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Review Article

REVIEW OF DRUGS AND ITSANALYTICAL METHODS TO TREAT ALLERGIC RHINITIS IN COMBINATION WITH OTHER DRUGS IN DIFFERENT DOSAGE FORM

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ABSTRACT

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

Keywords: Spectroscopy, RP-HPLC, Ambroxol, Levofloxacin, Gemifloxacin, Cefixime, Cefadroxil.

INTRODUCTION

Now a day, various Antibiotics drugs are available in combination with Mucolytic agents in market in different dosage form. Among them Flouroquinolones (e.g. Levofloxacin Hemihydrate, Gemifloxacin Mesylate) are the choice for treatment of serious bacterial infections, urinary tract infections, pyelonephritis and post exposure treatment for inhalation anthrax, Cephalosporins (e.g. Cefadroxil Monohydrate, Cefixime Trihydrate) are used for the prophylaxis and treatment of infections caused by bacteria while Mucolytic agents (e.g. Ambroxol Hydrochloride) are the first class of choice for cough suppression and also in the management for the relief of symptoms of seasonal allergic rhinitis, perennial (non-seasonal) allergic rhinitis in both adult and child. Few example of Mucolytic agent with Fluoroquinolones and Cephalosporins are as follow (Table 1).

Table 1: Combination of Mucolytic agent with Fluoroquinolones and Cephalosporins

S. No.	Drug combination	Marketed formulation	Manufacturer
1	Ambroxol HCl (75mg) + Levofloxacin Hemihydrate (500mg)	LEBACT AM[1]	Nicholas Piramal India Ltd.
2	Ambroxol HCl (75mg) + Gemifloxacin Mesylate (320mg)	G – CIN – A[2]	Lupin Pharmaceuticals
3	Ambroxol HCl (60mg) + Cefixime trihydrate (200mg)	CEFTAS – AL[3]	Intas Laboratories Pvt Ltd
4	Ambroxol HCl (30mg) + Cefadroxil monohydrate (250mg)	KEFDIL – AX[4]	Ajanta Pharma Ltd

Ambroxol Hydrochloride (AMB) (Fig. 1) is chemically Trans–4–(2–Amino-3, 5–dibromobenzyl amino)–cyclohexanol[5]. It is used in the treatment of tracheobronchitis, emphysema with bronchitis pneumoconiosis, chronic inflammatory pulmonary conditions, bronchiectasis, bronchitis with bronchospasm asthma[6]. It is official in Indian Pharmacopoeia (IP) and British Pharmacopoeia (BP). IP[5] describes High Performance Liquid Chromatography (HPLC) method and BP[7] describes HPLC, Spectrophotometric and Thin Layer Chromatography (TLC) method.

Levofloxacin Hemihydrate (LEV) (Fig. 2) is chemically t(-)-(S)-9-fluoro-2,3-dihydro-3-Methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6carboxylic acid hemihydrate[8]. It is official in IP and describes High Performance Liquid Chromatography (HPLC) method.

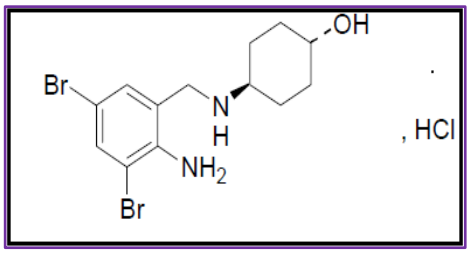

Fig. 1: Structure of Ambroxol Hydrochloride

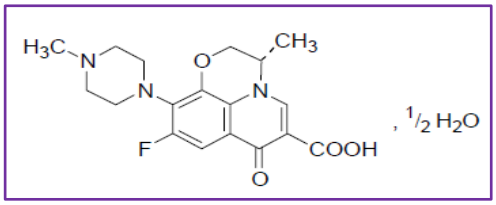

Fig. 2: Structure of Levofloxacin Hemihydrate

Gemifloxacin Mesylate (GEM) (Fig. 3) is chemically 7-[(4Z)-3-(aminomethyl)-4-(methoxyimino) pyrrolidin-1-yl]-1-cyclopropyl -6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid mono methane sulphonate[9]. It is not official in any Pharmacopoeia.

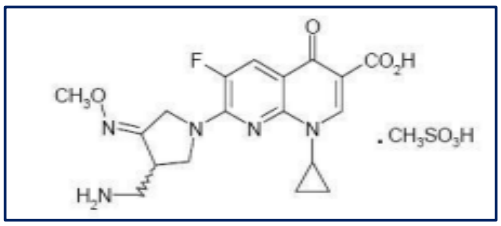

Fig. 3: Structure of Gemifloxacin Mesylate

Cefadroxil Monohydrate (CEF) (Fig. 4) ischemically (6R,7R)-7-[(2R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid mono hydrate[10].It is official in IP, BP and United state Pharmacopoeia (USP).

Cefixime Trihydrate (CEFI) (Fig. 5), chemically (6R,7R)-7- [(2Z)-2-(2-amino-1,3-thiazo l-4-yl)-2-[(carboxymethoxy)imino]acetamido]-3-ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid tri hydrate[11]. It is official in BP and USP.

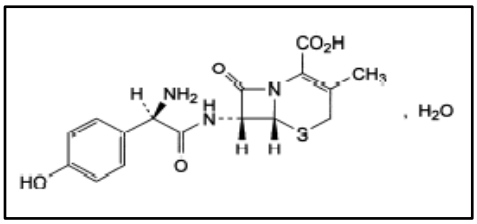

Fig. 4: Structure of Cefadroxil Monohydrate

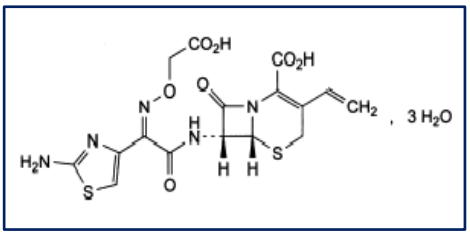

Fig. 5: Structure of Cefixime Trihydrate

Table 1: Introduction to Drugs

S. No.	Drug Name	Information of drug[12]-[20]
1	Ambroxol Hydrochloride	Category:Mucolytic Agent Molecular formula:$C_{13}H_{18}Br_2N_2O.HCl$ Molecular weight:414.62 gm/mol Melting Point:235- 240 °C pka value:8.2
2	Levofloxacin Hemihydrate	Category: fluoroquinolone antibacterial agent Molecular formula:$C_{18}H_{20}FN_3O_4$, ½ H_2O Molecular weight:361.36 gm/mol. Melting Point:224 - 229 °C pka value:6.05 and 8.22
3	Gemifloxacin Mesylate	Category:fluoroquinolone antibacterial agent Molecular formula:$C_{18}H_{20}FN_5O_4.CH_4O_3S$ Molecular weight:485.49 gm/mol Melting Point:235 – 237 °C pka value: 8.93
4	Cefadroxil Monohydrate	Category:Cephalosporin antibacterial agent Molecular formula:$C_{16}H_{17}N_3O_5S.H_2O$ Molecular weight:381.4 gm/mol Melting Point:197 °C pka value:9.48
5	Cefixime Trihydrate	Category:Cephalosporin antibacterial agent Molecular formula:$C_{16}H_{15}N_5O_7S_2.3H_2O$ Molecular weight:507.5 gm/mol Melting Point:218 - 225 °C pka value:3.26

Various methods are available for the detection of antihistaminic drugs along with antibiotics from their pharmaceutical formulations which helps in the estimation of the active products, impurities and the active pharmaceutical ingredients. However literature survey revealed that that there is no stability indicating method available. The methods can be selected for the quantitation of the drug based upon its cost effectiveness, its running time, ease of operating and its suitability. Here from the literature survey various methods have been shown along with their characteristic so form the given data one can produce better methods with short analysis time, and low running cost. Various analytical methods for the estimation of drugs are as follows (Table 2).

Table 2: Reported Methods to estimate drug alone and in combination with other drugs

S. No.	API and Sample matrix	Analytical Method	Experimental condition	Rf. No
1	Ambroxol HCl (Tablet)	First Order Derivative Method RP – HPLC	Diluent:- Distilled Water Linearity range:- 5 - 35 µg/ml for Ambroxol HCl λ:- 255 nm for Ambroxol HCl Column:- RP C_{18} Column Mobile phase:- Aqueous Phosphate (0.01 M): Acetonitrile: Glacial Acetic Acid(59: 40: 1 v/v/v) (pH 3.12) λ:- 252 nm	[21]
2	Ambroxol HCl + Guiaphensin (Tablet)	Simultaneous equation method	Diluent:- Methanol Linearity range:-5 - 50 µg/ml for Ambroxol HCl λ_{max}:- 242 nm Ambroxol HCl and 272 nm Guiaphensin	[22]
3	Ambroxol HCl + Levofloxacin Hemihydrate (Bulk drug and formulation)	Q analysis	Diluent:- Distilled Water Linearity range:- 5 - 35 µg/ml for Ambroxol HCl λ_{max}:- 219 nm (iso-absorptive point) and 287 nm	[23]
4	Ambroxol HCl + Gatifloxacin (Bulk drug and formulation)	Simultaneous determination	Diluent:- Methanol: Water Linearity range:- 10 - 50 µg/ml for Ambroxol HCl λ_{max}:-242 nm	[24]
5	Ambroxol HCl + Salbutamol (Tablet)	Absorbance Correction Method	Diluent:- 0.1 N HCl Linearity range:- 2 - 20 µg/ml for Ambroxol HCl λ_{max}:-300 nm	[25]

		First Order Derivative Method	Diluent:- 0.1 N HCl Linearity range:- 2 - 20 µg/ml for Ambroxol HCl λ:- 232 nm	
6	Ambroxol HCl + Loratadine (Tablet)	Simultaneous equation Method	Diluent:-Methanol Linearity range:- 10 - 50 µg/ml for Ambroxol HCl λ_{max}:- 245 nm Ambroxol HCl and 308 nm Loratadine	[26]
7	Ambroxol HCl + Amoxicillin Trihydrate (Tablet)	First Order Derivative Method	Diluent:-0.1M HCl Linearity range:- 10 - 90 µg/ml for Ambroxol HCl λ:- 259 nm AMB	[27]
		Area Under Curve Method	Diluent:- 0.1M HCl Linearity range:- 10 -70 µg/ml for Ambroxol HCl λ:- 243.6 nm, 245.6 nm Ambroxol HCl	
8	Ambroxol HCl + Salbutamol (Tablet)	Simultaneous equation Method	Diluent:- Methanol Linearity range:- 2 - 40 µg/ml for Ambroxol HCl λ_{max}:- 244 nm Ambroxol HCl and 223 nm Salbutamol	[28]
		Area Under Curve Method	Diluent:- Methanol Linearity range:- 2 - 40 µg/ml for Ambroxol HCl λ:- 252 nm, 237 nm	
9	Ambroxol HCl + Levocetrizine (Tablet)	Simultaneous equation method	Diluent:- Distilled Water Linearity range:- 10 - 50 µg/ml Ambroxol HCl λ_{max}:-242 nm Ambroxol HCl and 231 nm Levocetrizine	[29]
10	Ambroxol HCl + Cetirizine HCl (Tablet)	Simultaneous Equation Method	Diluent:- Distilled Water Linearity range:- 10 - 35 µg/ml for Ambroxol HCl λ_{max}:- 243 nm Ambroxol HCl and 229 nm Cetirizine HCl	[30]
11	Ambroxol HCl + Doxofylline (Bulk drug and Tablet)	Simultaneous equation Method	Diluent:- Distilled Water Linearity range:- 1 - 5 µg/ml for Ambroxol HCl λ_{max}:- 244.5 nm	[31]
		Absorbance Correction Method	Diluent:- Distilled Water Linearity range:- 1 - 5 µg/ml for Ambroxol HCl λ_{max}:- 308 nm	
12	Ambroxol HCl + Gemifloxacin Mesylate (Tablets)	Simultaneous Equation Method	Diluent:- Methanol Linearity range:- 6 - 30 µg/ml for Ambroxol λ_{max}:- 249.5 nm Ambroxol HCl and 272 nm Gemifloxacin Mesylate	[32]
		First Order Derivative Method	Diluent:- Methanol Linearity range:- 6 - 30 µg/ml for Ambroxol HCl λ_{max}:- 279 nm	
13	Ambroxol HCl + Cetirizine Hydrochloride (Tablet)	Absorbance Ratio Method	Diluent:- Distilled Water Linearity range:- 30 - 48 µg/ml for Ambroxol HCl λ:- 243 nm and 236 nm	[33]
		RP-HPLC	Column:- HIQ SIL - C_{18} (4.6 i.d., × 250 mm, 10 µm) Mobile phase:- Methanol: Acetonitrile: Water (40: 40: 20 v/v/v) λ:- 229 nm	
14	Ambroxol HCl + Desloratadine HCl (Tablet)	First Derivative Method	Diluent:- 0.1 N HCl Linearity range:- 10 - 80 µg/ml for Ambroxol HCl λ:- 256 nm	[34]
15	Ambroxol HCl + Desloratadine HCl (Tablet)	Q Absorbance ratio Method	Diluent:- 0.1 N HCl Linearity range:- 5 - 75 µg/ml for Ambroxol HCl λ_{max}:- 244 nm Ambroxol HCl and 308 nm	[35]
16	Ambroxol HCl (Bulk drug and formulation)	RP-HPLC	Column:- SS aokosil C_{18} (4.6 i.d., × 250 mm, 5 µm) Mobile phase:- Acetonitrile: Methanol: 0.5% Ammonium Acetate (44: 16: 40 v/v/v) (pH 5.0) λ:- 295 nm	[36]
17	Ambroxol HCl + Cetirizine Di hydrochloride	RP-HPLC	Column:- Kromasil RP C_8 (250 mm x 4.6 mm i.d., 5 µm) Mobile phase:- Acetonitrile: 0.1 % Tri ethyl Amine (50: 50 v/v) (pH 4.0) λ:- 230 nm	[37]
18	Ambroxol HCl + Cetirizine HCl (Bulk drug and formulation)	HPLC	Column:- Princeton C_8 (4.6i.d., × 250 mm, 5 µm) Mobile phase:- Methanol: 10 mM Potassium di- hydrogen phosphate buffer (80:20v/v) (Ph 3.5) λ:- 276 nm	[38]
19	Ambroxol HCl + Gatifloxacin (Tablet)	RP-HPLC	Stationary phase:- Phenomenex Luna C_{18} (4.6 i.d.,× 250 mm, 5 µm) Mobile phase:- 0.02 M dibasic Ammonium phosphate buffer: Acetonitrile (60: 40 v/v) (pH 7.0) λ:- 265 nm	[39]
20	Ambroxol HCl + Gatifloxacin (Tablet)	RP-HPLC	Stationary phase:- HIQ SIL C_{18} (4.6 i.d., × 250 mm, 5 µm) Mobile phase:- 0.01 M Potassium Di hydrogen Ortho phosphate buffer: Acetonitrile (70: 30 v/v) (pH 3.0) λ:- 247 nm	[40]
21	Ambroxol HCl + Levocetrizine 2HCl (Bulk drug and formulation)	RP-HPLC	Column:- RP - C_{18} column Mobile phase:- Acetonitrile: Phosphate buffer solution (60: 40 v/v) (pH 7.0) λ:- 230 nm	[41]
22	Ambroxol HCl + Roxithromycin (Bulk and Tablet)	RP-HPLC	Column:- Phenomenex Gemini C_{18} column (250 mm x 4.6 mm i.d., 5 µm) Mobile phase:- Water: Acetonitrile: Ortho phosphoric acid (50: 50: 0.1 v/v/v) λ:- 210 nm	[42]
23	Ambroxol HCl + Levofloxacin	RP-HPLC	Column:- Hypersil BDS C_{18} column (25cm x 4.6mm i.d., 5µm).	[43]

	(Bulk drug and formulation)		Mobile phase:- Buffer: Acetonitirile: Methanol (650: 250: 100 v/v/v) (pH 5.2) λ:- 220 nm	
24	Ambroxol HCl + Loratadine (Bulk drug and formulation)	RP-HPLC	Column:- Phenomenex Gemini C_{18} (25 cm x 4.6 mm i.d.,5µm) Mobile phase:- Acetonitrile: 50mM Ammonium Acetate (50: 50v/v) λ:- 255 nm	[44]
25	Ambroxol HCl + Gemifloxacin Mesylate (Bulk drug and formulation)	RP-HPLC	Column:- Phenomenex C_{18} Mobile phase:- Phosphate Buffer:Acetonitrile: Methanol (50: 25: 25 v/v/v) (pH 6.0) λ:- 246 nm	[45]
26	Ambroxol HCl + Gemifloxacin Mesylate (Bulk drug and formulation)	RP-HPLC	Column:- Phenomenex C_{18} Mobile phase:- Acetonitrile: Methanol: 0.1 % Trifluro acetic acid (50: 25: 25 v/v/v) λ:- 248 nm	[46]
27	Ambroxol HCl + Cetirizine HCl, Methylparaben and Propylparaben (Liquid formulation)	RP-UPLC	Column: - Agilent Eclipse plus C_{18}, 1.8 µm (50 x 2.1 mm i.d.) column Mobile phase:-mixture of 0.01 M phosphate buffer and 0.1 % triethylamine as a solvent-A and Acetonitrile as a solvent-B. λ:- 237 nm	[47]
28	Levofloxacin Hemihydrate + Cefpodoxime Proxetil	Q absorbance Ratio method	Diluent:- Methanol Iso absorptive point at 273 nm, 300 nm $\lambda_{max}$of Levofloxacin hemihydrate Concentration range – 2 - 10 µg/ml for Cefpodoxime Proxetil and 2.5 - 10.5 µg/ml Levofloxacin hemihydrate.	[48]
29	Levofloxacin Hemihydrate + Ornidazole	Simultaneous Equation Method	Diluent:- water λ:-289 nm and 320 nm Concentration range – 8 - 40 µg/ml for Ornidazole and 4 - 20 µg/ml Levofloxacin hemihydrate.	[49]
30	Levofloxacin Hemihydrate + Cefixime Trihydrate	Simultaneous Equation Method	Diluent:- Methanol λ:-240 nm and 296 nm Concentration range – 3 - 15 µg/ml for Levofloxacin hemihydrate and Cefixime trihydrate	[50]
		Q absorbance Ratio method	Diluent:- Methanol Iso absorptive point at 289 nm, 240 nm λ_{max} of Cefixime trihydrate concentration range – 3 - 15 µg/ml for Levofloxacin hemihydrate and Cefixime trihydrate	
31	Levofloxacin Hemihydrate	Spectro - photometric Method	Diluent:- Methanol λ:-298 nm Concentration range – 3 - 8 µg/ml Levofloxacin hemihydrates.	[51]
32	Levofloxacin Hemihydrate	Spectro-photometric Method	Diluent:- Distilled water λ:- 289 nm Concentration range – 0.5 - 8 µg/ml Levofloxacin hemihydrate.	[52]
33	Levofloxacin Hemihydrate	Spectro - photometric Method	Diluent:- Chloroform λ:-257.4 nm Concentration range – 5 - 30 µg/ml Levofloxacin hemihydrate.	[53]
34	Levofloxacin Hemihydrate + Ambroxol HCl	Q absorbance Ratio Spectroscopy method	Diluent:- water Isoabsorptive point at 219 nm, 287 nm λ_{max} of Levofloxacin hemihydrate Concentration range –2 - 14 µg/ml Levofloxacin hemihydrate and 5 - 35 µg/ml for Ambroxol HCl	[54]
35	Levofloxacin Hemihydrate	Spectro - photometric Method	Diluent:- 0.1 M HCl λ:-290 nm Concentration range –0.25 - 12 µg/ml Levofloxacin hemihydrate.	[55]
36	Levofloxacin Hemihydrate	HPLC	Column:- C_{18} RP – HPLC Column Mobile phase:- Potassium Dihydrogen Ortho Phosphate: Methanol: Acetonitrile (70: 15: 15 v/v/v), λ:- 295 nm Flow Rate :- 1.5 ml/min	[56]
37	Levofloxacin Hemihydrate	HPLC	Column:- 5µm intensil, C_{18} column (4.6 x 250mm x 5µm) Mobile phase:- 80: 20 v/v Phosphate buffer pH 2.5: Acetonitrile, λ:- 235 nm Flow Rate:-1 ml/min	[57]
38	Levofloxacin Hemihydrate + Ornidazole	RP- HPLC	Column:- XTerra RP_{18} Column (4.6 x 150 mm and 5 µm) Mobile phase:- 40: 60 v/v Phosphate buffer : Acetonitrile, λ:- 315 nm Flow Rate:- 0.5 ml/min	[58]
39	Levofloxacin HCl + Lomefloxacin HCl + Gatifloxacin + Sparfloxacin	RP- HPLC	Column:- Chromolith® Performance RP-$_{18}$ (100 x 4.6 mm) Mobile phase:- Methanol: 0.025 M KH_2PO_4 adjusted to pH 3 using ortho - phosphoric acid (20: 80 v/v), λ:- 290 nm Flow Rate:- 4 ml/min	[59]
40	Levofloxacin Hemihydrate + Ornidazole	RP- HPLC	Column:- Phenomenex Luna C_{18} column (5µ, 150 x 4.6mm i.d). Mobile phase:- triethylamine (0.5% v/v adjusted to pH 3 using orthophosphoric acid), Acetonitrile and Methanol (40: 30: 30 v/v/v), λ:- 310 nm Flow Rate:- 0.5 ml/min	[60]
41	Levofloxacin Hemihydrate + Ambroxol HCl	RP- HPLC	Column:- Hypersil $BDSC_{18}$ column (25cm x 4.6mm, 5µm). Mobile phase:- Buffer: Acetonitrile: Methanol (650: 250: 100 v/v/v) with Triethylamine and pH adjusted to 5.2 with dilute ortho phosphoric Acid, λ:- 220 nm Flow Rate:-1 ml/min	[61]

42	Gemifloxacin Mesylate	Difference Spectroscopy method	Diluent:- 0.1 M NaOH and 0.1 M HCl λ:-278nm and 320nm Concentration range –0.5-30 µg/ml	[62]
43	Gemifloxacin Mesylate + Ambroxol HCl	Simultaneous Equation Method	Diluent:- water λ:-271.0 nm and 245.5 nm Concentration range – 10-60 µg/ml for Gemifloxacin Mesylate and 2-12 µg/ml for Ambroxol HCl	[63]
		Q absorbance Ratio method	λ:- 271nm λmax of Gemifloxacin Mesylate and 244 nm Isobestic point Concentration range – 10-60 µg/ml for Gemifloxacin Mesylate and 2-12 µg/ml for Ambroxol HCl	
44	Gemifloxacin Mesylate	Spectroscopy method	Diluent:- Double Distilled Water λ:-269nm concentration range – 2 -10 µg/ml	[64]
45	Gemifloxacin Mesylate	Spectroscopy method	Diluent:- 0.05 N H_2SO_4 λ:- 267nm concentration range – 10 -70 µg/ml	[65]
46	Gemifloxacin Mesylate	Direct and Derivative Spectroscopy method	The method is based on chelate formation between GFX and Palladium (Pd II) in aqueous media. The complex showed an absorption maximum at 430 nm, 1st derivative at 480nm and Second derivative at 500nm respectively with apparent molar absorpitivities of 1.365 x 10^4 $LM^{-1}cm^{-1}$, 9.37x10^4 $LM^{-1}cm^{-1}$ for first order derivative, 1.59 x 10 $LM^{-1}cm^{-1}$ for2nd order derivative respectively. The solution of the complex obeyed beer's law in the concentration range of 2to14 µg/ml for zero order, 1 to 10 µg/ml for 1st order and 1to 15 µg/ml for 2nd order respectively.	[66]
47	Gemifloxacin Mesylate	HPLC	Column:- Cyano column (250 x 4.6 mm, 5µm particle size) Mobile phase:-1% v/v formic acid: Acetonitrile: Methanol 75:20:5 (v/v/v) λ:-292 nm, Flow Rate :-1 ml/min	[67]
48	Gemifloxacin Mesylate	HPLC	Column:- phenomenex C_{18}, pre-packed column Mobile phase:- phosphate Buffer: Acetonitrile: methanol(50:25:25 v/v/v)with triethylamine 0.2% adjusted to pH 6.0 with ortho phosphoric acid λ:-246 nm, Flow Rate :-1 ml/min	[68]
49	Gemifloxacin Mesylate+ Hydrochlorothiazide + furosemide	RP- HPLC	Column:- Purospher Start C_{18} (250 mm x 4.6 mm, 5 µm) column Mobile phase:- methanol: water: Acetonitrile (70:25:5v/v/v) adjusted to pH 3.0 via phosphoric acid 85% λ:-232 nm, Flow Rate :-0.8 ml/min	[69]
50	Gemifloxacin Mesylate	RP- HPLC	Column:-cyberlabcapcellpak ,ODS C_{18} (250 × 4.6 mm i.d., 5 µm particle size) column Mobile phase:-Buffer (KH_2PO_4 with pH 6.8): acetonitrile in the ratio of 80:20 (v/v) λ:-265 nm, Flow Rate :-1.2 ml/min	[70]
51	Gemifloxacin Mesylate	RP- HPLC	Column:-C_{18}column (250mm × 4.6mm i.d, 5 mm) Mobile phase:-methanol: 7% formicacid (80:20v/v)pH was adjusted to 2.1 λ:-260 nm, Flow Rate :-1 ml/min	[71]
52	Gemifloxacin Mesylate and H_2-receptor antagonists i.e. Cimetidine, Famotidine	RP- HPLC	Separation was achieved on the RP-Mediterranea column [C_{18} (250 x 4.6 mm, 5 µm)] at ambient temperature using mobile phase consisting of Acetonitrile: methanol: water (20:28:52 v/v/v pH 2.8 adjusted by phosphoric acid). Flow rate was 1.0 mL/min with an average operating pressure of 180 kg/cm^2. Gatifloxacin was used as an internal standard (IS).	[72]
53	Gemifloxacin Mesylate	RP- HPLC	Column:- Hypersil BDS C_{18} column Mobile phase:- citratebuffer (adjusted to 2.5 pH by citric acid):Acetonitrile (70: 30 v/v) λ:-267 nm, Flow Rate :-1 ml/min	[73]
54	Gemifloxacin Mesylate (Human Plasma)	RP- HPLC	The plasma sample was extracted using Chloroform: Acetic acid (5.4:0.1, v/v). A concentration range from 30 to 600ng/ml was used for calibration curve. The % recovery of Gemifloxacin Mesylate was found to be 80.06-84.88. The mobile phase used consist of Methanol: sodium acetate (1%): ortho phosphoric acid (65:35:0.5, v/v/v) with pH 2.1 and flow rate 0.8 ml/min in isocratic mode. The separation was carried out by UV-detector at wavelength 263 nm.	[74]
55	Cefadroxil Monohydrate	Visible Spectroscopy method	Cefadroxil with Ninhydrine reagent in methanol gives blue colour chromogen, maximum absorbance at 578 nm Concentration range:- 5 – 50 µg/ml	[75]
56	Cefadroxil Monohydrate	UV method	Diluent: - Methanol: water (50: 50 v/v) λ:-264 nm Concentration range- 10 – 50µg/ml	[76]
57	Cefadroxil Monohydrate	UV method	Diluent:- Methanol λ:-257 nm Concentration range -10 – 100µg/ml	[77]
58	Cefadroxil Monohydrate + Ceftriaxone	Colorimetric method	Derivatization with 1, 2-naphthaquinone- 4- sulfonic acid sodium in alkaline λ:-475 nm for Cefadroxil and 480 nm for Ceftriaxone Concentration range – 10 - 100 µg/ml Cefadroxil and 25 – 175 for Ceftriaxone	[78]
59	Cefadroxil Monohydrate	Bromination Method	Cefadroxil was brominated with bromate – bromide mixture under strong acidic conditions. After bromination, the excess mixture was treated with methylene blue result in formation of green complex. The absorbance was	[79]

			measured at 670 nm. Concentration Range:- 100 – 800 µg/ml	
60	Cefadroxil Monohydrate + Ambroxol HCl	HPLC	Column:- Purospher BDS C_{18} column (25cm x 4.6mm, 5µm) Mobile phase:-0.5M Ammonium acetate buffer- Acetonitirile (50:50v/v), pH adjusted to 7 using ortho phosphoric acid λ:-247 nm, Flow Rate:-1 ml/min	[80]
61	Cefadroxil Monohydrate	HPLC	Column:-supelco RP C_{18} column (250 mm × 4.6 mm) with 5 µm particle size. Mobile phase:-methanol and 0.05M disodium hydrogen orthophosphate buffer (60: 40 v/v) and with pH 3.0 adjusted with ortho phosphoric acid λ:-264 nm, Flow Rate:-0.75 ml/min	[81]
62	Cefadroxil Monohydrate	RP- HPLC	Column:-XTerra RP_{18} column(250 × 4.0 mm, 5 µm) Mobile phase:- mixture of phosphate buffer (pH 5) and acetonitrile (96:4%v/v) λ:- 254 nm, Flow Rate:-1 ml/min	[82]
63	Cefadroxil Monohydrate	RP- HPLC	Column:- Phenomenex-Luna RP_{18} (250 x 4.6mm, 5µm) column Mobile phase:- Acetonitrile: 0.05M phosphate buffer (45: 55 v/v) of pH 5.0 ± 0.2 λ:-257 nm, Flow Rate:-1 ml/min	[83]
64	Cefadroxil Monohydrate	RP- HPLC	Column:- C_{18}column (250mm × 4.6mm i.d, 5 µm) Mobile phase:- methanol: Double Distilled Water (60: 40 v/v) λ:-264 nm, Flow Rate:-1 ml/min	[84]
65	Cefixime + Ofloxacin	Q absorbance Ratio method Simultaneous Equation Method	Diluent:- Ethanol and Iso absorptive point at 282 nm, 297.4 nm λ_{max} of ofloxacin Concentration range:-5 - 25 µg/ml for Cefixime and 2 -10 µg/ml ofloxacin. Diluent:- Ethanol λ:-290.4 nm and 297.4 nm Concentration range – 5 - 25 µg/ml for Cefixime and 2 -10 µg/ml ofloxacin.	[85]
66	Cefixime Trihydrate + Linezolid	Q absorbance Ratio method Simultaneous Equation Method	Diluent:- Methanol Isoabsorptive point at 278.72 nm, 256.70 nm λ_{max} of Linezolid Concentration range - 2 - 10 µg/ml for Cefixime and 5 – 25 µg/ml Linezolid. Diluent:- Methanol λ:-288.72 nm and 256.70 nm Concentration range- 2 - 10 µg/ml for Cefixime and 5 – 25 µg/ml ofloxacin.	[86]
67	Cefixime + Ofloxacin	Q absorbance Ratio method Simultaneous Equation Method	Diluent:- Methanol Iso absorptive point at 275 nm, 296nm λ_{max} of ofloxacin Concentration range –4 - 20 µg/ml for Cefixime and 2 -10 µg/ml ofloxacin. Diluent:- Methanol λ:-234 nm and 296 nm Concentration range – 4 - 20 µg/ml for Cefixime and 2 -10 µg/ml ofloxacin.	[87]
68	Cefixime Trihydrate + Azithromycin Dihydrate	First Derivative Spectroscopy	Diluent:-water λ:-zero crossing point for Azithromycin dihydrate and Cefixime trihydrate was 326.4 nm and 226.8 nm, respectively Concentration range –10 - 40 µg/ml Cefixime trihydrate and 25 – 100 Azithromycin Dihydrate	[88]
69	Cefixime + Moxifloxacin	Q absorbance Ratio method Simultaneous Equation Method	Diluent:- 0.1 N HCl isoabsorptive point at 279 nm, 295 nm λ_{max} of Moxifloxacin Concentration range – 2 - 18 µg/ml for Cefixime and 2 -12 µg/ml Moxifloxacin. Diluent:- 0.1 N HCl λ:-286 nm and 295 nm Concentration range – 2 - 18 µg/ml for Cefixime and 2 - 12 µg/ml Moxifloxacin.	[89]
70	Cefixime + Moxifloxacin	First Derivative Spectroscopy	Diluent:- Methanol λ:-zero crossing point for Cefixime 316.4 nm and for Moxifloxacin 289 nm Concentration range –4 - 14 µg/ml for both Cefixime and Moxifloxacin	[90]
71	Cefixime Trihydrate + Azithromycin Dihydrate	Simultaneous Equation Method	Diluent:- water λ:-235 nm and 288 nm Concentration range –2 - 10 µg/ml for Cefixime and 10 - 50 µg/ml Azithromycin	[91]
72	Cefixime Trihydrate + Ornidazole	RP- HPLC	Column:-Phenomenex C_{18} column (25 cm ×4.6 mm i.d.) Mobile phase:- Acetonitrile: 40mM KH_2PO_4 in proportion of 40:60(v/v) with pH adjusted to 6±0.5 by using Triethylamine λ:-310 nm, Flow Rate:-1 ml/min	[92]
73	Cefixime Trihydrate + Moxifloxacin	RP- HPLC	Column:- Phenomix C_{18} (250×4.6 mm i.d, 5 µm) column Mobile phase:-Acetonitrile: 0.08M potassium Dihydrogen ortho phosphate (adjusted to pH 8 with NaOH) (40: 60 v/v) λ:-290 nm, Flow Rate:-1 ml/min	[93]
74	Cefixime + Ambroxol HCl	HPLC - PDA	Column:- Phenomenex-Gemini, RP_{18} column (250 x 4.6 mm, 5 µm size Mobile phase:-Acetonitrile: Methanol: 0.5% ammonium acetate buffer (pH 5.54) (44: 16: 40 v/v/v) λ:-220 nm, Flow Rate:-1 ml/min	[94]
75	Cefixime Trihydrate	RP- HPLC	Column:-C_{18} column (waters spherisorb 25 cm × 4.6 mm, 5µm), Mobile phase:- sodium Dihydrogen phosphate mono hydrate (0.1M aqueous) pH adjusted to 2.5 with diluted orthophospharic acid (10 % aqueous) and	[95]

			methanol in a ratio of 3:1 v/v λ:-254 nm, Flow Rate:- 1 ml/min	
76	Cefixime Trihydrate	RP- HPLC	Column:-SS aokosil II C_{18}, 250 x 4.6mm, 5µm column Mobile phase:- Acetonitrile: Methanol: 0.5% ammonium acetate (44:16:40 v/v/v) (PH 5). λ:-295 nm, Flow Rate:-0.8 ml/min	[96]
77	Cefixime + Cloxacillin	RP- HPLC	Column:-HiQsil C_8 (4.6 x 250 mm, internal diameter 5 µm) column Mobile phase:-Acetonitrile: tetra-butyl ammonium hydroxide buffer in the ratio of 45:55 v/v and pH adjusted to 4 with ortho phosphoric acid. λ:-225 nm, Flow Rate:-1ml/min	[97]
78	Cefixime Trihydrate + Ambroxol HCl	RP- HPLC	Column:-column C_{18} Mobile phase:- Acetonitrile: Methanol: Triethylamine (50: 50: 0.1 v/v/v), pH 3 λ:-254 nm, Flow Rate:- 1 ml/min	[98]
79	Cefixime + Ornidazole	RP- HPLC	Column:-Hypersil ODS C_{18} (150mm×4.6mm) Mobile phase:- Triethylamine buffer (pH 5.5): Acetonitrile (75:25) v/v λ:-295 nm, Flow Rate:-1 ml/min	[99]
80	Cefixime Trihydrate	RP- HPLC	Column:-C_{18} Hypersil ODS Mobile phase:- Tetrabutyl ammonium hydroxide solution: Acetonitrile (760:240 v/v) λ:-254 nm, Flow Rate:-2ml/min	[100]
81	Cefixime + Ofloxacin	RP- HPLC	Column:-HiQ-SiL C_8Neosphere column (150 × 4.6 mm i.d.) Mobile phase:-Methanol: 0.025 mM potassium dihydrogen phosphate buffer (70:30 v/v) λ:-290 nm, Flow Rate:-1 ml/min	[101]
82	Cefixime Trihydrate + Clavulanate	HPLC	Column:-L1 column (Hypersil Gold) 250mm x 4.6 mm, 5µm) Mobile phase:-0.0075 M Tetra Butyl Ammonium hydroxide of pH 6.8: Methanol (80:20 v/v) λ:-230 nm, Flow Rate:-1 ml/min	[102]
83	Cefixime + Cloxacillin	RP- HPLC	Column:-C_{18} column (5 µm, 25 cm x 4.6 mm, i.d) Mobile phase:- Phosphate buffer (pH 5.0): Acetonitrile: Methanol (80:17: 3 v/v/v) λ:-225 nm, Flow Rate:- 2ml/min	[103]
84	Cefixime + Ornidazole	RP- HPLC	Column:-C_{18} Hypersil ODS,4.6x250mm, 5 µm Mobile phase:-Acetonitrile: Water (30:70 v/v) and pH 3.4 with Ortho phosphoric acid λ:-237 nm, Flow Rate:-1ml/min	[104]
85	Cefixime Trihydrate+ Erdosteine	RP- HPLC	Column:- HiQSil C_8 column (25cm x 4.6mm, 5µm), Mobile phase:- TetraButyl Ammonium Hydroxide pH adjusted to 6.5 with Ortho phosporic acid (10% aqueous): Acetonitrile(2:1 v/v) λ:-254 nm, Flow Rate:-1ml/min	[105]
86	Cefixime + Dicloxacillin	RP- HPLC	Column:-C_{18} – inertstil Mobile phase:- Potassium hydroxide buffer:Acetonitrile (60:40 v/v) λ:-220 nm, Flow Rate:-1ml/min	[106]
87	Cefixime + Moxifloxacin	RP- HPLC	Column:-PurospherBDSC_{18} column Mobile phase:-Acetonitrile:0.01M KH_2PO_4 (40:60 v/v) λ:-276 nm, Flow Rate:-1ml/min	[107]
88	Cefixime Trihydrate+ Ofloxacin	RP- HPLC	Column:-Phenomenex C_{18}, 5µ, 250 mm × 4.6 mm Mobile phase:- Methanol: Water: Phosphate buffer, pH 4.9 (60: 20: 20 v/v/v) λ:-290 nm, Flow Rate:- 1 ml/min	[108]

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