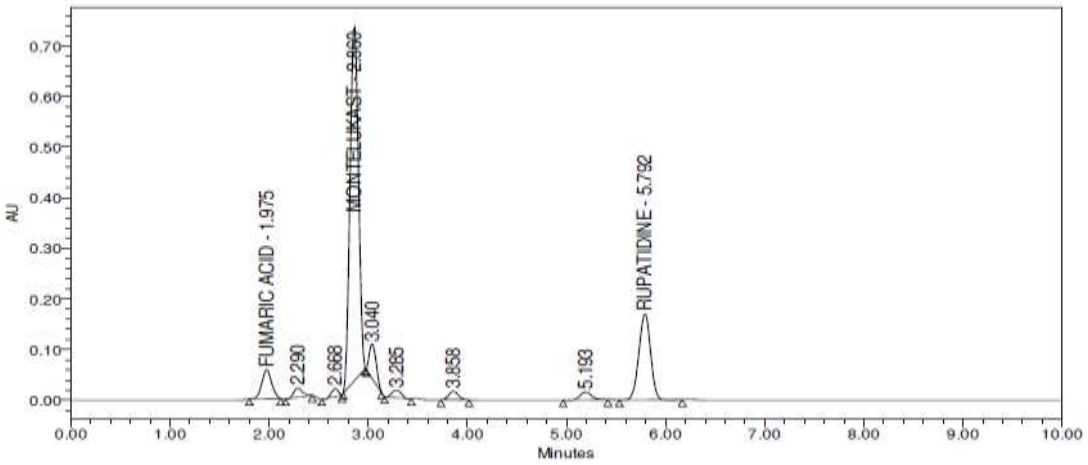

Figure 4C: Chromatogram of Montelukast and Rupatidine Forced Degradation specificity-Alkaline

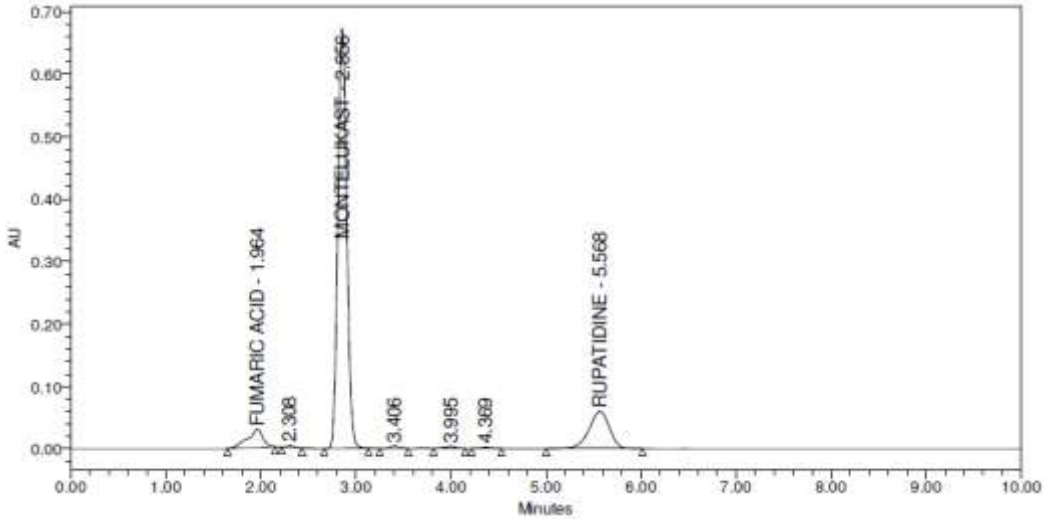

Figure 4D:.Chromatogram of Montelukast and Rupatidine Forced Degradation specificity-Thermal

Table 3 Linearity Data for Montelukast

Concentration	Area
0	0
5	1303568
10	2707157
15	3985992
20	5399845
25	6696227
30	7963414

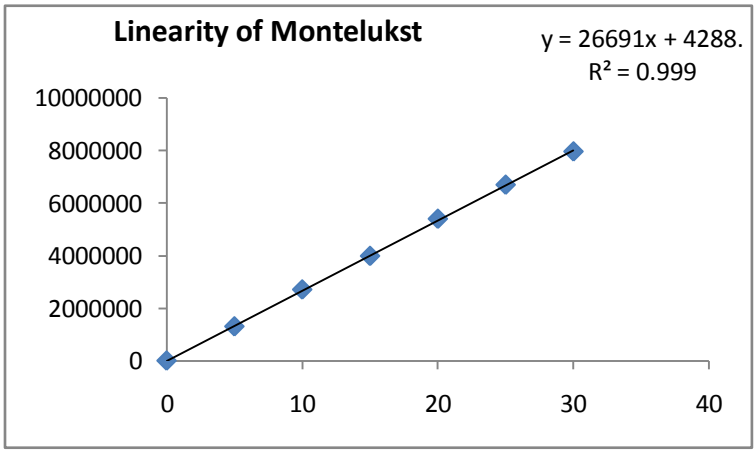

Figure 5A Calibration curve of Montelukast

Table 4 Linearity Data for Rupatadine fumerate

Concentration	Area
0	0
5	252992
10	536634
15	756634
20	1064216
25	1325524
30	1606428

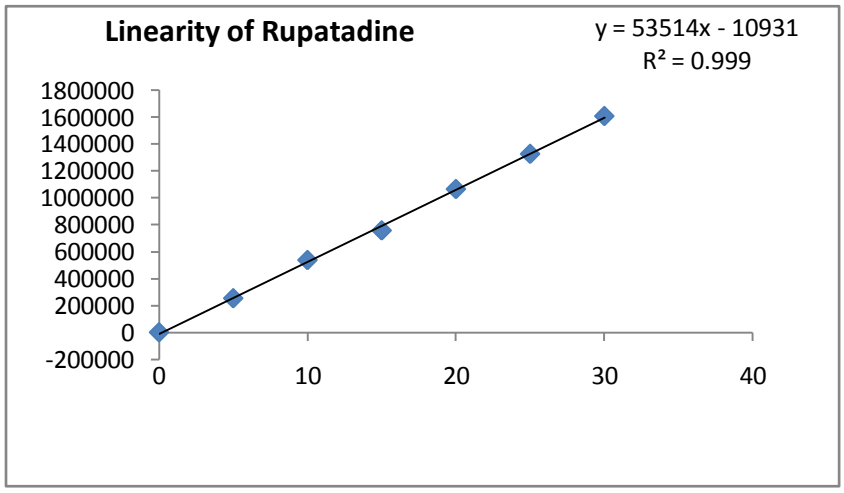

Figure 5B Calibration curve of Rupatadine fumerate

Table 5 Accuracy data for Montelukast and Rupatadine fumerate

S.No	Montelukast			Rupatadine fumerate		
	Area					
	50%	100%	150%	50%	100%	150%
Injection 1	4043452	5398905	6696576	794086	1066056	1336042
Injection 2	4087956	5398212	6705454	803656	1067123	1338090
Injection 3	4051326	5399540	6749840	809865	1071325	1336905
Average	4060911	5398885	6717290	802535	1068168	1337012
Amt recovered (µg)	50.06	99.49	148.20	49.55	99.06	149.16
% Recovery	100.11	99.49	98.80	99.11	99.06	99.44

***Each value is a mean of three readings**

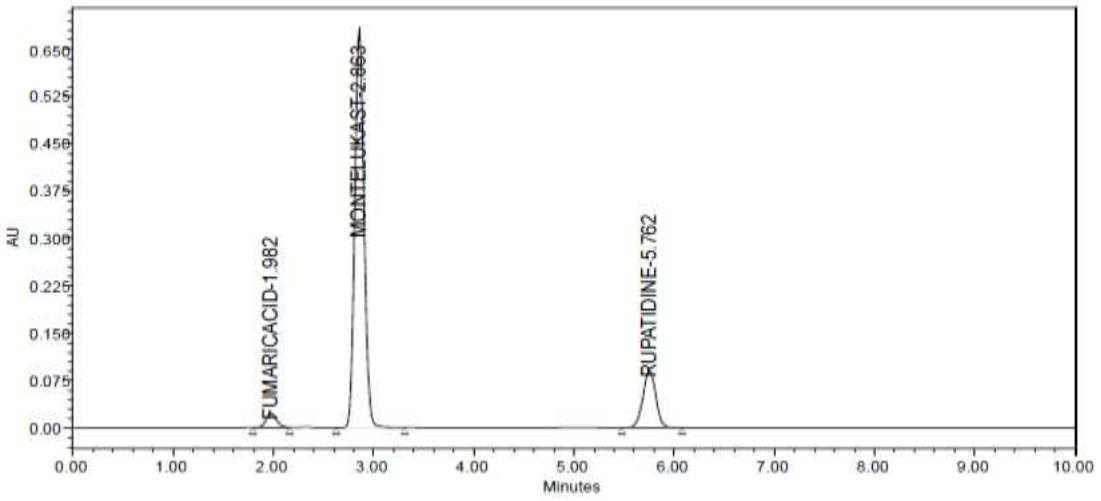

Figure : 6A Chromatogram of Accuracy f or Montelukast and Rupatadine fumerate (50%)

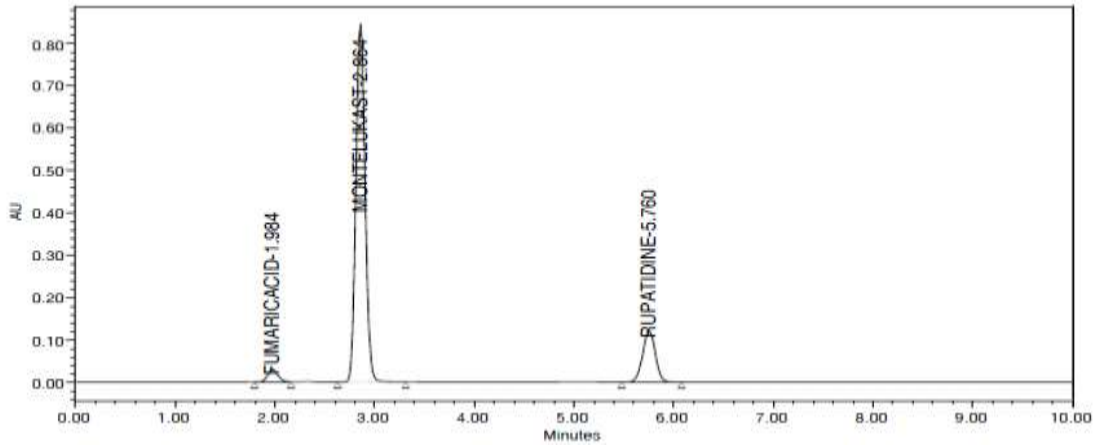

Figure: 6B Chromatogram of Accuracy for Montelukast and Rupatadine fumerate (100%)

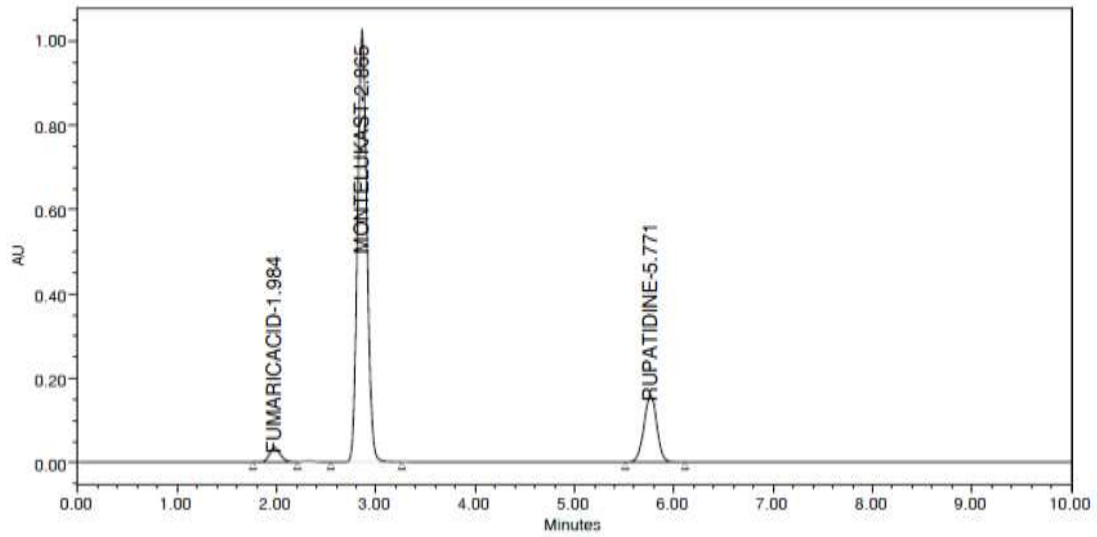

Figure : 6C Chromatogram of Accuracy for Montelukast and Rupatadine fumerate (150%)

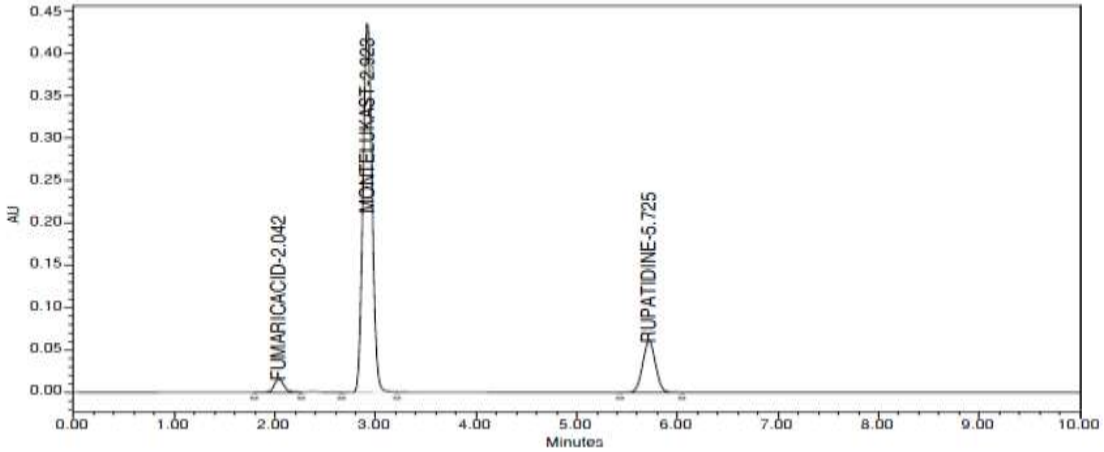

Figure :6D Chromatogram of Accuracy sample for Montelukast and Rupatadine fumerate

Table 6 Data for System precision of Montelukast and Rupatadine fumerate

S.NO	Montelukast Area	Rupatadine fumerate
Injection 1	5427344	1101465
Injection 2	5463872	1105949
Injection 3	5494493	1110790
Injection 4	5527307	1114051
Injection 5	5532945	1114479
Injection 6	5526507	1114051
Average	5495411.33	1110131
Std deviation	42477.7234	5341.552
LOD	5.2518	0.3293
LOQ	15.9146	0.9981
% RSD	0.77	0.48

Table.7 Data for method precision of Montelukast and Rupatadine fumerate

S. No	Montelukat	Rupatadine fumerate
	Area	
Injection 1	5461890	1106019
Injection 2	5465408	1104893
Injection 3	5462154	1102170
Injection 4	5458946	1108945
Injection 5	5458946	1104340
Injection 6	5513260	1104349
Average	5470100.67	1105119
Std.Dev	21279.8821	2253.694
LOD	2.63098	0.13898
LOQ	7.97268	0.42114
%RSD	0.39	0.20

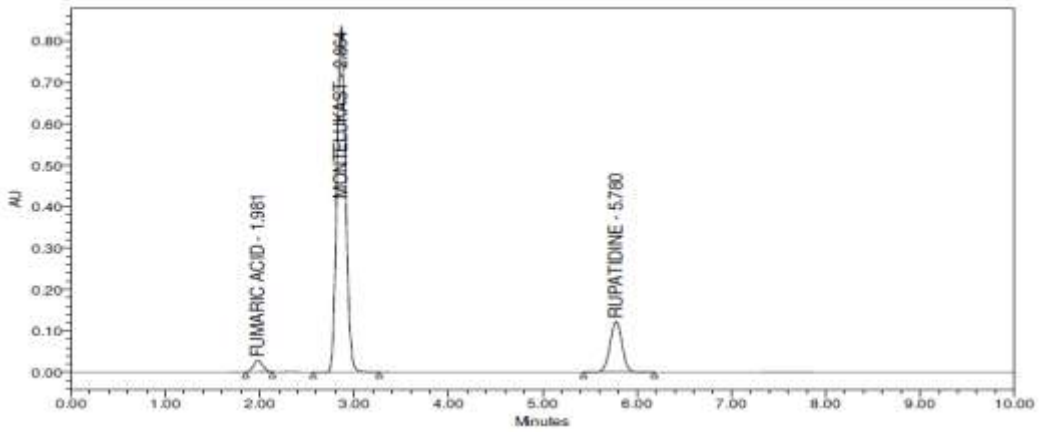

Figure 7 Chromatogram of System precision for Montelukast and Rupatadine fumerate

Table 8 Ruggedness Data for Montelukast and Rupatadine fumerate

Rupatidine			Montelukast		
S.No.	RT	Area	S.No.	RT	Area
1	2.862	5461890	1	5.763	1106019
2	2.863	5465408	2	5.761	1104893
3	2.864	5462154	3	5.763	1102170
4	2.867	5458946	4	5.768	1108945
5	2.865	5458946	5	5.766	1104340
6	2.866	5513260	6	5.769	1104349
7	2.861	5525046	7	5.745	1112165
8	2.862	5523276	8	5.746	1116064
9	2.864	5519856	9	5.747	1114389
10	2.865	5560547	10	5.748	1109864
11	2.866	5598056	11	5.749	1109976
12	2.867	5530959	12	5.75	1109658
Average	2.864	5506529	Average	5.756	1108569
Stdev	0.002015	45646.09	Stdev	0.009469	4312.963
%RSD	0.07	0.83	%RSD	0.16	0.39

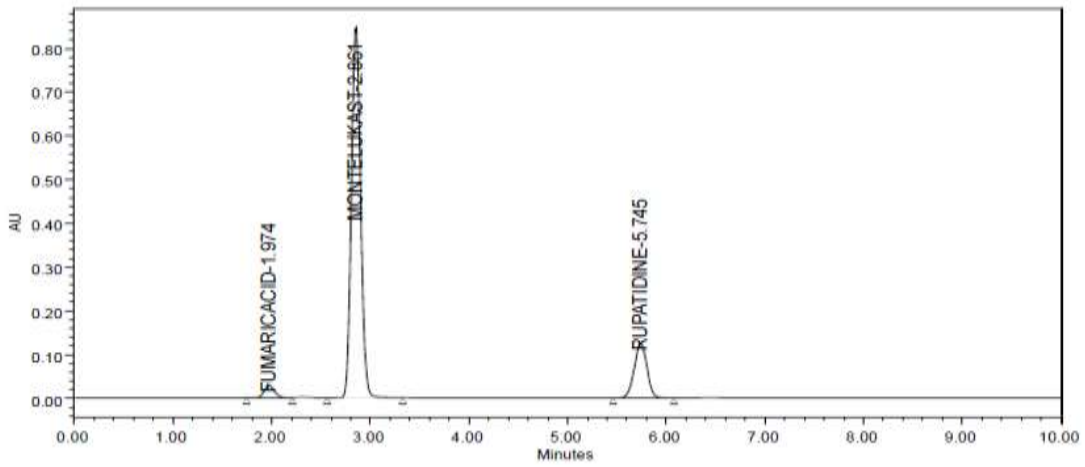

Figure 8 Chromatogram of Ruggedness for Montelukast and Rupatadine fumerate

Table 9 Data for limit of detection of Montelukast and Rupatadine fumerate

S.NO	LOD	
	System precision	Method precision
Montelukast(µg/mL)	5.25183	2.63098
Rupatidine (µg/mL)	0.3293	0.13898

Table.10 Data for limit of detection of Montelukast and Rupatadine fumerate

S.NO	LOD	
	System precision	Method precision
Montelukast(µg/mL)	5.25183	2.63098
Rupatidine (µg/mL)	0.3293	0.13898

Table 11Data for Robustness study of Montelukast and Rupatadine fumerate

Drug name	Variations	Chromatographic parameters				
		Retention time	Area	Height	Theoretical plates	Asymmetry
Montelukast	1.Change in buffer (50:50)	2.83	4910716	783843	4551.42	1.08
	2.Change in buffer (45:55)	2.82	4902232	788779	4611.56	1.08
	1.Change in flow rate at 0.9mL/min	3.15	6012527	900325	5011.21	1.09
	2.change in flow rate (1.1mL/min)	2.60	4801809	786090	4027.44	1.09
Rupatidine	1.Change in buffer (50:50)	5.39	997186	115981	8786.80	0.96
	2.Change in buffer (45:55)	5.06	994320	92394	4893.53	0.93
	1.Change in flow rate at 0.9mL/min	6.35	1223678	130479	10359.81	0.99
	2.change in flow rate (1.1mL/min)	5.27	977349	116721	8947.53	0.98

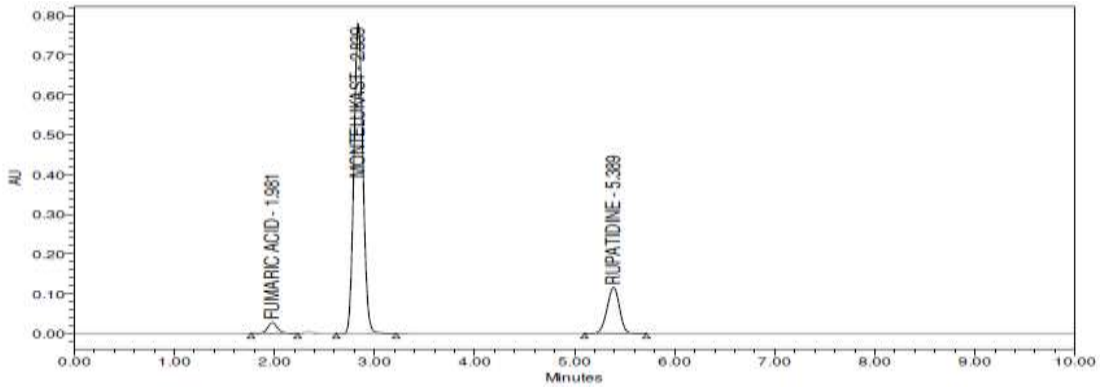

Figure 9A Chromatogram of robustness buffer for Montelukast and Rupatadine fumerate (50:50)

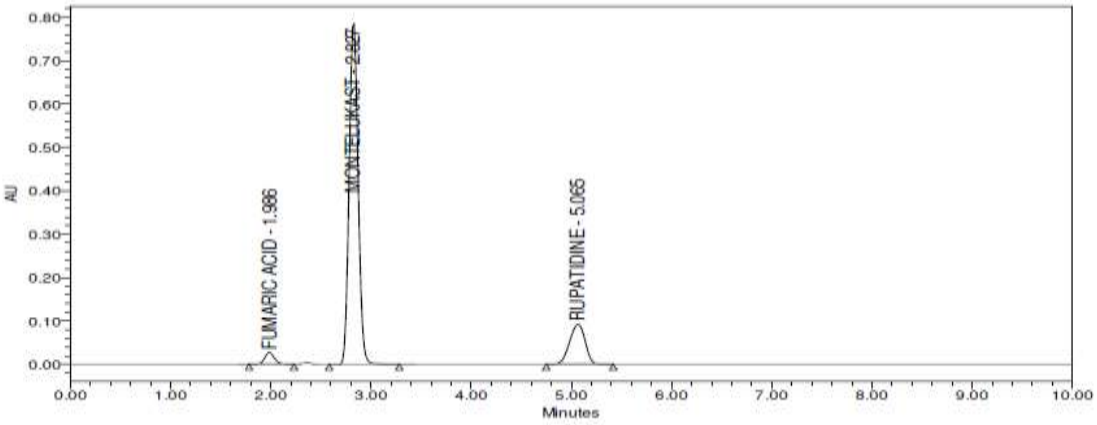

Figure 9B Chromatogram of robustness buffer for Montelukast and Rupatadine fumerate (45:55)

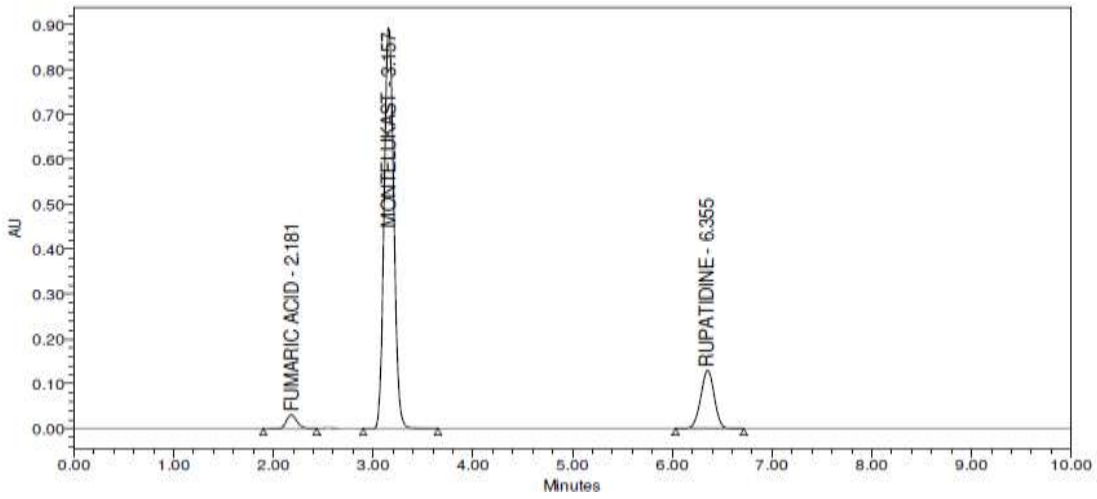

Figure 9C Chromatogram of robustness flow for Montelukast and Rupatadine fumerate (0.9mL/min)

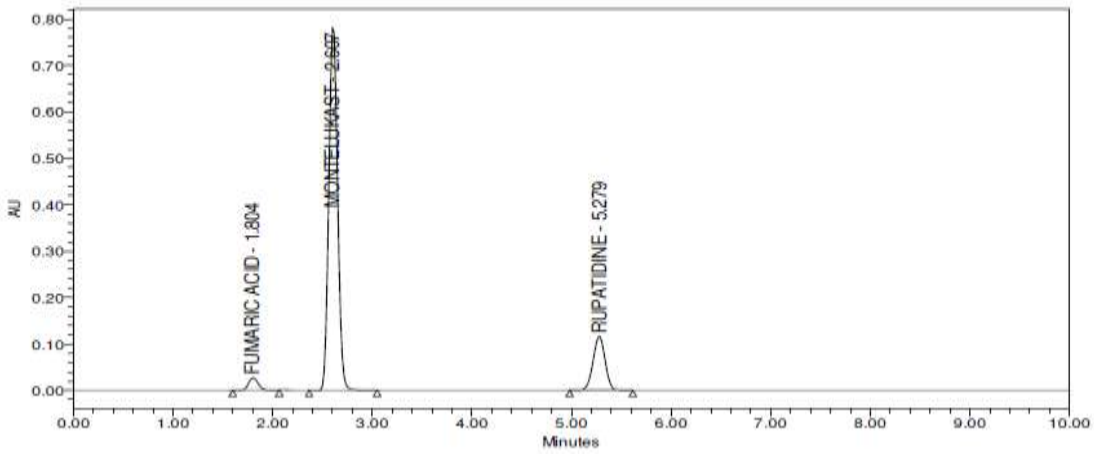

Figure 9D Chromatogram of robustness flow for Montelukast and Rupatadine fumerate (1.1mL /min)

CONCLUSION

The proposed high liquid chromatographic method has been evaluated over linearity , precision, accuracy and specificity proved to be convenient and effective for the quality control of Montelukast and Rupatidine fumerate in pharmaceutical dosage form. Result of validation parameters shows that result of method is directly proportional to the concentration of the analyte within in a given range shows a good linearity for both Montelukast and Rupatidine fumerate. Robustness of the method does not cause any change in the results which shows the stability and reproducibility of the proposed method. More over the low solvent consumption along with short retention time of 2.6and 5.7 for both Montelukast and Rupatidine to be cost effective when compared to other developed method shown in literature reviews. Recovery studies show that the method is highly accurate. Hence the proposed method found to be convenient, sensitive and specific for quality control of Montelukast and Rupatidine in tablet dosage form.

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