Review Article

Review on Various Quantitative Methods Available To Detect Antihistaminic Drugs Alone and in Combination with Other Drugs in Pharmaceutical Formulation

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ABSTRACT

Current paper describes various Analytical methods available for detection of Antihistaminic drugs alone and in combination from various pharmaceutical formulations. Hence a literature was undertaken replete with the publications on the development of methods of drug substance and drug products. Antihistaminic drugs like Desloratadine, Loratadine, Fexofenadine, Terfenadine etc in combination with Pseudoephedrine are the first class choice for the cough suppression and also in the management for the relief of symptoms of seasonal allergic rhinitis, perennial allergic rhinitis in both adult and child. The various analytical techniques have been discussed, from simple colorimetric methods of intermediate selectivity and sensitivity to highly sophisticated, selective and sensitive chromatographic methods applied in a modern analytical laboratory.

Keywords: Desloratadine, Fexofenadine, Loratadine, Pseudoephedrine, RP-HPLC, Terfenadine.

INTRODUCTION

Still present many analytical methods are available on traditional or classical methods and these are not assuring more accuracy for drug analysis. The regulatory guidelines mandated the need for establishing stability-indicating assay. The practical steps for establishing the stability indicating method are elusive in the regulatory guidelines and pharmacopoeias. Recent progress in methods development has been largely a result of improvements in analytical instrumentation. This is especially true for chromatographs and detectors. Isocratic and gradient reverse-phase HPLC have evolved as the primary techniques for the analysis of drugs. The HPLC detector of choice for many types of methods development is the photodiode array (PDA) detector because it can be used for both quantitative and qualitative analysis. The use of a PDA detector to determine peak purity of the active ingredient in stressed samples greatly facilitates the development of stability-indicating assays. The ultraviolet (UV) absorbance detector remains the most common HPLC detector for potency and impurity analysis. Once specificity has been demonstrated, the PDA detector is replaced with a variable wavelength detector and the HPLC effluent is monitored at fixed wavelengths. Stability-indicating and impurity methods often are required to measure analytes within a wide concentration range. The review of literature began with factual collection of large of number of methods reported over the past decades under the nomenclature. Now a day, various Antihistaminic drugs (e.g. Desloratadine, Loratadine, Fexofenadine, Terfenadine etc.) are available in combination with Pseudoephedrine in market in different dosage form. Few examples of Antihistaminic drugs with Pseudoephedrine are as below (Table 1).

Table 1: Combination of Antihistaminic drugs with Pseudoephedrine

Drug combination	Marketed formulation	Manufacturer
Desloratadine HCl (5mg) + Pseudoephedrine Sulphate (180mg)	Dyl –D[1]	Ajanta Pharma
Loratadine HCl (5mg) + Pseudoephedrine HCl (120mg)	LORFAST-D[2]	Cadila
Fexofenadine HCl (120mg) + Pseudoephedrine HCl (180mg)	Alvita- D[3]	Ranbaxy
Terfenadine HCl (60mg) + Pseudoephedrine HCl (120mg)	Terfed-D[4]	Cipla

Introduction to Pseudoephedrine and Some of Antihistaminic drugs given as below (Table 2)

Literature studies show various analytical methods reported for the estimation of individual, binary or tertiary combination of antihistaminic drugs. From the literature, many HPLC methods has been developed and validated for different antihistaminic drugs.

Some Analytical methods reported for Pseudoephedrine and it given as below (Table 3). Some Analytical methods reported for Desloratadine HCl and it given as below (Table 4). Some Analytical methods reported for Loratadine HCl and it given as below (Table 5).

Some Analytical methods reported for Fexofenadine HCl and it given as below (Table 6). Some Analytical methods reported for Terfenadine HCl and it given as below (Table 7).

Table 2: Introduction to Drugs

Drug Name	Information of drug[5-11]
Pseudoephedrine HCl	Category: Vasoconstrictor Agents, Adrenergic Agents, Sympatho mimetic, Central Nervous System Agents, Bronchodilator Agents, and Nasal Decongestants Molecular formula: $C_{10}H_{15}NO$ Molecular weight: 165.23 gm/mol IUPAC Name: (1S,2S)-2-(methyl amino)-1-phenylpropan-1-ol Melting Point: 117 - 118°C pka value: 9.4
Desloratadine HCl	Category: Cholinergic Antagonists, Antihistamines, Histamine H1 Antagonists and Non-Sedating Molecular formula: $C_{19}H_{19}ClN_2$ Molecular weight: 310.82 gm/mol IUPAC Name: 13-chloro-2-(piperidin-4-ylidene)-4-azatricyclo [9.4.0.0^{3,8}] pentadeca-1(11), 3,5,7,12,14- hexane Melting Point: 150 - 151 °C pka value[14]: 4.2 and 9.7
Loratadine HCl	Category: Antipruritics, Anti-Allergic Agents, Antihistamines, Histamine H1 Antagonists and Non-Sedating. Molecular formula: $C_{22}H_{23}ClN_2O_2$ Molecular weight: 382.88 gm/mol IUPAC Name: ethyl 4-{13-chloro-4-azatricyclo[9.4.0.0^{3,8}] pentadeca-1(11),3,5,7,12,14-hexaen-2-ylidene}piperidine-1-carboxylate Melting Point: 134- 136 ^{o}C pka value: 5.0
Fexofenadine HCl	Category: Anti-Allergic Agents, Antihistamines Histamine H1 Antagonists and Non-Sedating Molecular formula: $C_{32}H_{39}NO_4$ Molecular weight: 501.66 gm/mol IUPAC Name: 2- (4- {1-hydroxy-4- [4-(hydroxyl diphenyl methyl) piperidin-1-yl]butyl}phenyl)-2-methylpropanoic acid Melting Point: 142.5 ^{o}C pka value: 13.2
Terfenadine	Category: Antiarrhythmic Agents, Anti-Allergic Agents, Antihistamines, Histamine H1 Antagonists and Non-Sedating Molecular formula: $C_{32}H_{41}NO_2$ Molecular weight: 471.67 gm/mol IUPAC Name: 1-(4-tert-butyl phenyl)-4-[4-(hydroxyl diphenyl methyl) piperidin-1-yl]butan-1-ol Melting Point: 146.5-148.5^{o}C pka value: 14.52

Table 3: Analytical Methods available to detect Pseudoephedrine

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Pseudo-ephedrine sulphate	HPLC	The separation of isomer is by Diacel, Chiralpak AD-H 250mm X 4.6 mm with 5µ particle size. Column was maintained at 25°C. The UV/Vis detector was operated at 254 nm. Flow rate of the mobile phase was 2.0 ml/min.	12

Table 3: Analytical Methods available to detect Pseudoephedrine (Continued.....)

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Pseudo-ephedrine HCl + Loratadine	HPLC	Developed HPLC method is reverse-phase chromatographic method using Inertsil C_{18} column and methanol: ammonium acetate buffer in ratio of 80: 20 pH 7.5 as mobile phase. Nimesulide was used as internal standard for HPLC method.	13
Pseudo-ephedrine+ Fexofenadine + Loratadine	RP-HPLC	Separation was achieved by using C_{18}, 150 x 4.6 mm, 5 µm column at a temperature of 350^{0}C with a gradient mobile phase composed of sol-A: 0.01M pH 3.0 phosphate (KH_2PO_4) buffer, sol-B: Acetonitrile and gradient program was 0-5min, sol-A: 80-60; 5-10min- sol-A: 60-20; 10-15min- sol-A: 20-20; 15-17min- sol-A: 20-80 and 17-20min- sol-A: 80-80. Flow rate was 0.60 ml per min and measured the absorbance at 210nm. The retention time of Pseudoephedrine, Fexofenadine and Loratadine are 4.3min, 10.4 min and 17 min, respectively.	14
Pseudo-ephedrine + Chlorpheniramine (Human plasma)	HPLC	The two drugs were simultaneous determined by RP-HPLC with ultraviolet detection at 200 nm, using dextromethorphan as internal standard. A C_{18} column (250 mm x 46 mm ID) and a mobile phase containing Acetonitrile-water-triethylamine (46: 54: 0.2) containing 10 mmol x $L^{(-1)}$ sodium dodecyl sulphate (SDS) and 60 mmol x $L^{(-1)}$ NaH_2PO_4, adjusted pH to 2.6 with H_3PO_4) were used.	15
Pseudo-ephedrine+ Paracetamol + Cetirizine	RP-HPLC	Paracetamol, cetirizine and pseudoephedrine were separated using a Hypersil C_{18} column with a flow rate of 1.0 mL/min. The mobile phase composition was 25mM phosphate buffer (pH 5.0) – methanol – Acetonitrile (30: 60: 10) (v/v/v) and 100 mg of heptane sulphonic acid was added for every 100 mL of mobile phase at 240 nm.	16
Pseudo-ephedrine + Paracetamol + Cetirizine	RP-HPLC	Chromatography was carried out on a pre-packed Cosmosil C_8 (250 x 4.6) mm column using filtered and degassed mixture of Buffer and Acetonitrile in the ratio of 85: 15 as mobile phase at a flow rate of 1.0 ml/min and effluent was monitored at 215 nm.	17
Pseudo-ephedrine + Guaifenesin	RP-HPLC	Chromatography is carried out isocratically at 25°C ± 0.5°C on an Prontosil C_{18} column (4.6 x 250mm, 5µ particle size) with a mobile phase composed of Acetonitrile-methanol-phosphate buffer (pH-5.0) (72: 8: 20, v/v/v) at a flow rate of 1.2 mL/min. Detection was carried out using a PDA detector at 218 nm.	18
Pseudo-ephedrine + Ambroxol + Levocetrizine	RP-HPLC	The separation was carried out using a mobile phase consisting of methanol: 0.04 M potassium Dihydrogen phosphate with 0.5% Triethylamine, 65: 35 v/v (pH=3). The column used was Thermo electron Co. ODS Hypersil 5µ, 250 mm x 4.6 mm id with flow rate of 1 ml/min using UV detection at 212 nm. The described method was linear over a concentration range of 0.5-3.5 µg/ml, 3-21 µg/ml and 6-42 µg/ml for the Levocetrizine, Pseudoephedrine and Ambroxol respectively.	19

Table 3: Analytical Methods available to detect Pseudoephedrine (Continued…..)

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Pseudo-ephedrine + Fexofenadine/ cetrizine	RP-HPLC	The chromatographic separation of PSE, FEX and CET was achieved on a Zorbax C_8 (150 mm × 4.6 mm; 5 μm particle size) column using UV detection at 218 and 222 nm. The optimized mobile phase was consisted of TEA solution (0.5%, pH 4.5) methanol–acetonitrile (50: 20: 30, v/v/v). The retention times were 1.099, 2.714 and 3.808 min for PSE, FEX and CET, respectively. The proposed method provided linear responses within the concentration ranges 30–240 and 1.25–10 μg ml^{-1} with LOD values of 1.75 and 0.10 μg ml^{-1} for PSE and CET, respectively.	20
Pseudo ephedrine + Chlorpheniramine maleate + Paracetamol	HPLC	The separation of three components was performed on C_{18}, 150 x 4.6 mm, 5μ HPLC column using gradient mobile phase Methanol- Sodium Per chlorate (0.043M, 2mL Triethylamine, pH 5.0) at a flow rate of 1.0 mL, detection was at 204nm for Chlopheniramine maleate, Pseudoephedrine and 300 nm for Paracetamol	21
Pseudo- ephedrine + Desloratadine HCl	RP-HPLC	Column:- C_{18} column Mobile phase:- 10 mM Ortho-phosphoric acid: Acetonitrile(77: 23 v/v) λ:- 262 nm	22
Pseudoephedrine + Fexofenadine (Human plasma)	LC/MS/ MS	The compounds were chromatographed on an RP_{18} column with a mixture of ammonium acetate (10 mm, pH 6.4) and methanol as mobile phase. Quantification of the analytes was based on multiple reaction monitoring (MRM) of precursor-to-product ion pairs m/z 502 → 466 for fexofenadine, m/z 166 → 148 for pseudoephedrine, and m/z 389 → 201 for cetirizine. The linear calibration range for both analytes was 2–1, 700 ng mL^{-1} (r = 0.995), based on analysis of 0.1 mL plasma.	23
Pseudo-ephedrine HCl + Triprolidine HCl	Derivative Spectro-scopy	The second derivative amplitudes of PSE and TRI were measured at 271 and 321 nm, respectively. The calibration curves were linear in the range of 200 to 1,000 g/ml for PSE and 10 to 50 g/ml for TRI.	24
Pseudo-ephedrine HCl + Chlor- pheniramine maleate + Dextromethorphan HBr	Spectro-photo metric method	Diluent:- 0.1 M sodium acetate buffer at pH 5 λ:- 240 to 300 nm The sensitivity of this assay is 7.5 μg/mL for pseudoephedrine hydrochloride, 1.0 μg/mL for Chlorpheniramine maleate, and 5.0 μg/mL for dextromethorphan hydro bromide	25
Pseudo-ephedrine HCl + Loratadine	Spectro-photo metric method	Method involves first derivative spectroscopy using 308.6 nm and 263.0 nm as zero crossing points for pseudoephedrine HCl and Loratadine respectively. 0.2 M HCl was used as solvent. Linearity was observed in concentration range of 0-40 mg/ml of Loratadine and 0-800 mg/ml of pseudoephedrine HCl	26
Pseudo-ephedrine HCl +Ibuprofen (Tablet)	Ratio derivative spectra and multi variate spectro-scopy	In the first method, ratio spectra derivative spectrophotometry, analytical signals were measured at the wavelengths corresponding to both maximums and minimums for both drugs in their solution in 0.1 M HCl. In the other four Spectrophotometric methods, the concentration data matrixes were prepared by using the synthetic mixtures containing these drugs in methanol: 0.1 M HCl (3:1).	27

Table 4: Analytical Methods available to detect Desloratadine Hydrochloride

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Desloratadine HCl (Tablet) (Dog plasma)	HPLC	Column:- Hypersil CN Column (150 mm × 5mm i.d, 0.5 μm) Mobile phase:- Methanol: Acetonitrile: Phosphate buffer 0.01 mol/l (35: 35: 30 v/v/v) (pH-5.5) λ:- 241 nm	28
Desloratadine HCl (Bulk drug and formulation)	HPLC	Column:- Diamonsil BDS C_{18} column Mobile phase:- Methanol: 0.03 M Heptane sulphonic acid sodium: Glacial acetic acid (70: 30: 4 v/v/v) λ:- 247 nm	29
Desloratadine HCl (Tablet)	HPLC	Column:- Phenomenex 5μm ODS C_{18} (250 mm x 4.6 mm i.d) column Mobile phase:- 0.1% v/v ortho-phosphoric acid: Methanol (90: 10 v/v) λ:- 210 nm	30
Desloratadine HCl (Tablet)	HPLC	Column:- C_{18} column Mobile phase:- Phosphate buffer: Acetonitrile: Methanol (50: 40: 10 v/v/v) λ:- 247 nm	31
Desloratadine HCl (Bulk drug and formulation)	HPLC	Column:- C_{18} column Mobile phase:- Phosphate buffer: Methanol (35: 65 v/v)(pH-7.0) λ:- 254 nm	32
Desloratadine HCl (Tablet)	RP-HPLC	Column:-C_{18} RP column (250 mm × 3.3 mm i.d., 5μm) Mobile phase:- Acetonitrile: n-pentane sulphonic acid sodium salt monohydrate, adjusted to pH 3.0 ± 0.05 with phosphoric acid (60: 40 v/v) λ:- 254 nm	33
Desloratadine HCl (Tablet)	Gradient ion-pair Chromatography	Column:- YMC-Pack Pro C_{18} column (150 mm× 4.6 mm i.d., 3μm) Mobile phase:- Mobile phase A contains 3 mM SDS, 15 mM sodium citrate buffer at pH 6.2, 40 mM sodium sulphate and mobile phase B contains Acetonitrile, λ:- 267 nm	34
Desloratadine HCl+ Loratadine (Tablet)	HPLC	Column:- Cyano Propyl bonded stationary-phase Mobile phase:- 0.1 M SDS, 1% octanol, 10 % n-propanol and 0.3% triethylamine in 0.02 M phosphoric acid, pH 3.0 λ:- 247 nm	35
3-hydroxy Desloratadine (Human plasma)	LC/MS/ MS	Column:- CAPCELL PAK C_{18} column (50 mm× 2.0mmi.d,5 μm) Mobile phase:- 5mM Ammonium format in Water: Methanol: Acetonitrile (50: 30: 20 v/v/v)	36
Desloratadine HCl (Tablet)	Spectro-photo metric method	Diluent:-Methanol Linearity range:- 2 - 10μg/ml λ_{max} :- 242 nm	37

Table 4: Analytical Methods available to detect Desloratadine Hydrochloride (Continued.....)

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Desloratadine HCl (Bulk drug formulation)	Spectro-photo metric method	Diluent:- Acetone - Methanol (90: 10 v/v) medium in case of DCNP (2,4-dichloro-6-nitrophenol), (80: 20 v/v) medium in case of DNP (2,4-dinitro phenol) and in chloroform in case of PA (picric acid) Linearity range:- 3.11-93.35, 3.11-62.17 and 3.11-43.44 µg/ml of DES using DCNP, DNP and PA reagents, respectively λ_{max} :- 402, 426, and 352 nm for DCNP, DNP and PA reagents, respectively	38
Desloratadine HCl+ Montelukast (formulation)	Derivative method	Linearity range:- 3 - 18 µg/ml for DES λ:- 297.2 nm	39
Desloratadine HCl (formulation)	Difference Spectro-photo metric method	Produce a bathochromic shift in UV region under strong alkaline medium. The drug solution in basic medium is scanned over the UV region by taking the acidic drug solution as blank. Diluent:-Methanol Linearity range:- 100 - 600 µg/ml Two wave lengths - one at positive peak and another at negative peak. λ:- 210 nm, 260 nm	40
Desloratadine + Loratadine + Rupatadine	Spectro- photo metry	The method was based on the formation of colored ion pair complexes by the drugs with thiocynate ions. These ion pair complexes were quantitatively extracted under the experimental condition in chloroform. The absorbance values were measured at 618 nm, 614 nm and 616 nm respectively.	41

Table 5: Analytical Methods available to detect Loratadine Hydrochloride

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Loratadine HCl	RP-HPLC	Separation was achieved with Inertsil ODS-3V, 250 × 4.6 mm, 5µ column with gradient elution at a flow rate of 1.0 mL min^{-1}. UV detection was performed at 220 nm. The described method is linear over a range of LOQ (0.044, 0.088, 0.084, and 0.072 µg mL^{-1} for impurity-B, impurity-C, impurity-D, and impurity-E respectively) to 1.2 µg mL^{-1} (0.6 µg mL^{-1} of the specification limit) for all the impurities and degradation products.	42
Loratadine HCl	RP-HPLC	The process was carried out on Stainless - steel column (4.6mm x 15cm), packed with Octa silane chemically bonded to totally porous silica particles and Dibasic potassium phosphate buffer: Methanol: Acetonitrile (1: 2: 1 v/v/v) as mobile phase at a flow rate of 1ml/min.	43
Loratadine HCl (Human plasma)	RP-HPLC	After simple liquid-liquid extraction with 2-methyl butane: hexane (2:1 v/v) and evaporation of organic phase the compounds were re-dissolved in 0.01 M HCl, evaporated again and finally separated on a Supelcosil LC_{18}-DB column. The analyses were done at ambient temperature under isocratic conditions using the mobile phase: CH_3CN: water: 0.5 M KH_2PO_4: H_3PO_4 (440: 480: 80: 1, v/v/v/v). UV detection was performed at 200 nm with a limit of quantification of 0.5 ng/ml	44

Table 5: Analytical Methods available to detect Loratadine Hydrochloride (Continued…..)

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Loratadine HCl	RP-HPLC	The mobile phase consisted of methanol: buffer A (65: 35, v/v), being buffer A: H_3PO_4 10 mM (H_2O) brought up to pH 7.00 with triethylamine. UV detection was performed at 244 nm.	45
Loratadine + Ambroxol HCl	Spectro- photo metry	The method employs measurement of absorbance at two wavelengths, 308 nm and 245nm, of Ambroxol and Loratadine respectively. Beer's law obeyed in the concentration range of 10-50 µg/ml and 10-50 µg/ml for Ambroxol and Loratadine respectively	46

Table 6: Analytical Methods available to detect Fexofenadine Hydrochloride

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Fexofenadine (Tablet)	RP-HPLC	The resolution of drug was achieved on Symmetry C_{18} (150mm x 4.6mm i.d., 5mm particle size) column with UV detection at 254 nm and the mobile phase consists of Buffer and Methanol (30: 70 v/v). Using chromatographic conditions described Fexofenadine was well resolved with mean retention time of 3.399 min, respectively. Linear response (r^2>0.999) was observed over the range of 20 – 60 µg/mL	47
Fexofenadine HCl (tablet and serum)	RP-HPLC	The chromatography was carried out at 20 ± 2°C using two different chromatographs and five different stationary phases. The isocratic mobile phase was phosphate buffer pH 7.4 and methanol (methanol–phosphate buffer, 35: 65, v/v), detection was made at 218 nm and the mobile phase flowed at 1 ml min^{-1}.	48
Fexofenadine HCl (drug formulation)	Stability indicating HPLC	An isocratic separation was achieved using a Zorbax, Eclipse XBD, C_8 Column having 150 x 4.6 mm i.d., 5 µm particle size column with flow rate of 1.2 ml/min and using UV detector to monitor the elute at 210 nm. The mobile phase consist of phosphate buffer: acetonitrile: methanol (60: 20: 20; v/v/v) with pH 3.7 adjusted with o-phosphoric acid.	49
Fexofenadine HCl+ Montelukast sodium (Bulk drug and marketed formulation)	RP-HPLC	The chromatographic separation was performed in Water symmetry C_8 (150 x 4.6 mm, 5µm) and mobile phase 0.05 M potassium dihydrogen orthophosphate: acetonitrile in the ratio of 35: 65 and the pH – 6 adjusted by triethylamine. The flow rate was 1 ml/min and the wavelength selected for the quantization was 226 nm. The retention time was found to be 2.127 min for Fexofenadine and 5.650 min for Montelukast sodium .The linearity were found to be in the range of 4.8 - 28.8 µg/ml and 0.4 – 2.4 µg/ml for Fexofenadine and Montelukast respectively with the correlation co efficient of 0.999	50

Table 6: Analytical Methods available to detect Fexofenadine Hydrochloride (Continued…..)

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Fexofenadine HCl (Human plasma)	UPLC	With carbamazepine as internal standard, sample pre-treatment involved a one-step extraction with ethyl acetate from 980µl plasma. The sample was analyzed using 10mM KH_2PO_4 buffer pH 2.5 and acetonitrile (70: 30 v/v) as mobile phase. Chromatographic separation was achieved TM on an ACQUITY UPLC BEH (C_{18}) column (1.7 µm, 2.1mm x 100mm) using isocratic elution (at a flow rate of 0.25 ml/min). The peak was detected using UV-PDA detector set at 210 nm and the total time for a chromatographic separation was 10 min. Linear calibration curves were obtained in the concentration range of 30.09 - 1805.39 ng/ml	51
Fexofenadine HCl (bulk and dosage form)	Spectro- photo metry	The method is based on the chloroform-extractable pale yellow colour complex formed by the reaction of fexofenadine with bromothymol blue at pH 2.6. The chromogen can be estimated at 412 nm against a reagent blank. Range: of 10-50 µg/ml	52
Fexofenadine HCl	Spectro- photo metry	Two dyes malachite green and xylenol cyanol FF were used. Wavelength 615 and 612 nm was selected respectively.	53
Fexofenadine HCl	Colorimetry	The developed methods involve formation of extractable ion pair complex of drug with bromophenol blue, bromocresol purple and bromocresol green dyes in acidic medium. Chloroform is used as extracting solvent for bromophenol blue and 1% v/v amyl alcohol in chloroform is used for Bromocresol purple and bromocresol green. Extractable complexes shows maximum absorption at 416 nm, 412 nm and 419 nm, the drug in the worked experimental shows linearity range for bromophenol blue, bromocresol purple and bromocresol green in concentration ranges of 0-7 µg/ml respectively. The coloured chromospheres were found to be stable for 40 min. 60 min and 30 min respectively	54

Table 7: Analytical Methods available to detect Terfenadine Hydrochloride

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Terfenadine HCl (Human plasma)	HPLC	The compounds were isolated from plasma by liquid extraction with methyl-t-butyl ether: isopropyl alcohol (95: 5% v/v). The chromatographic separation was carried on cyanopropyl silane column (15 cm × 4.6 mm) with a mobile phase consisting of 0.001 M acetate buffer, pH 4.0: acetonitrile (25: 75% v/v). The eluent was monitored at 230 nm excitation and 300 nm emission wavelengths with a 270 nm cut-off filter.	55
Terfenadine HCl + Terfenadine acid metabolites	HPLC	For Terfenadine, the validated quantitation range of this method is 10.0 - 84.2 ng/ml with coefficients of variation of 5.7 - 30%. For Terfenadine acid metabolite, the validated quantitation range of this method is 8.2 - 500 ng/ml with coefficients of variation of 4.1 - 24%.	56

Table 7: Analytical Methods available to detect Terfenadine Hydrochloride (Continued…..)

API and Sample matrix	Analytical Method	Experimental Condition	Ref. No
Terfenadine HCl	Spectro-photo metric method	Beer's law is obeyed over the concentration ranges of 3-72, 3-96, 12-168 and 24-240 µg $mL^{(-1)}$ Terfenadine using TCNQ, TCNE, DDQ and p-CLA, respectively, with correlation coefficients 0.9999, 0.9974, 0.9997 and 0.9979 and detection limits 0.3, 0.4, 2.6 and 12.3 µg $mL^{(-1)}$, for the reagents in the same order.	57
Terfenadine HCl (Human plasma)	Spectro-photo metric method	The relation between the absorbance at 395 nm and the concentration is rectilinear over the range 0.5-5 µg $ml^{(-1)}$ (molar absorptivity is 1.405 x $10^{(5)}$ l $mol^{(-1)}$ $cm^{(-1)}$). The reaction product was also measured spectro-fluorimetrically at 435 nm after excitation at 395 nm. The fluorescence intensity was directly proportional to the concentration over the range 0.5-4 ng ml(-1) with minimum detectability (S/N = 2) of 0.07 µg $ml^{(-1)}$ (approximately 1.5 x $10^{(-10)}$ M)	58
Terfenadine HCl	Spectro-photo metric method	method is based on the formation of ion-pairs by the reaction of Terfenadine with chromotropic acid mono- and bis-azo dyes. Different variables affecting the ion-pair formation were studied. At the maximum absorption of 557, 521, 592 and 543 nm, Beer's law is obeyed in the range 0.2–18.6, 0.2–16.4, 0.2–25.0 and 0.2–22.2 µg ml^{-1} on using reagents I, II, III and IV, respectively.	59
Terfenadine HCl + astemizole + Flunarizine HCl	Spectro-photo metric method	The method does not involve solvent extraction. The colour of the produced complex is measured at 547.5 nm for (I) and (III), while (II) is measured at 540.7 nm. Appropriate conditions were established for the colour reaction and for the eosin: Pb(II): drug ratio to obtain maximum sensitivity. Under the proposed conditions, the method is applicable over concentration range of 4.1–37.6, 11.8–47.2 and 2.4–19.1 µg ml−1 with mean percentage recovery of 99.20±0.63, 99.76±0.39 and 99.60±0.47% for (I), (II) and (III), respectively.	60

CONCLUSION

Reference methods that have a chromatographic step to ensure sufficient selectivity must be available for the determination of each antihistaminic drug. It is highly desirable that the various steps of reference and routine methods be carefully investigated. Conditions chosen for the various steps should be characterized, including the determination of absolute recoveries and values for the separation parameters. The overall method performance in terms of imprecision and inaccuracy should be evaluated statistically and validated by comparison with existing methods. From literature review we can say that the proposed methods are expensive and usually require longer running times, apart from that there no clear stability indicative method which describe about degradants formed during the forced degradation studies. So we can say that there is a strong requirement of a method which can detect both the compounds economically with short analysis time. There is also a need of a method which can detect and identify the degradation product when drugs are exposed to the forced degradation studies.

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