

A COMPREHENSIVE REVIEW ON ANALYTICAL METHODS FOR THE SIMULTANEOUS ESTIMATION OF MONTELUKAST SODIUM AND FEXOFENADINE HYDROCHLORIDE

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ABSTRACT

Allergic rhinitis is one of the most common conditions in clinical practice. The combination therapy of Montelukast sodium and Fexofenadine hydrochloride provides enhancing and complimentary effects, thereby reducing the symptoms effectively. Various analytical methods used for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride have been reviewed in this paper. These include Chromatography and spectroscopic methods to determine the amount of drugs in pharmaceutical formulations and biological fluids.

KEYWORDS: Montelukast sodium, Fexofenadine hydrochloride, analytical methods, estimation, formulation, biological fluids.

INTRODUCTION

Drug analysis plays an important role in drug development, manufacture and its therapeutic use. Number of drugs and drug formulations introduced into the market by pharmaceutical industries is increasing at an alarming rate. Almost half of all marketed drugs are combination preparations. Therefore it is essential to determine two or more drugs simultaneously. Fexofenadine and Montelukast combination tablets were recently introduced as tablet formulation in Indian market that is used as antiasthmatic and antiallergic drug. It has been demonstrated in recent studies that the treatment of allergic rhinitis with concomitant administration of an anti-leukotriene and an antihistamine shows significantly better symptom relief compared with the modest improvement in rhinitis symptomatology with each of the treatments alone.^[1]

Montelukast sodium (**Fig 1**) is chemically (S, E)-2-(1-((1-(3-(2-(7-chloroquinolin-2-yl) vinyl) phenyl)3-(2-(2-hydroxypropan-2-yl)phenyl)propylthio)methyl)cyclopropyl) acetic acid ^[2] which is a leukotriene receptor antagonist used in the treatment of chronic asthma and allergic rhinitis ^[3-4]. Fexofenadine hydrochloride (**Fig 2**) (RS)-2-[4[1-Hydroxy-4-[4-(hydroxy-diphenyl methyl)-1-piperidyl] butyl]phenyl]-2-methylpropanoic acid is used to relieve the allergy symptoms of seasonal allergic rhinitis including runny nose; sneezing; and red, itchy, or watery

eyes; or itching of the nose, throat, or roof of the mouth in adults.^[5-6]

Fexofenadine hydrochloride ^[7-9] is an antihistamine drug used in the cure of hay fever and similar allergy symptoms. It was developed as a successor of and substitute to terfenadine, an antihistamine with potentially serious contraindications. Fexofenadine hydrochloride, like other second and third-generation antihistamines, does not freely cross the blood-brain barrier, and so causes less drowsiness than first-generation histamine-receptor antagonists. It works by being an antagonist to the H1 receptor. It has been termed as both second-generation and third-generation.^[10] Montelukast Sodium is a potent and selective cysteinyl leukotriene receptor antagonist which selectively antagonizes leukotriene D4 (LTD4) at the cysteinyl leukotriene receptor, CysLT1, in the human airway. Montelukast Sodium inhibits the actions of LTD4 at the CysLT1 receptor, preventing airway edema, smooth muscle contraction and enhanced secretion of thick, viscous mucus.^[11-12]

Both the drugs are official in IP 2010. Detailed survey of literature revealed several reported methods for their determination from pharmaceutical preparations.

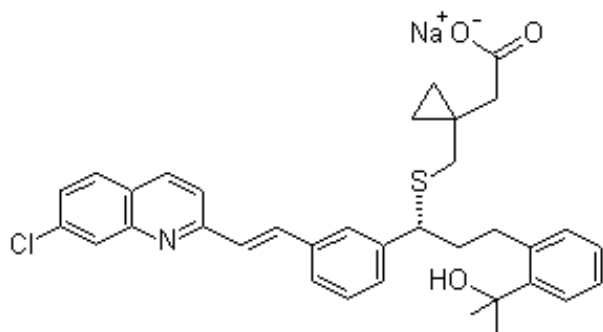


Figure 1: Montelukast sodium.

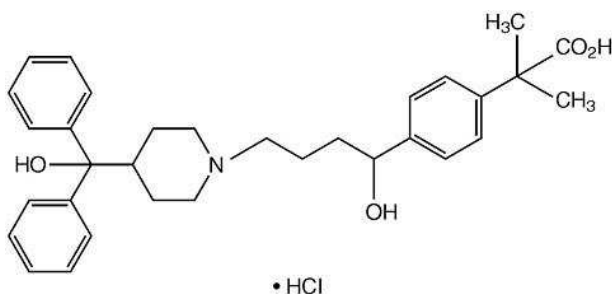


Figure 2: Fexofenadine hydrochloride

ANALYTICAL METHODS FOR SIMULTANEOUS ESTIMATION OF MONTELUKAST AND FEXOFENADINE

Many different analytical methods have been reported for the simultaneous estimation of Montelukast and Fexofenadine in pharmaceutical dosage form as well as in biological fluids.

FOR ESTIMATION IN PHARMACEUTICAL FORMULATION

Spectroscopic methods

Lata K thapapalli, et al^[13] (2012) developed two simple, accurate and reproducible spectrophotometric methods for the simultaneous estimation of Fexofenadine hydrochloride and Montelukast sodium in pharmaceutical dosage forms. The first method involves determination using the Simultaneous Equation Method while the second method is Multicomponent Mode Method. For both the methods sampling wavelengths selected were 259.0 nm and 282.0 nm over the concentration ranges of 24-144 $\mu\text{g/ml}$ and 2-12 $\mu\text{g/ml}$ for Fexofenadine hydrochloride and Montelukast sodium respectively. The results of the analysis were validated as per ICH guidelines & were found to be satisfactory to analyze the tablet dosage form.

Chabukswar et al^[14] (2012) developed a simple, precise and economical spectrophotometric method for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride in combined tablet dosage form. This study describes the development and validation for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride by the Ratio derivative UV spectroscopy method. Methanol is used as solvent. The amplitudes at 288.17nm and 289.12nm of the first derivative of ratio spectra were

selected to determine Montelukast sodium and Fexofenadine hydrochloride, respectively. Beer's law is obeyed in the concentration range of 2-10 $\mu\text{g/ml}$ and 24-120 $\mu\text{g/ml}$ for Montelukast sodium and Fexofenadine hydrochloride respectively. The % assay in commercial formulation was found to be 93.08% for Montelukast sodium and 98.91% for Fexofenadine hydrochloride by the proposed method. The method was validated with respect to linearity, precision and accuracy. Recovery was found in the range of 98.12-99.96% for Montelukast sodium and 99.12-99.97% for Fexofenadine hydrochloride by ratio derivative method. The relative standard deviation was found to be 2.0%. The present result shows that the proposed method can be successfully used for simultaneous estimation of the drug content in marketed formulations.

Dr. Rajeev Kumar and Rekha Rajeev Kumar^[15] (2017) developed a Q analysis of Montelukast sodium and Fexofenadine hydrochloride by derivative spectrophotometry. This method allowed the simultaneous determination of Montelukast sodium and Fexofenadine hydrochloride in fixed dosage form product. The method employed first order derivative spectroscopy for estimation of λ_{max} by taking 10 $\mu\text{g/ml}$ each of Montelukast sodium and Fexofenadine hydrochloride were scanned in 200-400 nm range. The absorbance values at 340 nm and 212.6 nm of the first derivative spectrum was used for the determination of Montelukast sodium and Fexofenadine hydrochloride respectively without related interference. This method obeyed Beer's law in the concentration range of 4-24 $\mu\text{g/ml}$ for montelukast sodium and 4-24 $\mu\text{g/ml}$ for Fexofenadine hydrochloride. The results of analysis have been validated statistically and recovery studies established the accuracy of the proposed method and low values of standard deviation confirmed correctness of the used method. The method was validated as per ICH guidelines.

Deepshikha Patle and Sohail Nagar^[16] (2017) developed a UV-Visible Spectrophotometric Estimation of Montelukast sodium and Fexofenadine hydrochloride by Simultaneous Equation Method in Bulk & Combined Tablet dosage form. Proposed method involves formation of 'simultaneous equations' at 259.60nm for Fexofenadine hydrochloride and 283.00 nm for Montelukast sodium using methanol as a solvent. The linearity was observed in the concentration range of 30-120 mg/ml for Fexofenadine hydrochloride and 6-20 mg/ml for Montelukast sodium. The correlation coefficient was found to be 0.9927 for Fexofenadine hydrochloride and 0.9985 for Montelukast sodium. The proposed method is reproducible which can be suitably applied for the estimation of Fexofenadine hydrochloride & Montelukast sodium in combined dosage forms. The results of analysis have been validated statistically by recovery studies.

G. Sowjanya and K. Trideva Sastri^[17] (2017) developed a simple simultaneous equation method by UV Spectrophotometry for estimation of Fexofenadine hydrochloride and Montelukast sodium in bulk and tablets. The maximum absorbance was measured at 259 nm and 344.5 nm for Fexofenadine hydrochloride and Montelukast sodium respectively in 0.1N NaOH. The calibration curves showed a linear relationship between absorbance and concentration in the range of 50-180 µg/ml for Fexofenadine hydrochloride and 1-35 µg/ml for Montelukast sodium with correlation coefficient of 0.998. The method was validated as per ICH guidelines and the outcome of the statistical analysis proved that the method was precise and the relative standard deviation was less than 2.0% for the assay calculated in intraday and interday precision. The mean percentage recoveries of Fexofenadine hydrochloride and Montelukast sodium calculated by standard addition were found to be 101.43 - 100.54% and 99.97-100.2%, indicating accuracy of the method. The developed method was also checked in multicomponent mode and the assay values obtained were within the limits. The acceptable results of validation for the present study indicate the suitability of the method for routine quality control analysis of the combined drugs in tablets.

Chromatographic methods

Hitesh Vekaria et al^[18] (2012) developed a RP- HPLC method for simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride in combined dosage form. The chromatographic separation was achieved on C_{18} column (250mm × 4.6mm, 5µm) as a stationary phase with a mobile phase comprising of 50mM sodium acetate buffer:acetonitrile:methanol (25:35:40) adjust PH at 8.2 with 5% o-phosphoric acid at a flow rate of 1.0ml/min with column temperature of 40 ± 2°C and UV detection 210nm. The retention time of Fexofenadine hydrochloride and Montelukast sodium was found to be 3.43min, and 8.22 min respectively. The linearity was found to be in the range of 12.5-37.5 µg/ml for Montelukast sodium and 150-450µg/ml for Fexofenadine hydrochloride with correlation coefficient of 0.999. The proposed method was validated as per ICH guidelines and successfully applied for the determination of investigated drug in tablets.

Rajeev Kumar et al^[19] (2012) developed a simple, fast and precise RP-HPLC method for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride. Efficient chromatographic separation was achieved on waters C_{18} column (150mm × 4.6mm, 5µm) as stationary phase with mobile phase comprising of 0.05 M of NaH_2PO_4 in water (PH 6.8):Methanol (55:45v/v) at a flow rate of 1ml/min at column temperature of 30°C and UV detection at 258nm. The retention time of Montelukast sodium and Fexofenadine hydrochloride was found to be 11.2min, and 18.8min respectively. The proposed method was validated for linearity, accuracy, precision, sensitivity, robustness and solution stability. The test solution was found to be stable for 72hr. This

method can be conveniently used for routine quality control analysis.

Anirudha R et al^[20] (2012) developed a high resolution RP-HPLC method for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride in pharmaceutical preparation. Separation was achieved by using kromasil C_{18} (250mm × 4.6mm, 5µm) column with the column temperature of 50°C and detector wavelength is 241nm. Gradient mobile phase comprising of sol-A: water, sol-B: Acetonitrile: Methanol (50:50) was used at a flow rate 1ml/min. The retention time of Montelukast sodium and Fexofenadine hydrochloride was 3.36 and 2.12 minutes respectively. The correlation coefficient of Montelukast sodium and Fexofenadine hydrochloride was found to be 0.999 and 0.999 respectively. The recovery values of Montelukast sodium ranged from 99.12- 99.24 and Fexofenadine hydrochloride ranged from 99.09-99.59.

N. Tamilselvi and K. Sruthik^[21] (2012) developed a simple, fast and precise HPLC method for simultaneous estimation of Fexofenadine hydrochloride and Montelukast sodium in tablet dosage form. An Efficient chromatographic separation was achieved on phenomenex C_{18} column (150mm x4.6 mm, 5µm) as stationary phase with a mobile phase of 0.5% Ortho phosphoric acid PH adjusted to 6 (tri ethyl amine); Acetonitrile (40:60 v/v) at a flow rate of 1.0 ml/minute . The linearity where found to be in the range of 72 to 120 µg/ml and 6 to 10 µg/ml for Fexofenadine hydrochloride and Montelukast sodium respectively with correlation coefficient of 0.999. The proposed method was validated for linearity, accuracy, precision, and sensitivity.

Mounikagodavarthi et al^[22] (2012) developed a method for the simultaneous determination of Fexofenadine hydrochloride and Montelukast sodium using RP-HPLC method. The separation was carried out on Agilent T.C – C_{18} column (2)4.6×250m.m with 5 µm internal diameter using Acetonitrile: TEA (PH 6) (80:20v/v) as mobile phase at the flow rate of 1ml/min. RP-HPLC separation of the two drugs was carried out in the absorbance mode at 220 nm. The drugs were resolved satisfactorily with Rt values of 3.21 ± 0.01 and 6.66 ± 0.01 for Fexofenadine hydrochloride and Montelukast sodium, respectively. The linear regression analysis data for the calibration plots showed good linear relationship with r^2 0.9996 and 0.9998 for Fexofenadine hydrochloride and Montelukast sodium, respectively in the concentration range of 12-144 µg/ml for Fexofenadine hydrochloride and 1-12µg/ml for Montelukast sodium. The method was validated for precision, robustness, specificity and accuracy. The limit of detection and quantization were 1.41 and 4.29 µg/ml, respectively for Fexofenadine hydrochloride and 0.02 and 0.06 µg/ml, respectively for Montelukast sodium. The proposed developed RP-HPLC method can be applied for identification and quantitative determination of Fexofenadine hydrochloride and Montelukast sodium in bulk drug and drug formulation.

K. Prashanth Kumar et al^[23] (2012) developed a simple, accurate, economical and reproducible RP-HPLC method for the simultaneous determination of Montelukast sodium and Fexofenadine hydrochloride in bulk and pharmaceutical formulations. The separation was achieved on a phenomenexC column (150 × 4.6 mm i.d, particle size of 5 μ) using a mixture of 0.1M potassium dihydrogen 18 orthophosphate buffer (pH 5.0) and methanol in the ratio of 60:40 v/v as mobile phase in an isocratic elution mode, at a flow rate of 1 ml/min. The detection was monitored at 220 nm. The retention time of montelukast sodium and Fexofenadine hydrochloride was found to be around 2.17 ± 0.12 min and 6.24 ± 0.14 min respectively. Excellent linearity range was found between 5-15 μ g/ml for Montelukast sodium and 10-100 μ g/ml for Fexofenadine hydrochloride. The method was validated with respect to linearity, robustness, precision and accuracy and was successfully applied for the simultaneous determination of Montelukast sodium and Fexofenadine hydrochloride from the combined dosage formulation.

M. Kalyankartukaram et al^[24] (2012) developed a simple and precise HPLC method for Montelukast sodium and Fexofenadine hydrochloride. HPLC separation was achieved with a hypersil ODS-C18 (5 μ , 250 mm x 4.6 mm, i.d.) as a stationary phase and methanol: acetonitrile: 1% trifluoroacetic acid (80:10:10 v/v/v) as eluent, at a flow rate of 1.0 ml/min, UV detection was performed at 210 nm. The retention time of Montelukast sodium and Fexofenadine hydrochloride were found to be 5.1 and 3.7 min respectively. Results of analysis were validated by recovery studies. Result of studies showed that the proposed RP-HPLC method is simple, rapid, accurate and precise which can be used for the routine determination of Montelukast sodium and Fexofenadine hydrochloride in bulk.

Ravisankar M et al^[25] (2012) developed a simple, precise and accurate RP-HPLC method for the simultaneous estimation of Montelukast sodium and Fexofenadine Hydrochloride. The chromatographic separation was performed in c8 column using 0.05M potassium di hydrogen ortho phosphjate: acetonitrile in the ratio 35:65 and pH adjusted to 6 with triethyl amine. The flow rate was 1ml/minute and the wave length of quantization was 226 nm. The retention time was found be 2.127minute for Fexofenadine and 5.65 minute for Montelukast sodium. The linearity were found to be in the range of 4.8 – 28.8 μ g/ml and 0.4 -2.4 μ g/ml for Fexofenadine and Montelukast respectively with the correlation coefficient of 0.999.The mean recoveries for Fexofenadine and Montelukast were 99.85 and 100.19 respectively. Relative standard deviation was less than 2%.Precision were performed as per ICH guidelines and the result shows relative standard deviation less than 2%.The assay value for Fexofenadine and Montelukast were found to be 100.55% and 100.40% respectively.

Mona Pankhaniya et al^[26] (2013) developed a simple, specific, accurate and stability- indicating RP-HPLC method for simultaneous determination of Montelukast sodium and Fexofenadine hydrochloride using a Lichrospher[®] 100, RP-18e Colum and a mobile phase composed of methanol: 0.1% *o*-phosphoric acid (90:10v/v), PH6.8.The retention times of Montelukast sodium and Fexofenadine hydrochloride were found to be 10.16 and 12.03 min, respectively. Linearity was established for Montelukast sodium and Fexofenadine hydrochloride were in the range of 2-10microgram/ml and 24-120 microgram/ml respectively. The percentage recovery of Montelukast sodium and Fexofenadine hydrochloride were found to be in range 99.09 and 99.81%, respectively. Both the drugs are subjected to acid and base hydrolysis, oxidation, photolytic and thermal degradation condition. The degradation products of Montelukast sodium and Fexofenadine hydrochloride were resolved from a pure drug with significant Differences in their retention time value.

Rameezuddin et al^[27] (2013) developed a simple, fast and precise reverse phase high performance liquid chromatographic method for the simultaneous determination of Montelukast sodium and Fexofenadine hydrochloride. The chromatographic separation was achieved on C8 column (250 mm x 4.6 mm,4 μ particle size) as stationary phase with a mobile phase comprising of ortho phosphoric acid (pH 6.2):methanol (40:60) with flow rate of 1.0 ml/min, column temperature of 28±2°C at a wavelength of 290nm. The retention time of Montelukast sodium and Fexofenadine hydrochloride were 5.0 min, and 3.2 min respectively. The linearity were found to be in the range of 2-6 μ g/ml and 24-72mg/ml for Montelukast sodium and Fexofenadine hydrochloride with correlation coefficient greater than 0.999.

P. Nagaraju et al^[28] (2013) developed a simple reverse phase high-performance liquid chromatographic (RP-HPLC) method for simultaneous determination of Fexofenadine Hydrochloride and Montelukast sodium in tablet dosage form. Chromatographic analysis was performed on a Hypersil ODS C18 (150x 4.6 mm, 5 μ m) with a mixture of Acetonitrile: 0.01 M Phosphate buffer (pH was adjusted to 3.0 with *o*-phosphoric acid) in the ratio 60:40 as mobile phase, at a flow rate of 1.0 ml/min. UV detection was performed at 230 nm. The method was validated for accuracy, precision, specificity, linearity and sensitivity. The retention times of Fexofenadine Hydrochloride and Montelukast sodium were 2.127 and 5.45min respectively. Calibration plots were linear over the concentration ranges 4.8-33.6 μ g/ ml and 0.4-2.8 μ g /ml for Fexofenadine Hydrochloride and Montelukast sodium respectively. The Limit of detection was 0.42 μ g/ ml and 0.03 μ g/ ml and the quantification limit was 1.23 μ g /ml and 0.11 μ g /ml for Fexofenadine Hydrochloride and Montelukast sodium respectively. The accuracy of the proposed method was determined by recovery studies and found to be 100.11% to 100.65% for Fexofenadine

Hydrochloride and 100.76% to 101.36% for Montelukast sodium.

Priyanka et al^[29] (2014) developed a simple fast and precise reverse phase high performance liquid chromatography method (RP-HPLC) for the determination & validation of Fexofenadine hydrochloride and Montelukast sodium in combined dosage form. The chromatographic separation was achieved on Hypersil-BDS C18 column (250mm × 4.6mm, 5 μ) as a stationary phase with a mobile phase comprising of water and methanol as a mixture in the ratio of (70:30) in an isocratic elution mode at a flow rate of 1.0ml/min maintaining the column temperature at ambient. The detection limit was monitored at 259nm. The retention time of Fexofenadine hydrochloride and Montelukast sodium were 2.95 and 3.52 minutes respectively. The linearity was found to be in the range of 10-80 μ g/ml for both Fexofenadine hydrochloride and Montelukast sodium. The calibration factor is greater than 0.999, The proposed method was validated according to the ICH guidelines and successfully applied for the determination of all the validation techniques such as Accuracy studies, Robustness, Ruggedness, Linearity, Precision etc., for the determination of Fexofenadine hydrochloride and Montelukast sodium.

K. Padmavathi and M. Subba Rao^[30] (2015) developed a new stability-indicating RP-HPLC method for the simultaneous determination of Fexofenadine hydrochloride and Montelukast in combined dosage form, using a Aligent, Zorbax (Make: 150 mmx4.6 mm I.D;particle size 5 μ m and a mobile phase composed of phosphate buffer (pH 4.0): Acetonitrile (60:40 v/v) at a flow rate of 1.0ml/min. The retention times of fexofenadine hydrochloride and montelukast were found to be 10.16 and 12.03 min, respectively. Linearity was established for fexofenadine hydrochloride and montelukast in the range of 10- 30 μ g/ml and 5.0-15 μ g/ml, respectively. The percentage recoveries of fexofenadine hydrochloride and montelukast were found to be in the range of 99.80 to 99.90 and 99.50 to 99.93 respectively. Both the drugs were subjected to acid and base hydrolysis, oxidation, photolytic, and thermal degradation conditions. The degradation products of fexofenadine hydrochloride and montelukast were well resolved from the pure drug with significant differences in their retention time values. This method can be successfully employed for simultaneous quantitative analysis of montelukast and fexofenadine hydrochloride in various combined formulations.

G. Swarnalatha et al^[31] (2016) developed a RP-HPLC Method for simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride in a pharmaceutical dosage form. The different analytical performance parameters such as linearity, accuracy, precision, specificity, LOD and LOQ were determined according to ICH guidelines. RP-HPLC was conducted on Hypersil BDS C18 (250 mm length x 4.6 mm ID,

5 μ m) column. The mobile phase consisting of mixed phosphate buffer pH-3 and acetonitrile in the ratio (20:80% v/v) and the flow rate was 1ml/min. Montelukast sodium and Fexofenadine hydrochloride were monitored using Shimadzu Prominence (Spinchrom ModuleLC-20AT) with auto sampling injector and UV detector. Linearity was observed in concentration ranges of 0.4-2.4 μ g/ml and 4.8-28.8 μ g/ml for Montelukast sodium and Fexofenadine hydrochloride respectively. Regression equation of Montelukast sodium is $y=42.98x+6.536$, and of Fexofenadine hydrochloride is $Y = 5.859+11.58$, Correlation coefficient was found to be 0.999 for both the drugs. The % recovery was found to be 99.74% for Montelukast sodium, 100.09% for Fexofenadine hydrochloride. LOD value of Fexofenadine hydrochloride and Montelukast sodium was found to be 0.13, 0.026, respectively. LOQ value of Fexofenadine hydrochloride and Montelukast sodium was found to be 0.397, 0.081 respectively.

Mohamed Mustafa et al^[32] (2017) developed a new simple, rapid and sensitive Gradient Ultra performance liquid chromatography (UPLC) Method for the determination of Fexofenadine hydrochloride and Montelukast sodium. The method employs for thermo scientific UPLC system on waters (symmetry) (C18 1.8 micron 4.6 x 50 mm) column. Best chromatographic separation was achieved by using Acetonitrile: 20 Mm potassium di hydrogen phosphate 80:30(v/v) adjusted to pH5.5 using ortho phosphoric acid as mobile phase at a flow rate of 1 ml/min and detection at 230 nm. Separation was completed within 10 min. The retention time of Fexofenadine hydrochloride and Montelukast sodium was found to be 1.022 and 3.281. The proposed method was found to have linearity in concentration range 80-120 microgram/ml and 96-144 microgram/ml. The proposed method has been statistically validated and was found to be simple, precise, reproducible and accurate. The Developed and validated method was successfully used for the quantitative analysis of commercially available dosage form.

Rajeev Kumar P and Rekha Rajeev Kumar^[33] (2017) developed a simple, speedy, precise, and accurate, stability-indicating reversed phase high performance liquid chromatographic method for simultaneous (Vieordt's method) determination of Montelukast sodium (MTK) and Fexofenadine hydrochloride (FXD). The sample injection volume was 20 μ l and the quantification was attained by UV-VISIBLE detector at 248 nm. The chromatographic separation was achieved on X bridge C18, 250 × 4.6 mm, 5 μ m particle column, using an isocratic mobile phase comprising of acetonitrile: buffer (10 mM potassium dihydrogen phosphate solutions): methanol of pH 4.5 and in the ratio of 50:30:20 v/v/v at a flow rate of 1.5 ml/ min. The retention times for Montelukast sodium and Fexofenadine hydrochloride were found to be 3.62 min and 7.43 min, respectively. The drugs were exposed to thermal, photolytic, hydrolytic, and oxidative stress conditions, and the

stressed samples were analyzed by the suggested method. Validation of the method was done as per International Conference on Harmonization (ICH) guidelines. Linearity was established for Montelukast sodium and Fexofenadine hydrochloride in the range of 0.020-0.100 mg/ml and 0.016-0.064 mg/ml, respectively. The limits of detection were 0.04 µg/ml and 0.07 µg/ml, respectively and the LOQ value 0.11 µg/ml and 0.023 µg/ml, for Montelukast sodium and Fexofenadine hydrochloride respectively.

Suparna S. Tandulwadkar et al^[34] (2012) developed a simple, precise, specific, and accurate HPTLC method for the simultaneous determination of Montelukast sodium and Fexofenadine hydrochloride in pharmaceutical dosage form. The separation was carried out on Merck HPTLC aluminum plates of silicagel G60 F₂₅₄, (20×10cm) with 250µm thickness using toluene: ethyl acetate: methanol: ammonia (30%) (0.5:7:2:0.5,v/v/v/v) as mobile phase. HPTLC separation of the two drugs followed by densitometry measurement was carried out in the absorbance mode at 220nm. The drugs were resolved satisfactorily with R_f values of 0.21±0.01 and 0.59±0.01 for Fexofenadine hydrochloride and Montelukast sodium, respectively. The linear regression analysis data for the calibration plots showed good linear relationship with r² =0.9996 and 0.9998 for Fexofenadine hydrochloride and Montelukast sodium, respectively, in the concentration range of 2400–10800ngspot⁻¹ for Fexofenadine hydrochloride and 200–900ngspot⁻¹ for Montelukast sodium. The method was validated for precision, robustness, specificity, and accuracy. The limits of detection and quantization were 100 and 300ngspot⁻¹, respectively, for Fexofenadine hydrochloride and 50 and 100ngspot⁻¹, respectively, for Montelukast sodium. The proposed developed HPTLC method can be applied for identification and quantitative determination of Fexofenadine hydrochloride and Montelukast sodium in bulk drug and drug formulation.

Hitesh Vekaria et al^[35] (2012) developed a simple, precise, specific and accurate high performance thin layer chromatographic method for the simultaneous determination of Fexofenadine hydrochloride (FEXO) and Montelukast sodium (MONT) in pharmaceutical dosage form. The separation was carried out on Merck HPTLC aluminum plates of silica gel G60F254, (20 × 10 cm) with 250 µm thickness using ethyl acetate: methanol: ammonia (30%) (7: 3: 0.5, v/v/v/v) as mobile phase. HPTLC separation of the two drugs followed by densitometric measurement was carried out in the absorbance mode at 215 nm. The drugs were resolved satisfactorily with R_f values of 0.84 ± 0.01 and 0.24 ± 0.01 for MONT and FEXO, respectively. The linear regression analysis data for the calibration plots showed good linear relationship with R²=0.9988 and 0.9995 for FEXO and MONT, respectively in the concentration range of 1800-9000 ng/spot for FEXO and 150-750 ng ng/spot for MONT. The method was validated for accuracy, precision, specificity and robustness. The limit

of detection and quantitation were 100.6079 and 304.8726 ng/spot, respectively for FEXO and 40.0191 and 121.8456 ng/spot, respectively for MONT. The proposed developed HPTLC method can be applied for identification and quantitative determination of FEXO and MONT in bulk drug and drug formulation.

Rajendraprasad Muppavarapu et al^[36] (2014) developed a rapid, simple, sensitive and selective LC-MS/MS-ESI method for the simultaneous quantification of Montelukast sodium and Fexofenadine hydrochloride in human plasma (200 µL) using Montelukast sodium-d₆ (MT-d₆) and Fexofenadine hydrochloride (FF-d₁₀), respectively as an internal standard (IS) as per the US Food and Drug Administration guidelines. The chromatographic resolution was achieved on a Chromolith RP 18e column using an isocratic mobile phase consisting of 20 mM ammonium formate–acetonitrile (20:80, v/v) at flow rate of 1.2 ml/min. The LC-MS/MS was operated under the multiple-reaction monitoring mode using electrospray ionization. The total run time of analysis was 4 min and elution of Montelukast sodium, Fexofenadine hydrochloride, MT-d₆ and FF-d₁₀ occurred at 2.5, 1.2, 2.4 and 1.2 min, respectively. The standard curve found to be linear in the range 2.00–1000 ng/ml with a coefficient of correlation of ≥0.99 for both the drugs.

Marwa A.A Ragab and Rasha M. Youssef^[37] (2013) developed a method for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride by using a Fourier transform convolution emission data under non- parametric linear regression method. This is a new hybrid chemometric method that has been applied to the emission response data. It deals with convolution of emission data using 8-points $\sin xi$ polynomials + (discrete Fourier functions) after the derivative treatment of these emission data. This new application was used for the simultaneous determination of Fexofenadine hydrochloride and Montelukast sodium in bulk and pharmaceutical preparation. It was found beneficial in the resolution of partially overlapping emission spectra of this mixture. The application of this chemometric method was found beneficial in eliminating different types of interferences common in spectrofluorimetry such as overlapping emission spectra and self-quenching. Not only this chemometric approach was applied to the emission data but also the obtained data were subjected to non-parametric linear regression analysis (Theil's method). The presented work compares the application of Theil's method in handling the response data, with the least-squares parametric regression method, which is considered the de facto standard method used for regression. So this work combines the advantages of derivative and convolution using discrete Fourier function together with the reliability and efficacy of the non-parametric analysis of data. Theil's method was found to be superior to the method of least squares as it could effectively circumvent any outlier data points.

CONCLUSION

After the scrutiny of literatures it has been observed that about 24 methods are reported for the simultaneous estimation of Montelukast sodium and Fexofenadine hydrochloride in bulk form, in formulation and in biological fluids. Different techniques available include Spectrophotometry, HPLC, LCMS, and HPTLC. 5 methods based on Spectrophotometry, 16 reported methods are based on HPLC, one is based on LCMS and 2 are based on HPTLC. Out of the five methods based on Spectrophotometry Q analysis of Montelukast sodium and Fexofenadine HCL in tablet formulation by derivative spectrophotometry by Rajeev Kumar et al is reported to be equally sensitive for both drugs and can be detected in the range of 4-24 µg/ml. Remaining methods shows more sensitivity towards Montelukast sodium than Fexofenadine. Out of the HPLC methods simultaneous estimation of Montelukast sodium and Fexofenadine HCL in pharmaceutical formulation by RP-LC-PDA by Anirudha R et al found to be more sensitive by which Montelukast can be detected in the range of 0.05-10 µg/ml and Fexofenadine can be detected in the range of 0.6 – 120 µg/ml. LCMS method by Rajendraprasad Muppavarapu et al is reported to be useful for the determination of this combination in biological fluids in the concentration range of 2-1000ng/ml. Out of the HPTLC methods ,method by Hitesh. Vekaria et al is reported to be more sensitive with a linearity range of 150- 750 ng/ml for Montelukast sodium and with a linearity range of 1800-9000 ng/ml for Fexofenadine hydrochloride.

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