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A REVIEW ON COMPARATIVE STUDY OF VARIOUS ANALYTICAL METHODS FOR ESTIMATION OF MONTELUKAST SODIUM AND LEVOCETIRIZINE HYDROCHLORIDE

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ABSTRACT

Starting from simple analytical methods to the recent development of advanced technological stages, various analytical methods have been designed for the multicomponent analysis of drugs. Simultaneous estimation of drugs in the combined dosage form has proved vital in the pharmaceutical analysis since it is cost-effective and time-saving. Levocetirizine, the peripheral H1-receptor antagonist and R-enantiomer of Cetirizine, serves as a non-sedative antihistamine for the treatment of chronic idiopathic urticaria, angioedema, and allergic rhinitis. In the treatment of allergic rhinitis, the combination of Levocetirizine and Montelukast Sodium, a selective cysteinyl leukotriene I receptor inhibitor acting as an anti-asthmatic agent in the bronchial tubes and lungs, is commonly utilized. This pharmaceutical formulation has demonstrated added benefits in efficiently reducing symptoms for patients. Within this review article, various analytical methods applied to estimate Levocetirizine and Montelukast Sodium in their combined dosage form are compared and addressed. The methodologies encompass UV Spectrophotometry, High-Performance Liquid Chromatography (HPLC), Ultra Performance Liquid Chromatography (UPLC), and High-Performance Thin-layer Chromatography (HPTLC). Furthermore, the article provides insights into the development of diverse analytical techniques for the estimation of Levocetirizine and Montelukast Sodium in conjunction with other drugs available in the market. The current paper recommends a suitable method for analyzing this pharmaceutical compound, contributing to the optimization of various analytical methods for their determination.

Keywords: Levocetirizine, Montelukast Sodium, Allergic Rhinitis, Spectrophotometry, Chromatography

INTRODUCTION:

Allergic rhinitis, a persistent inflammatory condition, manifests as an IgE-mediated hypersensitivity disease affecting nasal airways, primarily induced by airborne allergens like dust, pollen, molds, or animal dander1. Commonly known as hay fever, its symptoms include nasal congestion, rhinorrhea, an itchy nose, and a sore throat2. In the contemporary era, allergic rhinitis has emerged as a significant global health concern, impacting approximately 10-20% of the worldwide population3. Levocetirizine, the R-enantiomer of Cetirizine, identified chemically as 2-(2-{4-[(R)-(4-chlorophenyl) (phenyl)-methyl] piperazin-1-yl} ethoxy) acetic acid, acts as a peripheral H1-receptor antagonist. Employed as a non-sedative antihistamine, it proves effective in treating chronic idiopathic urticaria, angioedema, and allergic rhinitis4,5. Levocetirizine Dihydrochloride, with the molecular formula C21H25ClN2O3. 2HCL, represents the salt form of Levocetirizine, characterized by a molecular weight of 461.8 g/mol6,7. It is a water-soluble, white crystalline powder and is officially listed in IP-20078. Montelukast Sodium, the monosodium salt of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methyl ethyl) phenyl] propyl] thio] methyl] cyclopropane acetic acid, appears as a white to pale yellowish crystalline powder. Highly soluble in alcohol and dimethyl sulfoxide, it is freely water-soluble while practically insoluble in acetonitrile. The molecular formula and weight are C35H35ClNNaO3S and 608.2 g/mol, respectively 4, and it is officially listed in IP-20109, BP-201610, and USP-201611.

Functioning as an anti-asthmatic agent, Montelukast Sodium inhibits the selective cysteinyl leukotriene I receptor in the bronchial tubes and lungs12. The combination of Levocetirizine with Montelukast Sodium in a combined dosage form has demonstrated additional benefits, efficiently alleviating the symptoms of allergic rhinitis13. In the contemporary landscape, there is a substantial increase in the research and development of drugs in combined dosage forms due to their enhanced efficacy. The escalating demand has spurred the necessity for new analytical procedures that facilitate the swift analysis of combined drugs.

Simultaneous estimation of these drugs ensures the formulation's adherence to the labeled quantities of active pharmaceutical ingredients. A comprehensive array of both simple and advanced analytical methods exists for the simultaneous determination of Levocetirizine and Montelukast Sodium. A literature survey highlights that these drugs are routinely analyzed through various methods, including spectrophotometric and chromatographic techniques **[2,14]**.

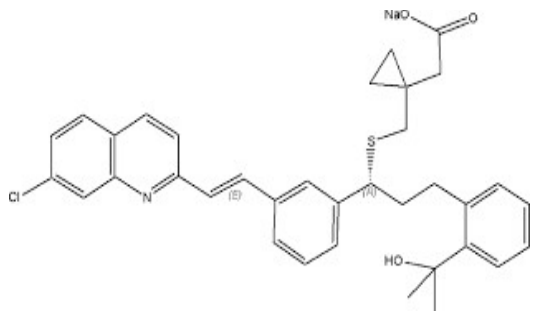

Figure 1: Chemical Structure of Levocetirizine

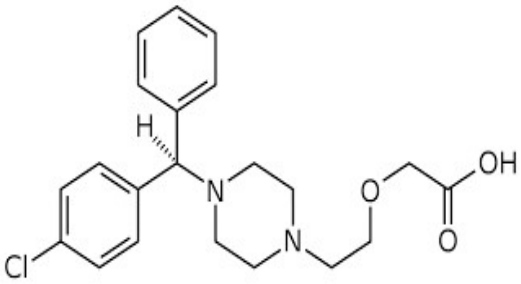

Figure 2: Chemical Structure of Montelukast Sodium

METHODOLOGY:

Utilizing the conventional data retrieval approach, this investigation involved searching for information through widely used search engines such as Google and Yahoo. The acquired data primarily originated from established electronic sources, with a focus on prominent platforms like Scopus, PubMed, and Science Direct. Emphasis was placed on referencing and cross-referencing to rectify errors and ensure the presentation of high-quality, accurate data.

ANALYTICAL METHODS:

Analytical method development and validation play a crucial role in multiple stages of drug development and manufacturing[15]. In the context of this, the primary objective of method development is to establish an analytical method capable of measuring the concentration of an Active Pharmaceutical Ingredient (API) in a specific compounded dosage form. This process involves a subsequent method validation step, aiming to verify and ensure the reliability of the developed method. Various validation parameters, including linearity, range, accuracy, precision, specificity, detection limit, quantitation limit, and robustness of the methods, are studied during this validation process. The suitability of the developed method for determining pharmaceutical compounds from both bulk substances and pharmaceutical formulations is thereby indicated[2,16]. Analytical methods specifically tailored for estimating Levocetirizine and Montelukast Sodium are outlined as follows:

SPECTROPHOTOMETRIC METHOD:

The study involved the investigation of spectrophotometric methods for the assessment of Levocetirizine (LEV) and Montelukast Sodium (MKT) in both bulk and combined pharmaceutical dosage forms are mentioned in the **Table 1**.

Table 1: UV Spectrophotometry Method

Sr. No.	Drug Combination	Method	Descriptions	References
1	Levocetirizine Hydrochloride and Montelukast Sodium in Tablet Dosage Form	Absorbance correction method	Solvent: Methanol Detection wavelength: 287nm (λ max of MKT) 232nm (λ max of LEV) Recovery range: 99.70 % (MKT) 100.49 % (LEV) Linearity range: 2-40 µg/mL (MKT at 287 nm, 232 nm) 1-40 µg/mL (LEV at 232 nm) r2 value: 0.9997 (MKT at 287 nm) 0.9999 (MKT at 232 nm) 0.9996 (LEV at 232 nm) % RSD (label claim):0.4422 % (MKT) 1.0826 % (LEV) %	17
2	Levocetirizine Hydrochloride and Montelukast Sodium in Tablet Dosage Form	Multi wavelength method	Solvent: Methanol Detection wavelength: 229 nm, 232.2 nm, 232 nm % Recovery range: 98.58 % (MKT) 100.49 % (LEV) Linearity range: 5-40µg/mL (MKT at 229 nm, 232.2nm) r2 value: 0.999921(MKT at 229 nm) 0.999795(MKT at 232.2 nm) % RSD (label claim): 1.3069 (MKT) 0.1802 (LEV)	17
3	Levocetirizine Hydrochloride and Montelukast Sodium in Tablet Dosage Form	First-order derivative method	Solvent: Methanol Detection wavelength: 231.1 nm (zero crossing point for LEV) 216.5nm (zero crossing point for MKT) % Recovery range: 99.76 % (MKT) 99.82 % (LEV) Linearity range: 10-40µg/mL (MKT at 231.1nm) 10-40 µg/mL(LEVat 216.5 nm) r2 value: 0.99970 (MKT at 231.1 nm) % RSD (label claim): 1.71029 (MKT) 1.0215 (LEV)	17

4	**Montelukast Sodium and Levocetirizine Hydrochloride in a binary mixture**	**Simultaneous equation method**	**Solvent: Methanol Detection wavelength: 284 nm (λmax of MKT) 229 nm (λmax of LEV) % Recovery: 98.5 %-101.1 % % Purity: 99.08 %-99.87 % (MKT) 98.5 %-101 % (LEV) Linearity range: 4-20 µg/mL (MKT) 2-10 µg/mL (LEV) r2 value: less than 1 for both drug % RSD (Precision, Accuracy): less than 2 LOD: 1.1µg/mL(MKT), 3.3 µg/mL (LEV) LOQ: 0.7µg/mL(MKT), 2.1 µg/mL(LEV)**	**18**
5	**Montelukast Sodium and Levocetirizine Dihydrochloride in Tablet Dosage Form**	**AUC curve method**	**Solvent: Methanol Detection wavelength: 263.6 nm-293.6 nm 222 nm-242nm % Purity: 98.90% for MKT 98.75 % for LEV % Recovery: near to 100% Linearity range: 5-30 µg/mL for both API r2 value: 0.9969, 0.9988 for MKT at both wavelength range, 0.9991 for LEV at 222 nm-242nm %RSD (Precision): less than 2 % LOD (µg/mL): 1.60 at 222 nm-242 nm (MKT) 1.06 at 263.6 nm-293.6 nm (MKT) 1.23 at 222 nm-242nm (LEV) LOQ (µg/mL): 4.80 at 222 nm- 24nm (MKT) 3.1 at 263.6 nm-293.6 nm (MKT) 3.71at 222 nm-242nm (LEV)**	**19**
6	**Levocetirizine Dihydrochloride and Montelukast Sodium in Tablet Dosage Form**	**Ratio difference method**	**Solvent: Methanol Detection wavelength: 216 nm, 232 nm (LEV) 296.4 nm, 344.2 nm (MKT) % Recovery: 100.5 % (LEV) 99.01 % (MKT) Linearity range: 4–28 µgmL-1 for both drugs r2 value: 0.9979 (LEVat 216 nm, 232 nm) 0.9986 (MKT at 296.4 nm, 344.2 nm) LOD(µg/mL): 0.229 (LEV) 0.352 (MKT) LOQ(µg/mL): 0.764 (LEV) 1.152 (MKT) %RSD (Precision, Accuracy): less than 2 %**	**20**
7	**Levocetirizine Dihydrochloride and Montelukast Sodium in**	**Dual wavelength Method**	**Solvent: Methanol Detection wavelength:208 nm, 214.4 nm (MKT) 355 nm, 390 nm (LEV)**	**20**

	Tablet Dosage Form		**% Recovery: 99.11 % (LEV) 98.62 % (MKT)** **Linearity range: 4–28 µgmL-1 for both drugs** **r2 value: 0.9990 (LEV at 208 nm, 214.4 nm)** **0.9989 (MKT at 355nm, 390 nm)** **LOD (µg/mL): 0.374 (LEV) 0.273 (MKT)** **LOQ (µg/mL): 1.249 (LEV) 0.190 (MKT)** **%RSD (Precision, Accuracy): less than 2**	
8	**Levocetirizine Dihydrochloride and Montelukast Sodium in Tablet Dosage Form**	**Bivariate calibration algorithm Method**	**Solvent: Methanol** **Detection wavelength: 220 nm, 230 nm** **Recovery: 99.41 % (LEV) 100.58 % (MKT)** **Linearity range: 4–28µg mL-1 for both drugs** **r 2 value: 0.9991 (LEV) 0.9992 (MKT)** **LOD (µg/mL): 0.261 (LEV) 0.079 (MKT)** **LOQ (µg/mL):0.893 (LEV) 0.264 (MKT)** **% RSD (Precision, Accuracy): less than 2 %**	**20**
9	**Levocetirizine Dihydrochloride and Montelukast Sodium in Tablet Dosage Form**	**Second derivative spectrophotometric method**	**Solvent: Methanol** **Detection wavelength: 244 nm, 293.2 nm, 335.6 nm** **% Recovery: 99.16 % (LEV at 244 nm)** **100.53 % (MKT at 293.2 nm)** **102.00 % (MKT at 335.6 nm)** **Linearity range: 4–28 µgmL-1 for both drugs** **r 2 value:0.9990(LEV at 244nm)** **0.9986 (MKT at 293.2 nm, 335.6 nm) LOD (µg/mL): 1.177 (LEV at 244 nm)** **0.785 (MKT at 293.2 nm)** **0.884 (MKT at 335.6 nm) LOQ(µg/mL): 3.921 0(LEVat 244nm)** **2 .61 (MKT at 293.2nm)** **2.818 (MKT at 335.6nm)** **%RSD (Precision, Accuracy): less than 2%**	**20**

Various spectrophotometric methods have evolved over time for the estimation of Levocetirizine and Montelukast Sodium levels in combined pharmaceutical formulations. The developed methods, including the Multi-wavelength method, Absorbance correction method, Derivative spectrophotometric method, AUC curve method, Simultaneous equation method, Bivariate calibration algorithm method, Dual-wavelength method, Ratio difference method, and Absorbance Factor method, have been demonstrated under different analytical conditions. Upon scrutinizing spectrophotometric methods designed for estimating Montelukast Sodium and Levocetirizine in combined dosage forms, it was observed that methanol emerged as the most commonly used solvent. The detection wavelengths ranged from 200 to 400 nm.

The Simultaneous equation method, also known as Vierordt's method, is frequently employed due to its simplicity and time efficiency compared to other methods that necessitate laborious sample preparation. The Derivative spectrometry method, extensively utilized, addresses the issue of interference in co-formulated drugs due to spectral overlapping. Derivative spectra exhibit superior resolution, aiding in the identification of compounds with closely situated λ max values. The Bivariate calibration algorithm method, developed by Noha S. Rashed *et al*. in 2015, emerged as the most sensitive method, boasting the lowest LOD values and a linearity range of 4-20 µg/ml for Montelukast Sodium and 2-10 µg/ml for Levocetirizine, respectively **[20]**.

The ratio derivative spectroscopic method, with the advantage of selecting a suitable divisor concentration, prevails over other methods in terms of sensitivity and accuracy. Importantly, all the developed spectrophotometric methods for estimating Levocetirizine and Montelukast Sodium were characterized by their simplicity, precision, accuracy, and reproducibility.

CHROMATOGRAPHY:

A comprehensive study and summary of chromatographic methods for the estimation of Levocetirizine and Montelukast Sodium in both bulk and combined pharmaceutical dosage forms were conducted as mentioned in **Table 2**.

Table 2: Chromatographic Method

Sr. No.	Drug Combination	Method	Descriptions	Reference
1.	Montelukast Sodium and Levocetirizine Dihydrochloridein Tablet Dosage Form	HPTLC	Mobile phase: Ethyl acetate: methanol: triethylamine (5:5:0.02 v/v/v) Stationary phase: Silica gel 60F254 aluminum plate (20x 10 cm) Detection wavelength:240 nm Run time: 7 min Internal standard: Paracetamol Rf value: 0.29, 0.50, 0.6 (LEV, MKT, PARA) Linearity range:400–1200 ng/spot (MKT) 200–600 ng/spot (LEV) LOD: 20.63 ng/spot (MKT) 21.12 ng/spot (LEV) LOQ: 62.5 ng/spot (MKT) 64 ng/spot (LEV) r 2 value:0.9993 (MTK), 0.9985 (LEV) % RSD (Precision, Accuracy): less than 2 % % Recovery: 90% to 120.0%	21
2	Levocetirizine Dihydrochloride and Montelukast Sodium in Tablet Dosage Form	RP HPLC	Mobile phase: Disodium hydrogen phosphate buffer (0.02M): Methanol (25:75 v/v) Stationary phase: BDS Hypersil C18column (250 mmx4.6mm) Detection wavelength: 231 nm, Flow rate: 1.0 mL/min Retention time: 3.558 min, 7.450 min (LEV, MKT) Linearity range: 1 – 10 µg/ mL (LEV) 2 – 20 µg /mL (MKT) LOD: 0.5 µg/mL (LEV), 0.2 µg/mL (MKT) LOQ: 0.8 µg/mL (LEV), 0.6 µg/mL (MKT) r 2 value: 0.9987 (LEV), 0.9980 (MKT) % RSD (Precision): less than 2% % Purity:99.76 % (LEV) 100.15 % (MKT)	22
3	Montelukast Sodium and Levocetirizine Hydrochloride in Tablet Dosage Form	HPTLC	Mobile phase:n- Hexane: chloroform: methanol: acetic acid (3.5:5.0:1.2:0.3 v/v/v/v) Stationary phase: Silica gel 60 F254 aluminum sheets (10 x 10 cm) Detection wavelength: 302 nm Rf value: 0.29, 0.65 (MKT, LEV) Linearity range: 5-15 µg/mL (MKT) 2.5-7.5 µg/mL (LEV) LOD (ng/spot): 100, 110(MKT, LEV) LOQ (ng/spot): 210, 240 (MKT, LEV) r 2 value:0.9993, 0.9998 (MKT, LEV) % RSD (Precision): 0.28, 0.31(MKT, LEV) % Purity: 99.02% (MKT), 100.04% (LEV)	12
4	Montelukast Sodium and Levocetirizine Hydrochloride in Tablet Dosage Form	RP HPLC	Mobile phase: Buffer: Methanol (35: 65 v/v) Stationary Phase: Inertsil ODS column (250 x 4.6 mm, 5µ) Detection wavelength: 234 nm Flow rate: 1.5 mL/min	12

			Run time: 10 min Linearity range: 4-20 µg/mL (MKT) 2-10 µg/mL (LEV) LOD: 1.85µg/mL(MKT), 1.63 µg/mL(LEV) LOQ: 3.42 µg/mL(MKT), 4.14 µg/mL (LEV) r 2 value: 0.999847 (MKT) 0.999824 (LEV) %RSD (Precision): 0.5 (MKT), 0.3 (LEV) % RSD (Accuracy): 0.4 (MKT), 0.3 (LEV) % Purity: 99.02% (MKT), 100.04% (LEV)	
5	Montelukast Sodium and Levocetirizine Dihydrochloride in Liquid Dosage Forms	RP UPLC	Mobile phase: Potassium dihydrogen phosphate(2.72 gm) to 1 L of Milli Q water Stationary Phase: AQUITY BEH phenyl column (50mm x 2.1mm, 1.7µm) Diluent: Water: methanol (10:90 v/v) Flow Rate:0.4 mL/min Detector: PDA (photo diode array) detector Detection wavelength: 231 nm Run time:3.5 min Retention Time:0.587 min, 1.626 min (LEV, MKT) r 2 value: 0.999 for both API % RSD (Accuracy, Precision): less than2.0 %	23
6	Montelukast Sodium and Levocetirizine Dihydrochloride in Tablet Dosage Form	HPTLC	Mobile phase: Chloroform: methanol: toluene: glacial acetic acid (10:5:3:0.5v/v/v/v) Stationary Phase: Silica gel 60 F254aluminum plate (10 x 10 cm) Detection wavelength: 269.0 nm, 302 nm Linearity range: 400-4500 ng LOD (µg/mL): 1.536, 2.864 (MKT, LEV) LOQ (µg/mL): 2.536, 3.453 (MKT, LEV) r 2 value: 0.9998 Rf value: 0.89 and 0.64 (MKT and LEV)	24
7	Montelukast and Levocetirizine in Liquid dosage Form	RP HPLC	Mobile phase: Phosphate buffer: acetonitrile (55:45) Stationary Phase: Hypersilwaters C18 column (4.6mm × 250mm ×5µm) Flow rate: 1 mL/min Detection wavelength: 228 nm Run time: 6 min Retention time: 2.47 min, 2.823 min (MKT, LEV) Linearity range:40-20 µg/mL for MKT 25-75 µg/mLfor LEV r 2 value: 0.999 % Recovery: 99.10 %, 99.38 % (MKT, LEV) % RSD (Accuracy, Precision): less than 2 % % Purity:98.65%,99% (MKT, LEV)	25
8	Montelukast Sodium and Levocetirizine Hydrochloride in	HPTLC	Mobile phase: Chloroform: benzene: methanol: toluene (5:7.2:1:0.2 v/v/v/v) Stationary phase: Silica gel 60F 254 aluminium sheets (20 x 10 cm) Detection wavelength: 286 nm	26

	Tablet Dosage Form		**Linearity range: 500-1500 ng spot-1 (MKT) 1000-5000 ng spot-1 (LEV) r 2 value: 0.9992, 0.9995 LOD: 170 ng/spot, 20 ng/spot (MKT, LEV) LOQ: 570 ng/spot, 70 ng/spot (MKT, LEV) (MKT, LEV) . % RSD (Peak area value): 1.09, 1.17 (MKT, LEV) % Purity: 100.40 % (MKT) 98.40 % (LEV)**	
9	**Levocetirizine Dihydrochloride and Montelukast Sodium in Tablet Dosage Form**	**RP HPLC**	**Mobile phase: Phosphate buffer: acetonitrile (40:60% v/v) Stationary phase: Hypersil BDS C18column (250×4.6 mm, 5µm) Detection wavelength: 230 nm Flow rate: 1.0 mL/min Run time: 10 min Retention time:3.06 min,6.76 min (LEV, MKT) Linearity range:12.56–37.68 µg/mL (LEV) 23.78–71.20 µg/mL (MKT) LOD: 0.079 µg/mL (LEV), 0.156 µg/mL (MKT) LOQ: 0.239 µg/mL (LEV), 0.473 µg/mL (MKT) r 2 value: 0.9998 % Purity: 99.55 %(LEV), 98.37 % (MKT) %RSD (Precision, Accuracy): less than 2 %**	**27**
10	**Levocetirizine and Montelukast Sodium in Tablet Dosage Form**	**RP HPLC**	**Mobile phase: Acetonitrile: ammonium acetate (65:35 % v/v), Stationary Phase: Atlantis C18 analytical column (4.6×150 mm, i.d.5µm) Detection Wavelength: 230nm Flow rate: 1.0 mL/min Run time: 13 min Retention time: 3.03min, 6.28 min (LEV, MKT) Linearity range:25-75 µg/mL (LEV) 50-150 µg/mL(MKT) LOD: 0.05 µg/mL, 0.10 µg/mL (LEV, MKT) LOQ: 0.17 µg/mL, 0.33 µg/mL(LEV, MKT) r 2 value: 0.999 % Purity: 99.2%- 102.4 % %RSD (Precision, Accuracy): less than 2 %**	**28**
11	**Levocetirizine dihydrochloride and Montelukast sodium in Tablet Dosage Form**	**RP HPLC**	**Mobile phase: Acetonitrile: 0.5% triethylamine in water (90:10 v/v) Stationary Phase: Phenomex-luna 5µ C8 (2) column (100Å, 250 X 4.6 mm) Flow rate: 0.8 mL/min Detection Wavelength: 231 nm Retention time: 3.8 and 5.2 min (LEV and MKT) Linearity range (µg/mL): 2- 32, 3-30(LEV, MKT) LOD (µg/mL): 0.00028, 0.0032(LEV, MKT) LOQ (µg/mL): 0.00086, 0.0094 (LEV, MKT) r 2 value:0.9997, 0.9994(LEV, MKT) % Purity: Montek-LC-99.18%,100.26% (LEV, MKT) Montair LC-99.83%, 98.28% (LEV, MKT) % RSD (Accuracy, Precision): below 2.0 %**	**29**

12	**Levocetirizine Dihydrochloride and MontelukastSodium in Tablet Dosage Form**	**HPTLC**	**Mobile phase: Toluene: ethyl acetate: methanol: ammonia (2.5: 7: 2.5: 1,v/v/v/v) Stationary phase: Silica gel60 F254aluminum plate(20 × 10 cm) Detection wavelength: 231 nm Run time: 25 min Rf value: 0.31, 0.44 (LEV, MKT) Linearity range:500-2500 ng spot-1 (LEV) 1000-5000 ng spot-1 (MKT) r 2 value: 0.9981 (LEV) 0.9982 (MKT) % (Precision, Accuracy): less than 2% % Purity: 99.72 % (LEV) 100.19 % (MKT) LOD: 90 ng spot-1 (LEV), 50 ng spot-1 (MKT) LOQ: 200 ng spot-1 (LEV), 110 ng spot-1 (MKT)**	**22**
13	**Levocetirizine Hydrochloride and Montelukast Sodium in Tablet Dosage Form**	**HPTLC**	**Mobile phase: Toluene: Ethyl Acetate: Methanol (2.5: 5: 2.5v/v/v) Stationary Phase: Silica gel aluminum plate 60 F254 (20 ×10 cm) Detection wavelength: 240 nm Rf value: 0.17, 0.76 (MKT, LEV) Linearity range:2-10µL for both API r 2 value: less than0.99 % RSD (Precision):less than 2 % Purity: 99.14 % (LEV), 99.28 % (MKT) LOD (ng band-1): 44.43, 29.12 (MKT, LEV) LOQ (ng band- 1):134.66, 88.24(MKT, LEV)**	**30**

The assessment of Levocetirizine and Montelukast Sodium levels in combined dosage forms has been conducted through various chromatographic methods. Upon scrutinizing the plethora of chromatographic methods designed for quantifying Levocetirizine and Montelukast Sodium in combined pharmaceutical formulations, it is discerned that the RP-HPLC method holds prominence over other chromatographic methods due to its noteworthy specificity and sensitivity. The optimization of the developed analytical methods has been systematically undertaken under diverse analytical conditions, encompassing different mobile phases and pH variations. The criteria for optimization include resolution, asymmetric factor, and peak area for both Levocetirizine (LEV) and Montelukast Sodium (MKT). Notably, methods utilizing water and methanol as the mobile phase have been identified as cost-effective.

For the detection of compounds within the wavelength range of 200-400 nm, Photodiode-Array Detectors (PDA) are commonly employed. The RP-HPLC method, as reported by R. Swethan Babu *et al*. in 2012, stands out as the most sensitive method among all developed techniques, demonstrating the lowest Limit of Detection (LOD) values for Levocetirizine and Montelukast Sodium. Utilizing an optimized mobile phase of acetonitrile (90%) with 0.5% triethylamine in water (10%), the separation was successfully accomplished on a Phenomenex Luna 5µ C8 Column (100Å, 250 X 4.6 mm) **[29]**. Furthermore, the RP-UPLC method, developed by J. Bharati *et al*. in 2015, emerges as a rapid and efficient technique for estimating Montelukast Sodium and Levocetirizine. This method exhibits a commendable resolution between the two drugs, with a minimal run time of 3.5 minutes and retention times of 0.587 minutes and 1.626 minutes for Levocetirizine and Montelukast Sodium, respectively. The mobile phase employed in the experiment consisted of Potassium dihydrogen phosphate (2.72 gm) dissolved in 1 L of Milli Q water, and the chromatographic column utilized was the AQUITY BEH Phenyl column (50mm x 2.1mm, 1.7µm), operating at a flow rate of 0.4 mL/min **[23]**.

Considering the enhanced sensitivity and selectivity, along with the expedited method and minimal solvent consumption, the RP-UPLC technique emerges as the most suitable approach. Therefore, it should be regarded as the primary method for the determination of Levocetirizine and Montelukast Sodium, surpassing the RP-HPLC and HPTLC techniques. The substantial recovery values observed in the HPTLC method further affirm the suitability of this developed approach for determining the mentioned pharmaceuticals in their combined dosage form. Optimal Rf values were achieved in the HPTLC methods as reported by Ambadas Rote *et al*. (2011) and Atul S. Rathore *et al*. (2010) **[21, 22]**. Apart from method development, Deshpande *et al*. (2016) and Jitendra K. Sonawane *et al*. (2020) conducted a force degradation study in their

respective works to assess the specificity and stability of the drugs **[27, 31]**. Under stress conditions of oxidation, photolysis, acid hydrolysis, base hydrolysis, and thermal degradation, both drugs underwent evaluation. The analytical methods developed effectively resolved the obtained degradation products, affirming the specificity of the employed techniques.

ANALYTICAL METHODS FOR ESTIMATION OF MONTELUKAST SODIUM WITH OTHER DRUGS IN COMBINED DOSAGE FORM:

Apart from Levocetirizine, Montelukast Sodium is commercially available in combination with various other drugs in pharmaceutical formulations. The most frequently encountered drugs co-formulated with Montelukast Sodium include Doxofylline, Fexofenadine Hydrochloride, Theophylline, Ebastine, Bambuterol Hydrochloride, and Loratadine. A comprehensive investigation into simultaneous determination methods, encompassing both spectroscopic and chromatographic approaches for Montelukast in conjunction with these drugs, has been conducted and summarized in **Table 3**.

Table 3: Analytical Methods for Estimation of Montelukast Sodium

Sr. No.	Drug Combination	Method	Descriptions	Reference
1	Montelukast Sodium and Fexofenadine Hydrochloride in Tablet Dosage Form	RP-HPLC	Mobile phase: Sodium acetate buffer: acetonitrile: methanol (25:35:40) Stationary Phase: X-bridge C18 column (250 mm x 4.6 mm, 5 mm) Flow rate: 1.0 mL/min Detection wavelength: 210 nm Retention time: 3.43 min (MKT) 8.22 min (FEX) Linearity range: 12.5-37.5 mg/mL (MKT) 150-450 mg/mL (FEX) r2 value: 0.9997(MKT) 0.9994 (FEX) % RSD (Accuracy, Precision): less than 2 % % Purity: 99.73 % (MKT) 100.06 % (FEX)	31
2	Theophylline and Montelukast Sodium in Tablet Dosage Form	RP- HPLC	Mobile Phase: Methanol Detection Wavelength: 210nm Stationary Phase:ODS C- 18 Kromacil column (250 mm × 4.60 mm) Retention time: 4.173 min (TPH) 2.910 min (MKT) r 2 value: 0.9960 for both API %RSD (Accuracy, Precision): less than 2 %	32
3	Montelukast Sodium and Bambuterol Hydrochloride in Tablet Dosage Form	Dual wavelength method	Solvent: Chloroform Detection wavelength:322.0 nm (MKT) 266.0 nm(BAM) % Recovery: 98.9 %-99.2 % %RSD (Accuracy, Precision): less than 2 % Linearity range: 10-80 µg/mL for MKT 40-240 µg/mL for BAM r 2 value:0.9997 (BAM) 0.9998 (MKT)	33
4	Montelukast and Ebastine in Tablet Dosage Form	RP-HPLC	Mobile phase: Methanol: water (0.1% triethylamine) (90:10) Stationary Phase: Grace Smart RP C18 column (250 mm × 4.6 mm I.D. 5µ particle size) Flow rate: 1.2 mL/min Detection wavelength: 246 nm Retention time: 2.36 min (MKT) 4.90 min (EBA) Linearity range: 5-15 µg/mL(MKT, EBA) r 2 value: 0.999	34
5	Montelukast Sodium and FexofenadineHydrochloride in Tablet Dosage Form	RP-HPLC	Mobile phase: Methanol:0.1% o-phosphoric acid (90:10 v/v) Stationary Phase: Lichrospher® 100RP-18e column Flow rate: 1 mL/min Detection wavelength: 226 nm Retention time: 10.16 min (MKT) 12.03 min(FEX) Linearity range: 2-10 µg/mL (MKT) 24-120 µg/mL (FEX) % Recovery: 99.09, 99.81% (MKT, FEX)	35
6	Montelukast Sodium and Loratadinein Tablet Dosage Form	HPLC	Mobile phase: Sodium phosphate buffer: acetonitrile (20:80, v/v) Internal standard:5- Methyl 2-nitrophenol Stationary phase: Symmetry C18 column Flow rate: 1.0 mL/min.	36

			Detection wavelength: 225 nm **Linearity range: 100-600mg/mL (MKT) 116-580mg/mL (LTD)** **r 2 value: less than 1** **%RSD (Accuracy, Precision): less than 2%**	
7	**Montelukast Sodium and Doxofyllinein Tablet Dosage Form**	**HPLC**	**Mobile phase: Methanol: phosphate buffer (10:90)** **Stationary Phase: C18 analytical column (150 mm × 4.6 mm, 5µm)** **Flow rate: 1.0 mL/min** **Detection wavelength: 280 nm** **Run time: 20 min** **Retention time: 4.78 min (MKT) 1.97 min (DOX) Linearity range:0.005-0.015 mg/mL (MKT) 0.2-0.6 mg/mL (DOX)** **r2 value: 0.9941 (MKT) 0.9935 (DOX)** **% Purity: 99.8 %-100.3%**	**37**
8	**Montelukast and Ebastine in Tablet Dosage Form**	**RP-HPLC**	**Column: Grace Smart RP C18 column (250 mm × 4.6 mm I.D. 5µ particle size)** **Mobile phase: Methanol: water(0.1%triethylamine) (90:10)** **Flow rate: 1.2 mL/min** **Detection wavelength: 246 nm** **Retention time: 2.36 min (MKT) 4.90 min (EBA) Linearity range: 5-15 µg/mL(MKT, EBA)** **r 2 value: 0.999**	**38**

ANALYTICAL METHODS FOR ESTIMATION OF LEVOCETIRIZINE WITH OTHER DRUGS IN COMBINED DOSAGE FORM:

Table 4: Analytical Methods for Estimation Of Levocetirizine

Sr. No.	Drug Combination	Method	Descriptions	Reference
1	**Ambroxol and Levocetirizine in Tablet Dosage Form**	**RP-HPLC**	**Mobile Phase: 0.01M Potassium dihydrogen orthophosphate: Acetonitrile (60:40 v/v)** **Stationary phase: Phenomenex C18 column (150 × 4.6 mm, 5µ)** **Flow rate: 1 ml/min** **Detection wavelength: 230nm** **Retention time: 3.60min (LEV) 4.68min (AMB)** **Linearity range:12-120 µg/mL for AMB 1- 10µg/mL for LEV** **r2 value: 0.9991 for both drugs** **% Purity: 100.2 %, 98.2 % (AMB, LEV)**	**39**
2	**Levocetirizine Dihydrochloride and Phenylephrine Hydrochloride in**	**First-order derivative Spectrophotom etric method**	**Solvent: Methanol** **Detection wavelength: 240nm, 283.2nm** **% Purity: Levocet-D: 99.66 % (LEV, PHE) Rinostat-L: 99.63 %, 100.3 % (LEV, PHE)** **%RSD (Accuracy, Precision): less than 2 %**	**40**

	Tablet Dosage Form		**Linearity range:4–24 µg/mL (LEV) 8–48 µg/mL (PHE)** **r 2 value: 0.9964 ,0.9972 (LEV, PHE)**	
3	**Levocetirizine and Phenylephrine Hydrochloride in Tablet Dosage Form**	**RP-HPLC**	**Mobile phase: Methanol: potassium dihydrogen phosphate buffer(70:30)** **Stationary Phase: Luna 5u C18column (20mm X 4mm)** **Detection wavelength: 251nm** **Flow rate: 1.0 mL/min** **Retention time: 8.42 min (LEV) 2.70 min (PHE)** **Linearity range: 30 -150%** **r 2 value:0.9984, 0.9983 (LEV, PHE)** **% Recovery: 100.64 % (LEV) 100.40 % (PHE)**	**41**
4	**Levocetirizine hydrochloride and Phenylephrine Hydrochloride in Tablet Dosage Form**	**First-order derivative method**	**Solvent: Methanol** **Detection wavelength: 216 nm, 230 nm** **% Purity: 99.19 % (PHE) 99.88 % (LEV)** **Linearity range: 3-9µg/mL (LEV) 6-18 µg/mL (PHE)** **r 2 value: 0.9993 (LEV) 0.9996 (PHE)** **% RSD (Precision, Accuracy): less than 2**	**42**
5	**Ambroxol Hydrochloride and Levocetirizine Dihydrochloride in Tablet Dosage Form**	**Simultaneous equation method**	**Solvent: Distilled water** **Detection wavelength: 242 nm, 231 nm** **% Recovery: 99.13 to 99.52% (AMB) 98.88 to 99.42% (LEV)** **%RSD (Accuracy, Precision): less than 2 %** **Linearity range:10-50 µg/mL (AMB) 8-24 µg/mL (LEV)** **r 2 value: 0.999 for both API**	**43**
6	**Levocetirizine and Phenylephrine in Tablet Dosage Form**	**RP-HPLC**	**Mobile phase: Methanol: water (50:50 v/v)** **Stationary Phase: Eclipse Plus C18 column (4.6 mm × 150 mm)** **Flow rate: 1 mL/min** **Detection wavelength: 277 nm** **Retention time: 3.37 min (LEV) 6.40 min (PHE)** **Linearity range: 5-25µg/mL (LEV) 2.5-12.5µg/mL (PHE)** **r 2 value: 0.999**	**44**
7	**Levocetirizine and Pseudoephedrine in Tablet Dosage Form**	**Absorbance ratio method**	**Solvent: Distilled water** **Detection wavelength: 231 nm, 257 nm** **Linearity range: 5-30 µg/mL (LEV) 120-960 µg/mL (PSEUDO)** **r 2 value: 0.9994 (LEV) 0.9993 (PSUEDO)** **% Purity: 101.81 (LEV) 100.04 (PSUEDO)** **%RSD (Accuracy, Precision): less than 2 %**	**45**
8	**Levocetirizine and Pseudoephedrine in Tablet Dosage**	**Simultaneous equation method**	**Solvent: Distilled water** **Detection wavelength:231 nm, 257 nm** **Linearity range:5-30 µg/mL (LEV) 120-960 µg/mL (PSEUDO)** **r 2 value: 0.9992 (LEV) 0.9991 (PSUEDO)** **% Purity: 100.03 % (LEV) 100.31 % (PSUEDO)** **% RSD (Accuracy, Precision): less than 2 %**	**46**

ANALYTICAL METHODS FOR ESTIMATION OF LEVOCETIRIZINE AND MONTELUKAST SODIUM WITH OTHER DRUGS IN COMBINED DOSAGE FORM:

A comprehensive overview of studies conducted for the concurrent determination of Montelukast Sodium and Levocetirizine in combination with various other drugs are summarized in **Table 5**.

Table 5: Analytical Methods for Estimation of Levocetirizine And Montelukast Sodium

Sr. No.	Drug Combination	Method	Descriptions	Reference
1	Acebrophylline, Montelukast and Levocetirizine DihydrochlorideForm	Simultaneous equation method	Solvent: Methanol Detection wavelength:250.14 nm ((λ max of ABP) 284.79 nm((λ max of MKT) 231.27 nm ((λ max of LEV) Linearity range: 6-18 µg/mL (ABP, MKT) 3- 12µg/mL for (LEV) r2 value: 0.999 for all drugs % Purity: 100 % (ABP) 101 % (MKT) 99 %(LEV) % RSD (Precision): less than 2 %	46
2	Montelukast Sodium, Levocetirizine Dihydrochloride and Acebrophylline in Tablet Dosage Form	RP-HPLC	Mobile phase: Methanol, acetonitrile and 20 mM ammonium acetate buffer (60:30: 10v/v) Stationary Phase: Hypersil ODS C18 column (250 × 4.6 mm, 5µm) Flow rate: 0.8 mL/min Elution time: 10 min Linearity range: 2-12 µg/mL for MKT and LEV 20-120µg/mL ABP r2 value: 0.999 % Purity: 99.89(LEV) 100.30%(ABP) 100.59% (MKT) % RSD (Precision, Accuracy): less than 2 %	47
3	Doxofylline, Montelukast, and Levocetirizine Dihydrochloride in Tablet Dosages Form	RP-HPLC	Mobile phase: Ammonia acetate Buffer: ACN) pH 3.5 Stationary Phase: C18 (150 x 250 x 4.6 mm) Agilent column Retention time: 4.425 min (DOX) 7.409 min (MKT) 8.558 min (LEV) Linearity range: 10-15 µg/mL for all drugs r2 value: less than 1 % Purity: 101.21 % (DOX) 98.90 % (MKT) 100.40 % (LEV)	48

CONCLUSION:

In recent years, there has been a proliferation of analytical methods for the quantitative estimation of drugs in combined pharmaceutical dosage forms, employing both spectrophotometric and chromatographic techniques. This article provides a comprehensive summary of the analytical methods reported for the simultaneous estimation of Levocetirizine and Montelukast Sodium. The investigations cover assessments in bulk, combined pharmaceutical formulations, and combinations with various other drugs available in the market. A literature review indicates that RP-HPLC emerges as the most frequently employed method, surpassing different spectroscopic and chromatographic alternatives for the determination of these drugs. RP-UPLC, equipped with a PDA detector, showcases excellent resolution between the two drugs and stands out as the swiftest analytical method for pharmaceutical compound determination. Consequently, it is reasonable to assert that both RP-UPLC and RP-HPLC should be the preferred methods, considering their superior sensitivity, rapidity, and reliability. Although spectrophotometric methods are characterized by their economical nature, simplicity, and high levels of accuracy and precision, they serve as viable alternatives to mitigate the complexities associated with chromatographic methods. Chromatographic techniques, due to their intricate nature, time-consuming processes, costly setup requirements, and the need for skilled operators, can be complemented by the more straightforward and cost-effective spectrophotometric methods. In summary, both spectrophotometric and chromatographic methods demonstrate efficacy in simultaneously estimating pharmaceutical drug products in bulk and combined pharmaceutical dosage forms. All developed methods for Levocetirizine and Montelukast Sodium underwent validation according to ICH guidelines, meeting the acceptance criteria.

CONFLICT OF INTEREST:

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