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Review Article

# Analytical Methods for Determination of Salbutamol, Ambroxol and Fexofenadine

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## Abstract

In this review article, we will introduce all reported methods that have been developed for determination of certain a nti-tussive and anti-histaminic drugs such as salbutamol, ambroxol and fexofenadine in their pure form, combined fo rm with other drugs, combined form with degradation products, and in biological samples. We also will shed the ligh t on the most important combination of drugs that are used for treatment of asthma and related diseases.

**Keywords:** salbutamol; ambroxol; fexofenadine

## 1. Methods for analysis of Salbutamol

### 1.1. Chromatographic methods:

#### 1.1.1. HPLC methods:

| Stationary phase | Mobile phase | Detection | Specification | REF |
|---|---|---|---|---|
| **a Nova-pak $C_{18}$ column** | acetonitrile: water (15:85, v/v) and acetonitrile: water (30:70, v/v) | 196 and 210 nm | Determination of salbutamol and clenbuterol residues in swine serum and muscle. | [1] |
| **Acquity UPLC(®) BEH $C_{18}$ column** | 0.1% formic acid solution/methanol (95:5, v/v). | 165 and 204nm | Determination of clenbuterol, salbutamol and ractopamine in milk by reversed-phase liquid chromatography tandem mass spectrometry with isotope dilution. | [2] |
| **$C_{18}$ column** | acetonitrile/0.1% formic acid in aqueous solution | 2 MRM via an electrospray ionization source in a positive mode | Rapid analysis of three β-agonist residues in food of animal origin by automated on-line solid-phase extraction coupled to liquid chromatography and tandem mass spectrometry. | [3] |
| **$C_{18}$ column** | methanol/acetic acid/$H_2O$ | 198 and 215 nm | Novel method for the rapid and specific extraction of multiple β2 -agonist residues in food by tailor-made Monolith-MIPs extraction disks and detection by gas chromatography with mass spectrometry. | [4] |
| **octadecylsilane column** | water and Acetonitrile (40:60 v/v) | 239 and 227 nm | Reverse phase isocratic HPLC method for simultaneous estimation of salbutamol sulphate and beclomethasone dipropionate in rotacaps formulation dosage forms | [5] |
| **$C_8$, 5µm; 250 mm × 4.6 mm column** | disodium hydrogen-ortho-phosphate buffer (pH 4.5) and methanol | 220 nm | Development of HPLC method for simultaneous estimation of ambroxol, guaifenesin and salbutamol in single dose form | [6] |

| | | | | |
|---|---|---|---|---|
| **$C_{18}$ column** | acetonitrile : methanol : ammonium hydroxide (10 : 85 : 5 v/v/v) | 254 nm | Two-dimensional TLC method for identification and quantitative analysis of salbutamol and related impurities in pharmaceutical tablet formulation | [7] |
| **ODS column** | methanol-phosphate buffer (pH 7) 6:4 | 230 nm | Simple HPLC Method for the Analysis of Some Pharmaceuticals | [8] |
| **SHISEIDO $C_{18}$ column (250 x 4.6mm i.d; 5µm)** | acetonitrile and potassium dihydrogen phosphate adjusted to a pH- 4 in the ratio of 70 : 30 (% v/v) | 215 nm | Simultaneous estimation of salbutamol, ambroxol and guaifenesin in tablet dosage forms by using RP-HPLC | [9] |
| **Thermo $C_{18}$ column (4.6 mm i.d × 250 mm)** | acetonitrile: 0.025M potassium dihydrogen orthophosphate buffer (pH adjusted to 3.5 with orthophosphoric acid) | 227 and 244 nm | Development and Validation of Spectrophotometric and HPLC Method for the Simultaneous Estimation of Salbutamol Sulphate and Prednisolone in Tablet Dosage Form | [10] |
| **Inertsil ODS $C_{18}$ column** | phosphate buffer pH 6.3 and Methanol: Water: Acetate Buffer 60:35:05 v/v | 239 nm | Development and Validation of Stability-indicating RP-HPLC method for the simultaneous analysis of Salbutamol, Theophylline and Ambroxol | [11] |
| **NX $C_{18}$ column (250 × 4.6 mm, 5 µm)** | acetonitrile-0.25 M sodium hexanesulphonate-0.2 M ammonium acetate, and pH 3.0-water (35:4:10:51, % v/v/v/v) | 254 nm | A Versatile HPLC Method for the Simultaneous Determination of Bromhexine, Guaifenesin, Ambroxol, Salbutamol/Terbutaline, Pseudoephedrine, Triprolidine, and Chlorpheniramine Maleate in Cough–Cold Syrups | [12] |
| **Agilent ODS 5 µm, 4.6×250 mm, $C_{18}$** | acetonitrile and water (adjusted to pH = 3 using orthophosphoric acid) (90: 10, v/v) | 220 nm | Solid-Phase Extraction and HPLC-DAD for Determination of Salbutamol in Urine Samples | [13] |
| **$C_{18}$ column (150 mm × 4.6 mm; 5 µm)** | Sodium dihydrogen phosphate buffer pH 3.0: Acetonitrile: Methanol in the ratio of 65:10:25 | 276 nm | Development and Validation of RP-HPLC Method for the Simultaneous Estimation of Salbutamol Sulphate, Guaifenesin and Ambroxol Hydrochloride in Oral Liquid Dosage form | [14] |
| **reversed-phase $C_{18}$ column (150 mm × 4.6 mm; 5 µm)** | isocratic solvent system consisting of methanol and de-ionized water in ratio of 40:60 | 298 nm | Simultaneous HPLC method development and validation for estimation of salbutamol in combination with vasicine | [15] |
| **Lichrosorb RP-$C_{18}$ analytical column (4.6 × 200 mm, 5 µm)** | CH3OH/(NH4)H2PO4 (67 mM) (pH 3.0) / triethyl amine (TEA), 50/50/0.02 (v/v/v %)} | 228 and 310 nm | A new reverse phase HPLC method with fluorescent detection for the determination of salbutamol sulfate in human plasma | [16] |
| **Hibar R250 × 4.6 mm** | methanol : water (50:50, v/v) | 274 nm | A new RP-HPLC method development for simultaneous estimation of salbutamol sulphate, theophylline and furosemide. | [17] |
| **Shim-pack $C_{18}$ (250 mm×4.6mm, 5µ) column** | acetonitrile: 0.1M potassium dihydrogen phosphate buffer (35:65) with pH adjusted to 3.0 | 225 nm | Estimation of salbutamol sulfate (SAL) in pharmaceutical dosage forms. | [18] |
| **SS Wakosil-II $C_{18}$ column** | acetonitrile, methanol and phosphate buffer, pH 4 in the ratio 60:20:20 v/v | 224 nm | Simultaneous Determination of Salbutamol Sulphate and Bromhexine Hydrochloride in Tablets by Reverse Phase Liquid Chromatography | [19] |

### 1.1.2. Thin Layer Chromatographic methods:

| Stationary phase | Mobile phase | Detection | Specification | REF |
|---|---|---|---|---|
| **silica gel G60 F254** | methanol: ethyl acetate: toluene:ammonia (3:1:3:0.15) | 232 nm | A sensitive high-performance thin layer chromatography method for simultaneous determination of salbutamol sulphate and beclomethasone dipropionate from inhalation product | [20] |
| **silica gel 60 F254** | ethylacetate: hexane: methanol: ammonia (65:35:15:2, | 227 nm | Simultaneous Determination of Guaifenesin, Salbutamol Sulfate or Dextromethorphan HBr and Guaifenesin Impurity (Guaiacol) by HPTLC Method | [21] |
| **aluminium plates of silica gel 60 F254** | acetone: methanol: formic acid (9:3:0.01) | 275 nm | HPTLC-Densitometric and RP-HPLC method development and validation for determination of salbutamol sulphate, bromhexine hydrochloride and etofylline in tablet dosage forms | [22] |

| | | | | |
|---|---|---|---|---|
| **silica gel GF254** | methanol: n-hexane (2: 1) | 227 nm | Thin Layer Chromatodraphy method for the determination of ternary mixture containing salbutamol sulphate, bromhexine hydrochloride and etofylline | [23] |
| **aluminum plates of silica gel 60 F254** | benzene: methanol: triethylamine (10:1.5:0.5 v/v/v) | 230 nm | Development and validation of simultaneous spectrophotometric and TLC-spectrodensitometric methods for determination of beclomethasone dipropionate and salbutamol in combined dosage form | [24] |
| **silica gel** | acetonitrile : methanol : ammonium hydroxide (10 : 85 : 5 v/v/v) | 254nm | Two-Dimensional TLC method for identification and quantitative analysis of salbutamol and related impurities in pharmaceutical tablet formulation | [25] |
| **silica gel 60 F254** | Ethyl acetate: Chloroform: methanol (6.0: 4.0:1.0 v/v/v) | 230 nm | UV Spectroscopic and Stability-Indicating TLC-Densitometric Method for Simultaneous Estimation of Salbutamol sulphate and Prednisolone in Pharmaceutical Dosage Form | [26] |

### 1.2. Spectrophotometric methods:

| Method of determination | Detection | Specification | REF |
|---|---|---|---|
| **Simultaneous equation** | 241, 224 and 245 nm | Simultaneous spectrophotometric estimation of Salbutamol, Theophylline and Ambroxol three component tablet formulation using simultaneous equation methods | [27] |
| **Cloud Point Method** | 558 and 564 nm | Application of Cloud Point Method for Spectrophotometric Determination of Salbutamol Sulphate and Methyldopa. | [28] |
| **Dual wavelength method** | (226-247 nm), (207-224 nm) | Different spectrophotometric methods manipulating ratio spectra for simultaneous determination of salbutamol and bromhexine in binary mixture. | [29] |
| **Simultaneous equation** | 410 nm | Simultaneous Spectrophotometric Determination of Salbutamol by Coupling with Diazotized 4-Aminobenzoic acid | [30] |
| **Flow injection** | 460 and 530 nm | Spectrophotometric Determination Methyldopa and Salbutamol by Oxidative Coupling, Cloud Point and Flow Injection in Pharmaceutical Formulations | [31] |
| **Simultaneous equation** | 274 and 224 nm | Novel simultaneous and second order derivatve method development of doxofylline and salbutamol sulphate in pure and fixed dose combination by uv – spectrophotometry | [32] |
| **zero crossing wavelength method** | 275, 262 and 243 nm | Derivative Uv-Spectroscopic determination of theophylline, salbutamol sulfate and glycerylguaicolate in syrup mixture | [33] |
| **zero crossing wavelength method** | 275, 262 and 243 nm | Development of methods for determining theophylline, salbutamol sulfate and glycerylguaiacolate in a simultanneous multicomponent syrup preparation using ultraviolet spectrophotometry derivative | [34] |

### 1.3. Spectrofluorimetric methods:

A basic, exact, reproducible and precise spectrofluorimetric strategy for estimation of Salbutamol sulfate (SAL) in mass medication and different measurements structures has been created. This technique depends on development of incorporation complex of SAL in β-cyclodextrin (BCD) which gives fluorescence at excitation frequency of 279.6 nm and emanation frequency of 609.8 nm in water. Arrangement of consideration complex of medication with BCD improves fluorescence power of medication prompts expanded affectability [35].

A basic, quick and touchy spectrophotometric technique for the assurance of sulbutamol in unadulterated structure and in various pharmaceutical arrangements has been created. The charge move (CT) response between salbutamol as electron giver and 2,6-dichloroquinone chlorimide (DCQ) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) as a π-electron acceptor have been spectrophotometrically contemplated. The ideal exploratory conditions for these CT responses have been concentrated cautiously. Brew's law is complied with over the focus scope of 1.0–30.0 μg ml−1 and 2.0–20.0 μg ml−1 for salbutamol utilizing DCQ and TCNQ, individually. For more exact outcomes, Ringbom ideal fixation extend is determined and seen as 10.0 to 30.0 and 8.0 to 20 μg ml−1 for salbutamol utilizing DCQ and TCNQ, individually. The Sandell affectability is seen as 0.011 and 0.010 g cm−2 for salbutamol utilizing DCQ and TCNQ, separately, which show the high affectability of the proposed strategies. Relative standard deviations (R.S.D.) of 0.27 to 0.68% and 0.20 to 1.40% (n=5) were acquired for five reproduces of salbutamol utilizing DCQ and TCNQ, individually. The outcomes got by the two reagents are practically identical with those gotten by British pharmacopeia examine for the assurance of salbutamol in crude materials and in pharmaceutical arrangements [36].

### 1.4. Capillary electrophoresis methods:

A strategy for the assurance of clenbuterol and salbutamol in takes care of by capillary electrophoresis was set up. The states of test pretreatment and electrophoretic investigation were enhanced. The recuperations of clenbuterol were between 83.2 % and 94.5% with a discovery breaking point of 0.02? μg/mL, while the recuperations of salbutamol were somewhere in the range of 82.5% and 93.7% with a recognition cutoff of 0.03? μg/mL [37].

Another technique for sorption and centralization of salbutamol in pee joined to fine electrophoresis with UV identification was performed. The strategy depends on the sorption of salbutamol on dissolvable impregnated pitches that is set up by an impregnation procedure utilizing Aliquat 336 as extractant and XAD-4 sap as the base polymer. Group contemplates indicated an effective sorption/desorption results when the salbutamol arrangement contains NaOH 0.05 mol L− 1 and the eluent is 0.5 mol L− 1 NaCl. Linearity was acquired in the scope of 1000–10,000

ng mL− 1 of salbutamol. The constraint of measurement was 999 ng mL− 1. The dissolvable impregnated gum was utilized for 10 cycles without a huge loss of the salbutamol measurement limit. The strategy was applied to examine salbutamol in pee tests at levels valuable for global wellbeing associations [38].

## 2. Metods for analysis of Ambroxol

### 2.1. Chromatographic methods:

#### 2.1.1. HPLC methods:

| Stationary phase | Mobile phase | Detection | Specification | REF |
|---|---|---|---|---|
| **Platisil $C_{18}$ column (150 × 4.6 mm, 5 µm)** | methanol–0.01% formic acid (70:30, v/v) | 379 → 264 m/z | Quantitative Detection of Ambroxol in Human Plasma Using HPLC-APCI-MS/MS: Application to a Pharmacokinetic Study | [39] |
| **a Phenomenex $C_{18}$ column** | methanol, pH, and flow rate in the range of 55%–65% (v/v) | 220 nm | Chemometric-assisted RP-HPLC method for the simultaneous determination of ambroxol hydrochloride, terbutaline sulfate, and guaiphenesin in combined dosage form | [40] |
| **BDS Hypersil $C_8$ (250 × 4.6 mm, 5 µm) RP-column** | 25 mM of $KH_2PO_4$ (pH 3.5) in aqueous mobile phase, 65% MeOH | 210nm | Quality by Design Strategy for Simultaneous HPLC Determination of Bromhexine HCl and Its Metabolite Ambroxol HCl in Dosage Forms and Plasma | [41] |
| **Princeton sphere $C_8$ 25 cm × 4.6 mm (Rankem) analytical column** | 0.1 M potassium dihydrogen phosphate and its pH was adjusted to 4.5 with 10% ortho-phosphoric acid and methanol (58:42 v/v) | 220 nm | Development and validation of a novel RP-HPLC method for simultaneous determination of salbutamol sulfate, guaifenesin, and ambroxol hydrochloride in tablet formulation | [42] |
| **$C_{18}$ column (4.6 mm × 150 mm, 5 µm i.d.)** | 0.025 M Sodium dihydrogen Phosphate buffer: ACN in the ratio of (40:60, 15:85 and 30:70 v/v) | 210 nm | Development and Validation of UV-Spectrophotometric and RP-HPLC Methods for Simultaneous Estimation of Fexofenadine Hydrochloride, Montelukast Sodium and Ambroxol Hydrochloride in Tablet Dosage Form | [43] |
| **column symmetry shield RP$C_8$, 5 microm 250 x 4.6 mm** | (methanol/$H_3PO_4$ 8.5 mM/triethylamine pH=2.8) 40:60 v/v | 247 nm | A Rapid and Simultaneous Determination of Ambroxol Hydrochloride, Methyl Parabene and Propyl Paraben in Mucol Ambroxol Syrup Dosage Form. | [44] |
| **$C_{18}$ column** | buffer: acetonitrile in the ratio 80: 20 (buffer − 0.1% v/v triethyle amine pH-3.0) | 220 nm | RP-HPLC-UV method development and validation for simultaneous determination of terbutaline sulphate, ambroxol HCl and guaifenesin in pure and dosage forms | [45] |
| **Phenomenex Luna Phenyl-Hexyl, 50 x 4.6 mm, 5 µm Column** | methanol; formic acid; ammonia water | 240.25 → 148.10 m /z. 377.10 → 263.95 m /z; 379.05 → 263.95 m /z. 199.15 → 122.10 m z; | Development and Validation of Salbutamol, Bromhexine, Ambroxol and Guauaifenesin Determination in Human Plasma by HPLC-MS/MS Method | [46] |

#### 2.1.2. Thin Layer Chromatographic methods:

| Stationary phase | Mobile phase | Detection | Specification | REF |
|---|---|---|---|---|
| **silica gel G60 F254** | diethyl ether–n-butanol–ammonia (9:0.9:0.1, v/v) | 276 nm | Stability-indicating high-performance thin-layer chromatographic method for the estimation of ambroxol hydrochloride and doxofylline in a pharmaceutical formulation using experimental design in robustness study | [47] |
| **silica gel 60 F254** | methanol-triethylamine (4:6 v/v) | 254 nm | Stability-indicating HPTLC determination of ambroxol hydrochloride in bulk drug and pharmaceutical dosage form | [48] |
| **aluminium plates of silica gel 60 F254** | chloroform: methanol (9:1v/v) | 216 nm | Stability indicating high performance thin-layer chromatography method for simultaneous estimation of ambroxol hydrochloride and loratadine in pharmaceutical dosage form | [49] |
| **silica gel 60F 254** | chloroform: methanol: ethyl acetate: acetic acid (70: 8: 12:10, by volume) | 270 nm | Simultaneous determination of Ambroxol Hydrochloride and Guaifenesin by HPLC, TLC-Spectrodensitometric and multivariate calibration methods in pure form and in Cough Cold Formulations | [50] |

| | | | | |
|---|---|---|---|---|
| **aluminum plates of silica gel 60 F254** | chloroform: methanol: toluene: ammonia (10: 6: 3: 0.8 v/v/v/v) | 245 nm | Simultaneous determination of levofloxacin hemihydrate and ambroxol hydrochloride in tablets by thin-layer chromatography combined with densitometry | [51] |
| **aluminum plates of silica gel 60 F254** | n-butanol: 1.0 M ammonium acetate: methanol (7.5:2.0:1.5) (v/v/v) | 222 nm | Validated HPTLC Method for Simultaneous Estimation of Amoxycillin trihydrate and Ambroxol hydrochloride in Pharmaceutical Dosage Form. | [52] |
| **silica gel 60 F254** | Toluene - Methanol - Chloroform - Glacial Acetic Acid (6.5:1.5:1.5:0.5 v/v/v/v) | 275 nm | Development and validation of RP-HPLC and HPTLC method of analysis for simultaneous estimation of ambroxol HCL, Dextromethorphan HBR and Guaifenesin in pharmaceutical cough cold preparation and statistical comparison of developed methods | [53] |

### 2.2. Spectrophotometric methods:

| Method of determination | Detection | Specification | REF |
|---|---|---|---|
| **zero crossing wavelength method** | 210 and 220.0 nm | Validated derivative and ratio derivative spectrophotometric methods for the simultaneous determination of levocetirizine dihydrochloride (LCD) and ambroxol hydrochloride in pharmaceutical dosage form | [54] |
| **Simultaneous equation** | 244 nm. | Dissolution Determination of Ambroxol Hydrochloride Orally Disinegreting Tablets | [55] |
| **Simultaneous equation** | 230-240 nm | Advanced chemometrics manipulation of UV-spectroscopic data for determination of three co-formulated drugs along with their impurities in different formulations using variable selection and regression model updating. | [56] |
| **Simultaneous equation** | 306 nm | Analytical method development and validation of ambroxol hydrochloride by UV spectroscopy and forced degradation study and detection of stability. | [57] |
| **Simultaneous equation** | 246 and 298 nm | Simultaneous Estimation of Ambroxol Hydrochloride and Olopatadine in Formulated Tablet Dosage Form by UV Spectroscopic Method | [58] |

### 2.3. Capillary electrophoresis methods:

A sensitive and rapid capillary electrophoretic method combined with laser-induced fluorescence detection has been created for the assurance of ambroxol. Tests were derivatized with 5·10−4 M fluorescein isothiocyanate. A straight connection among fixation and pinnacle region was gotten in the focus run 0.008–42 μg ml−1 with a relationship coefficient of 0.9999. The strategy is likewise valuable for the assurance of ambroxol in pharmaceutical arrangements. [59].

Expectorant drugs ambroxol (AMB) and bromhexine (BX) were dictated by fine isotachophoresis (ITP) with conductimetric location. The main electrolyte (LE) was a cradle arrangement that contained 5 mM picolinic corrosive and 5 mM potassium picolinate (pH 5.2). The ending electrolyte (TE) was 10 mM formic corrosive. The driving current was 80 microA (for roughly 200 s) or 50 microA (for around 350 s) and the location current was 20 microA (a solitary investigation took around 8 min). The successful mobilities of AMB and BX (assessed with tetraethylammonium as the portability standard) were 18.8 x 10(- 9) m2 V(- 1) s(- 1) and 14.3 x 10(- 9) m2 V(- 1) s(- 1) separately. The alignment charts relating the ITP zone length to the grouping of the analytes were rectilinear (r = 0.9993-0.9999) in the range 10 mg L(- 1) (20 mg L(- 1) for BX) to 200 mg l(- 1) of the medication standard. The relative standard deviations (RSD) were 1.2 1.6% (n = 6) while deciding 100 mg l (- 1) of the analytes in unadulterated test arrangements. The strategy has been applied to the measure of AMB or BX in seven business mass-created pharmaceutical arrangements. As per the approval strategy dependent on the standard expansion procedure the recuperations were 97.5-102.7% of the medication and the RSD esteems were 0.11-2.20% (n = 6) [60].

## 3. Metods for analysis of Fexofenadine

### 3.1. Chromatographic methods:

#### 3.1.1. HPLC methods:

| Stationary phase | Mobile phase | Detection | Specification | REF |
|---|---|---|---|---|
| **Hypersil® BDS $C_{18}$ column (250 × 4.6 mm, 5µm)** | 20 mM sodium dihydrogen phosphate-2 hydrate (pH adjusted to 3 with phosphoric acid)–acetonitrile at a ratio of 52:48, v/v | 215 nm | HPLC Determination of Fexofenadine in Human Plasma For Therapeutic Drug Monitoring and Pharmacokinetic Studies | [61] |
| **$C_{18}$ column (150mm×4.6mm, with 5µm particle size)** | Acetonitrile:methanol (50:50, v/v). | 210 nm | Development of a Simple and Efficient Method for Preconcentration and Determination of Trace Levels of Fexofenadine in Plasma and Urine Samples. | [62] |
| **Cap Cell Pack $C_{18}$ column (250 × 4.5 mm, 5µ) column** | acetonitrile: water (50:50 % v/v) | 224 nm | Development and validation of RP-HPLC method for determination of fexofenadine in pharmaceutical dosage form by using levocetirizine as an internal standard | [63] |
| **Phenomenex $C_{18}$ column (250×4.6 mm, 5 µm)** | 5 Mm acetate buffer: acetonitrile (50:50; v/v) | 254 nm | A Validated RP-HPLC Method and Force Degradation Studies of Fexofenadine Hydrochloride in Pharmaceutical Dosage Form. | [64] |

| | | | | |
|---|---|---|---|---|
| **double end-capped $C_{18}$ column (250 mm × 4 mm, 5 µm)** | acetonitrile (% v/v) and methanol (% v/v) | 218 nm | A Simple and Improved HPLC-PDA Method for Simultaneous Estimation of Fexofenadine and Pseudoephedrine in Extended Release Tablets by Response Surface Methodology. | [65] |
| **Sunfire $C_{18}$ (4.6×250mm) 5µ column** | Water and Acetonitrile (60:40% v/v) | 220 nm | Simultaneous estimation of montelukast and fexofenadine in pure and pharmaceutical dosage form by using RP-HPLC method | [66] |
| **$C_{18}$ Grace Column (4.6×250 mm, 5 um)** | Methanol and Water (70: 30, v/v) | 241 nm | Analytical Method Development and Validation for Simultaneous Estimation of some drugs in Pharmaceutical Dosage Form. | [67] |
| **Purospher® STAR RP-18 end capped (5 µm, 25 × 0.46 cm) column** | methanol: water (65:35 v/v) | 230 nm | HPLC method development, validation and its application to investigate in vitro effect of pioglitazone on the availability of H1 receptor antagonists. | [68] |
| **Polaris $C_{18}$ (15 x 4.6 mm i.d.) with 5 µ particle size column** | buffer and acetonitrile (65:35 % v/v) | 220 nm | Determination of fexofenadine hydrochloride in pharmaceutical dosage form by reverse phase high performance liquid chromatography method | [69] |
| **Hypersil BDS $C_{18}$ analytical column (250 × 4.6 mm, i.d., 5 µm)** | phosphate buffer containing 0.1 gm% of 1-octane sulphonic acid sodium salt monohydrate and 1% (v/v) of triethylamine, pH 2.7 and methanol (60:40, v/v) | 215 nm | Development of validated stability-indicating chromatographic method for the determination of fexofenadine hydrochloride and its related impurities in pharmaceutical tablets | [70] |
| **Zorbax, Eclipse XBD, $C_8$ Column having 150 x 4.6 mm i.d** | phosphate buffer: acetonitrile: methanol (60:20:20; v/v/v) | 210 nm | Stability Indicating RP-HPLC Method for Estimation of Fexofenadine Hydrochloride in Pharmaceutical Formulation. | [71] |
| **Phenomenex $C_8$, 5 µm, 25 cm × 4.6 mm i.d. column** | ACN: Acetate buffer= 6.5:3.5 | 222 nm | RP-HPLC Method Development and Validation for the Determination and Stability Indicative Studies of Montelukast in Bulk and its Pharmaceutical Formulations. | [72] |
| **Xterra $C_{18}$ 5µm (4.6*250mm) column** | Phosphate buffer (0.05M) pH4.6: ACN (55:45%v/v) | 255 nm | A stability indicating RP-HPLC method development and validation for simultaneous estimation of montelukast and fexofenadine hydrochloride in bulk and pharmaceutical dosage form | [73] |
| **X bridge $C_{18}$, 250 × 4.6 mm, 5 µm particle column** | acetonitrile: buffer (10 mM potassium dihydrogen phosphate solutions): methanol of pH 4.5 and in the ratio of 50:30:20 v/v/v | 248 nm | Validated Stability-Indicating Isocratic RP-HPLC Method of Estimation of Montelukast Sodium and Fexofenadine Hydrochloride in Bulk and in Solid Dosage by Vieordtâ`s Method | [74] |

**3.1.2. Thin Layer Chromatographic methods:**

| Stationary phase | Mobile phase | Detection | Specification | REF |
|---|---|---|---|---|
| **Silica gel 60F254 aluminum plate** | Hexane: Methanol: Tri-Ethyl amine (6:4:0.1 v/v/v) | 234 nm | Stability indicating HPTLC method development for fexofenadine hydrochloride | [75] |
| **Silica gel aluminum plates 60 F-254** | Toluene: ethyl acetate: methanol: ammonia (30%) (0.5: 7: 3: 0.6 v/v/v/v) | 220 nm | Stability indicating TLC determination of fexofenadine hydrochloride as bulk drug: Application to forced degradation study | [76] |
| **Aluminum plates of silica gel G60 F254, (20 × 10 cm)** | Ethyl acetate: methanol: ammonia (30%) (7: 3: 0.5, v/v/v/v) | 215 nm | Development and validation of HPTLC method for simultaneous estimation of montelukast sodium and fexofenadine hydrochloride in combined dosage form | [77] |
| **Aluminum Plates Of Silica gel G60 F254, (20 × 10 cm)** | Toluene: ethyl acetate: methanol: ammonia (30%) | 220 nm | Method development and validation for the simultaneous determination of fexofenadine hydrochloride and montelukast sodium in drug formulation using normal phase high-performance thin-layer chromatography. | [78] |

| | | | | |
|---|---|---|---|---|
| **Aluminum plates of silica gel G60 F254, (20 × 10 cm)** | hexane: ethyl acetate: propanol (2: 5: 3, v/v/v) | 230 nm | Development of validated HPTLC method for simultaneous estimation of fexofenadine hydrochloride and montelukast sodium in tablet dosage form. | [79] |
| **Aluminum plates of silica gel 60 F254** | methanol and distilled water/ethanol (1:1) | 220 nm and 247 nm for FEX and pseudoephedrine hcl | Estimation of fexofenadine hcl and pseudoephedrine hcl by spectrophotometer and TLC in combined tablet dosage form | [80] |

### 3.2. Spectrophotometric methods:

| Method of determination | Detection | Specification | REF |
|---|---|---|---|
| **Simultaneous equation** | 259 nm and 344.5 nm | UV Spectrophotometric method development and validation for simultaneous determination of fexofenadine hydrochloride and montelukast sodium in tablets | [81] |
| **Based on the measurement of tri-iodide ion** | 360 nm | Application of Bromate-Bromide Mixture as a Green Brominating Agent for the Determination of Fexofenadine Hydrochloride in Pharmaceutical Dosage Form | [82] |
| **Based on the charge transfer reaction of the cited medicates, as n-electron donor, with DDQ and TCNQ, as π-acceptors** | 460-840 nm | Charge-transfer interaction between antihistamine antiallergic drugs, diphenhydramine, fexofenadine, cetirizine and two π-acceptors in pharmaceutical forms | [83] |
| **Simultaneous equation** | 220 and 247 nm | Estimation of fexofenadine hcl and pseudoephedrine hcl by spectrophotometer and TLC in combined tablet dosage form | [80] |
| **Based on determination of residual oxidant b** | 615 nm. | New Method for the Spectrophotometric Determination of Fexofenadine Hydrochloride. | [84] |
| **Evaluation of the analytical parameters of linearity, precision, accuracy, limits of detection, and quantitation and specificity.** | 220 nm | Validation of UV Spectrophotometric Method for Fexofenadine Hydrochloride in Pharmaceutical Formulations and Comparison with HPLC | [85] |

### 3.3. Capillary electrophoresis methods:

A basic, precise, and viable capillary electrophoresis strategy with bright absorbance recognition was created and approved for the quantitation of the antihistamine fexofenadine in cases. The partition was performed with an uncoated melded silica fine (47 cm x 75 microm id) and was worked at 20 kV potential. Temperature was kept up at 25 degrees C. The run support was set up with 20mM Na2B4O7 x 10 H2O. Programming was utilized for framework control, information procurement, and examination. Technique approval was performed by assessment of the systematic boundaries linearity, exactness, precision, cutoff points of discovery and quantitation, and explicitness. The strategy was direct (r = 0.9999) at fixations running from 20 to 100 microg/mL, exact (relative standard deviation intra-measure = 1.2, 1.6, and 1.8% and interassay = 1.5%); precise (recuperation = 98.1%); and explicit. The constraints of discovery and quantitation were 0.69 and 2.09 microg/mL, individually. The strategy was contrasted with the fluid chromatography technique grew already by the writers for a similar medication, and no huge distinction was found between the 2 strategies in fexofenadine hydrochloride quantitation [86].

Capillary electrophoresis (CE) methods for the assurance of FEX in pharmaceuticals were done. It was exhibited that FEX could be viably broke down in free arrangement cationic CE at low pH. Another diagnostic methodology contemplated depended on cyclodextrin (CD) changed CE where profoundly charged CD subordinates filled in as analyte transporters. Along these lines, the partition go was spread to physiological pH area and a CE examination of FEX, present really in its zwitterionic structure, could be cultivated. A few boundaries influencing the partitions were examined, including the sort and grouping of transporter particle, counterion, analyte transporter, and pH of the cradle. The techniques dependent on the free arrangement CE and CD-adjusted CE were analyzed one another, approved, and applied for the assurance of FEX in tablets. [87].

### 3.4. Luminescence methods:

Technique for the assurance of Fexofenadine (FEX), in pharmaceutical details is accounted for. The strategy depends on the refinement of terbium (Tb3+) by complex development with FEX. The glow signal for Tb–FEX complex is enormously upgraded by the expansion of triethylamine (ET3N) and zinc nitrate in methanol arrangement. Observing of the sign is practiced when the instrument is in the glow mode with the excitation and emanation frequencies set at λex = 220 nm and λem = 550 nm separately. Ideal conditions for the arrangement of the complex in methanol were 2.25 × 10−6 M of Tb3+, 5.00 × 10−6 M of Et3N and Zn2+ which takes into consideration the assurance of 10–800 ppb of FEX in the clump mode with a recognition cutoff of 0.3 ppb. The proposed strategy was effectively applied for the assurance of FEX in pharmaceutical plans [88].

### 3.5. Graphite Electrode methods:

A new electrochemical approach for the attending assurance of fexofenadine hydrochloride and montelukast sodium by developing three new graphite cathodes covered with a polymeric film. The first cathode was built utilizing ammonium molybdate reagent as a particle pair with fexofenadine cation for the assurance of fexofenadine sedate, the subsequent anode was developed utilizing cobalt nitrate as a particle pair with montelukast anion for the assurance of montelukast medicate, the third terminal was set up by fusing the two beforehand notice particle sets in a similar graphite sensor, which cause this sensor touchy to each to fexofenadine and montelukast tranquilize. The covering material was a polymeric lm includes Poly Vinyl Chloride (PVC), Di-butyl phthalate as a plasticizer (DBP), particle sets of medications with recently referenced reagents. The terminals indicated a Nernstian reaction with a mean adjustment chart slants of [58.97, 28.43, (59.048, and 28,643)] mv.decade$^{-1}$ for the three pencil anodes separately. The anodes work successfully over pH run (2-4.5) for fexofenadine hydrochloride and (5-

9.5) for montelukast sodium. The effect of the proposed meddling species was negligible. The viability of the cathodes proceeded in a timeframe (45-69) days. The recommended sensors exhibited valuable expository highlights for the assurance of the two medications in mass powder, in lab arranged blends and their consolidated dose structure [89].

## Conclusion

This literature review represents an up to date survey about all reported methods that have been developed for determination of salbutamol, ambroxol and fexofenadine in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples such as liquid chromatography, spectrophotometry, spectroflourimetry, etc...

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