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Review Article

A Review on Analytical Methods for Determination of Guaifenesin Alone and In Combination with Other Drugs in Pharmaceutical Formulations

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Abstract: Guaifenesin is an expectorant and it is use to treat cough and congestion caused by the common cold, bronchitis, and breathing illness. The drug is official in Indian Pharmacopoiea, British Pharmacopoeia, and United States Pharmacopoeias. This article reviews the different analytical methods available for detection of Guaifenesin alone and in combination from various pharmaceutical formulations. They are many analytical techniques have been reported for simultaneous estimation of Guaifenesin and its combined pharmaceutical dosage form but only fewer methods have been reported for estimation of Guaifenesin alone. Some of those techniques are UV spectrophotometry, high-performance liquid chromatography (HPLC), high-performance thin layer chromatography (HPTLC), liquid chromatography - mass spectrometry (LC-MS), gas chromatography (GC), and ultraperformance liquid chromatography (UPLC). Amongst, various analytical methods are available for the quantification of single and multicomponent dosage forms.
Keywords: Guaifenesin, Spectrophotometry, Chromatography, Expectorant, Pharmaceutical formulations

INTRODUCTION

Guaifenesin is an expectorant, which increases the output of phlegm and bronchial secretions by reducing surface tension and adhesiveness. The increased flow of less viscous secretions promotes cillary action and changes a dry, unproductive cough to one that is more productive and less frequent. By reducing the viscosity and adhesiveness of secretions, guaifenesin increases the efficacy of the mucociliary mechanism in removing accumulated secretions from the upper and lower airway. Guaifenesin is use to treat coughs and congestion caused by the common cold, bronchitis, and breathing illness [1].

Guaifenesin (GUA), chemically (+)-3-(2-Methoxyphenoxy)-propane-1,2 -diol. It occurs as a fine, white to slightly gray, crystalline, slight characteristic odor with a bitter aromatic taste. It is freely soluble in ethanol, soluble in chloroform, glycerol, propylene glycol, N, N-dimethylformamide, moderately soluble in benzene and practically insoluble in petroleum ether. Its molecular formula is $C_{10}H_{14}O_4$ and molecular weight is 198.2 g/mol. Its melting point is 78.5-79 ^oC and boiling point is 215 ^oC [1]. Its structural formula has shown in fig 1.

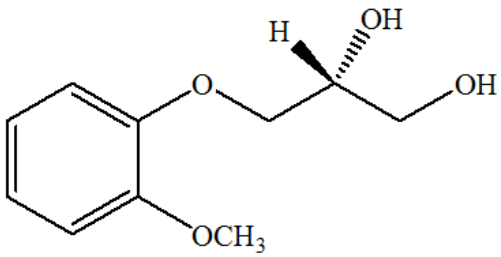

Fig-1: Structure of Guaifenesin

The present literature review stated that various analytical methods reported for the estimation of individual, binary, or tertiary combination of guaifenesin. Drug profile of guaifenesin and its combination of drugs has given as table1. Some Spectrophotometric methods reported for guaifenesin and it given as table2. Some HPLC methods reported for guaifenesin and it given as table3.

Table-1: Information of drugs [1, 2]

S.No.	DRUG NAME	INFORMATION OF DRUG
1.	Guaifenesin (GUA)	Category: Expectorant Molecular Formula: $C_{10}H_{14}O_4$ Molecular weight: 198.216 g/mol IUPAC Name: 3-(2-methoxyphenoxy)propane-1,2-diol Melting Point: 78.5-79°C pka value: 13.62
2.	Dextromethorphan (DEX)	Category: Antitussive Molecular Formula: $C_{18}H_{25}NO$ Molecular weight: 271.404 g/mol IUPAC Name: (1S,9S,10S)-4-methoxy-17-methyl-17-azatetracyclo-heptadeca-2(7),3,5-triene Melting Point: 122-124°C pka value: 9.85
3.	Chlorpheniramine (CHL)	Category: Asthamatic, Antihistaminics Molecular Formula: $C_{16}H_{19}ClN_2$ Molecular weight: 274.788 g/mol IUPAC Name: 3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-yl-propan-1-amine Melting Point: 130-135°C pka value: 9.13
4.	Bromhexine (BRO)	Category: Expectorant Molecular Formula: $C_{14}H_{20}Br_2N_2$ Molecular weight: 376.136 g/mol IUPAC Name: 2,4-dibromo-6-[[cyclohexyl(methyl)amino]methyl] aniline Melting Point: 232-235°C pka value: 19.89
5.	TerbutalineSulfate (TER)	Category: Bronchodilator Molecular Formula: $C_{12}H_{19}NO_3$ Molecular weight: 225.2842 IUPAC Name: 5-[2-(tert-butylamino)-1-hydroxyethyl]benzene-1,3-diol Melting Point: 119-122°C pka value: 8.86-9.76
6.	Phenylephrine (PHE)	Category: Mydriatic, Nasal decongestant, and Cardiotonic agent Molecular Formula: $C_9H_{13}NO_2$ Molecular weight: 167.208 g/mol IUPAC Name: 3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol Melting Point: 140-145°C pka value: 8.97
7.	Ambroxol HCl (AMB)	Category: Secretolytic agent Molecular Formula: $C_{13}H_{19}Br_2ClN_2O$ Molecular weight: 414.566 g/mol IUPAC Name: 4-[(2-amino-3,5-dibromophenyl)methylamino] cyclohexan-1-ol; hydrochloride Melting Point: 233-234.5°C pka value: 15.26
8.	Phenylpropanolamine (PPL)	Category: Stimulant, decongestant Molecular weight: 151.206 gm/mol Molecular Formula: $C_9H_{13}NO$ IUPAC Name: (1S,2R)-2-amino-1-phenylpropan-1-ol Melting Point: 190-194°C pka value: 9.44
9.	Pseudoephedrine HCl (PSE)	Category: Vasoconstrictor agents, Adrenergic agents, Sympathomimetic, 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
10.	Sodium benzoate (SBT)	Category: Antifungal preservative Molecular Formula: C_6H_5COONa/ $NaC_7H_5O_2$ Molecular weight: 144.105 g/mol IUPAC Name: Sodium benzoate Melting Point: >300°C pka value: 4.20
11.	Diphenylpyraline HCl (DIP)	Category: Antihistamine with anticholinergic Molecular Formula: $C_{19}H_{23}NO$ Molecular weight: 281.392 g/mol IUPAC Name: 4-benzhydryloxy-1-methyl-piperidine Melting Point: 206°C pka value: 8.87
12.	Pheniramine (PRM)	Category: Antihistamine with anticholinergic Molecular Formula: $C_{16}H_{20}N_2$ Molecular weight: 240.35 g/mol IUPAC Name: N,N-dimethyl-3-phenyl-3-pyridin-2-yl-propan-1-amine Melting Point: < 25 °C pka value: 9.48
13.	Pyrilamine (PYM)	Category: Antihistamine with anticholinergic Molecular Formula: $C_{17}H_{23}N_3O$ Molecular weight: 285.391 g/mol IUPAC Name: N-[2-(dimethylamino)ethyl]-N-[(4-methoxyphenyl) methyl]pyridin-2-amine Melting Point: 100-101°C; pka value: 8.85
14.	Dexchlorpheniramine maleate (DCP)	Category: Antihistamine with anticholinergic Molecular Formula: $C_{16}H_{19}ClN$ Molecular weight: 390.864 g/mol IUPAC Name:(Z)-but-2-enedioic acid;3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-ylpropan-1-amine Melting Point: 142°C
15.	Paracetamol (PAR)	Category: Analgesic and antipyretic Molecular Formula: $C_8H_9NO_2$ Molecular weight: 151.1626 IUPAC Name: N-(4-hydroxyphenyl)acetamide Melting Point: 169-171°C pka value: 9.46
16.	Loratadine (LOR)	Category: Antipruritics, Anti-Allergic agents, Antihistamines, Histamine H_1 antagonists and Non-Sedating Molecular Formula: $C_{22}H_{23}ClN_2O_2$ Molecular weight: 382.888 g/mol IUPAC Name: Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate Melting Point: 134-136 °C pka value: 4.33
17.	Doxylamine succinate (DOX)	Category: Antihistamine Molecular Formula: $C_{21}H_{28}N_2O_5$ Molecular weight: 388.464g/mol IUPAC Name: Butanedioic acid; N,N-dimethyl-2-(1-phenyl-1-pyridin-2-ylethoxy)ethanamine Melting Point: 103-108°C
18.	Oxomemazine (OXO)	Category: Antihistamine with anticholinergic Molecular Formula: $C_{18}H_{22}N_2O_2S$ Molecular weight: 330.446 g/mol IUPAC Name: 3-(5,5-Dioxido-10H-phenothiazin-10-yl)-N,N,2-trimethylpropan-1-amine Melting Point: 115°C
19.	Salbutamol sulphate (SAB)	Category: Asthmatic

		Molecular Formula: $C_{26}H_{44}N_2O_{10}S$ Molecular weight: 576.702 g/mol IUPAC Name: 4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxy methyl)phenol; sulfuric acid Melting Point: 147-149°C pka value: 10.12
20.	Cetrizine (CET)	Category: Antihistamine and asthmatic Molecular Formula: $C_{21}H_{25}ClN_2O_3$ Molecular weight: 388.892 g/mol IUPAC Name: 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid Melting Point: 112.5°C
21.	Saccharin (SAC)	Category: Sweetener Molecular Formula: $C_7H_5NO_3S$ Molecular weight: 183.181 g/mol IUPAC Name: 1,1-dioxo-1,2-benzothiazol-3-one Melting Point: 228.8 °C pka value: 1.6
22.	Theophylline (THP)	Category: Diuretic, smooth muscle relaxant, bronchial dilation, cardiac and central nervous system stimulant Molecular Formula: $C_7H_8N_4O_2$ Molecular weight: 180.164 IUPAC Name: 1,3-Dimethyl-7H-purine-2,6-dione Melting Point: 273 °C pka value: 8.81
23.	Guaiacolsulfonate (GCS)	Category: Expectorant Molecular Formula: $C_7H_8O_5S$ Molecular weight: 204.201 g/mol IUPAC Name: 4-hydroxy-3-methoxy-benzenesulfonic acid Melting Point: 63.5 °C
24.	Carbetapentane citrate (CBPC)	Category: Antitussive Molecular Formula: $C_{26}H_{39}NO_{10}$ Molecular weight: 525.595 g/mol IUPAC Name: 2-[2-(diethylamino)ethoxy]ethyl-1-phenylcyclo pentane-1-carboxylate; 2-hydroxypropane-1,2,3-tricarboxylic acid Melting Point: 90–95°C
25.	Methylparaben (MHB)	Category: Antimicrobial agent, preservative, flavouring agent Molecular Formula: $C_8H_8O_3$ Molecular weight: 152.15 g/mol IUPAC Name: Methyl-4-hydroxybenzoate Melting Point: 125 - 128°C
26.	Propylparaben (PHB)	Category: Antimicrobial agent, preservative, flavouring agent Molecular Formula: $C_{10}H_{12}O_3$ Molecular weight: 180.2 g/mol IUPAC Name: Propyl-4-hydroxybenzoate Melting Point: 96 to 99 °C
27.	Acetylcysteine (ACS)	Category: Mucolytic agent Molecular Formula: $C_5H_9NO_3S$ Molecular weight: 163.195 g/mol IUPAC Name: (2R)-2-acetamido-3-sulfanylpropanoic acid Melting Point: 109 - 110°C
28.	Benzoic acid (BA)	Category: Mucolytic agent Molecular Formula: $C_5H_9NO_3S$ Molecular weight: 163.195 g/mol IUPAC Name: (2R)-2-acetamido-3-sulfanylpropanoic acid Melting Point: 109 - 110°C

METHODS FOR DETERMINATION OF GUAFENESIN IN COMBINATION WITH OTHER DRUGS

Spectrophotometric methods:

Based on literature survey, several spectrophotometric methods have developed for estimation of Guaifenesin and its combined dosage form. Conditions for UV spectrophotometric analysis of Guaifenesin in various drug combinations listed in table 2.

Table-2: UV Spectrophotometric methods for analysis of Guaifenesin either alone or in combination with other drugs in pharmaceutical dosage form

S. No.	Name of the drug	Method	Detection	Solvent	Limit of detection (µg/ml)	Sample matrix	Ref.No
1.	GUA+ PSE	1.Simultaneous equation method	272 257	Methanol	-	Tablet	[3]
		2.Q –Value analysis	272 265.5	Methanol	-		
2	GUA	Simultaneous equation method	240	Distilled Water	0.104	Tablet	[4]
3	GUA+ PSE	1.Ratio derivative method	227 217.8	Methanol	0.886 1.0271	Tablet	[5]
		2.Ratio difference method	227.2 & 278.8 213 & 227.8	Methanol	1.028 2.157		
4	GUA	Simultaneous equation method	224.6	Methanol	5.96	Tablet	[6]
5	GUA	Spectrophotometric method	273	Methanol	48.63	Tablet	[7]
6	GUA+ ACS+ PAR	Simultaneous equation method	284 193 287	Methanol	0.45 1.71 0.37		[8]
7	GUA+ AMB	Simultaneous equation method	242 272	Methanol	-	Tablet	[9]
8	GUA+ AMB+ TER	Simultaneous equation method	279.4 307.5 244.5	0.1N NaOH	1.77 0.2 0.35	Syrup	[10]
9	GUA+ AMB	Absorption Ratio	238 255	Double distilled water	0.6 0.5	Tablet	[11]
		First order derivative spectroscopy	223 273	Double distilled water	0.5 0.4		
10	GUA + AMB+ CET+ PHE	Multivariate analysis	273 246 231 274	0.1 N HCl : Methanol (1:9)	1.07 1.01 0.48 2.11	Tablet	[12]
11	GUA+ BRO+ CHL	Simultaneous equation method	274 249 261	Methanol	0.3126 0.1026 0.1696	Syrup	[13]

Chromatographic methods

Literature survey revealed that various HPLC and HPTLC methods have reported for estimation of Guaifenesin with other drugs. The methods have been found to be simple, accurate, robust and suitable for routine analysis of drug samples in their formulations. The conditions for HPLC analyse of Guaifenesin in its combined dosage form listed in table 3.

Table-3: HPLC methods for analysis of Guaifenesin either alone or in combination with other drugs in pharmaceutical dosage form

S. No.	Name of the drug	Column (Internal diameter and Particle size)	Mobile phase	Flow rate (ml/ min)	Detection λ_{max} nm	Sample matrix	Ref.No
1.	GUA+ DEX+ CHL+ BRO	Chromatopak C_{18} (25cm x 4.6mm and 5µm)	MET : ACN : 0.025 M phosphate buffer (50:25:25 v/v/v)	1	265	Tablet	[14]
2	GUA+ TER+ AMB+	X-Terra RP18 (25cm x 4.6mm and 5µm)	Solution (A) 0.02 M ammonium dihydrogen ortho phosphate with 1.0% of 1 -heptane sulphonic acid sodium salt buffer (pH - 2.6 adjusted with OPA): ACN: MET (950:40:10 v/v/v). Solution (B) 0.02 M ammonium dihydrogen ortho phosphate with 1.0% of 1 heptane sulphonic acid sodium salt buffer (pH - 9.5 adjusted with diluted ammonia): ACN (400: 600 v/v).	1	222	Syrup	[15]
3	GUA+ DEX	Sunfire C_{18} (25cm x 4.6mm and 5µm)	0.01 M sodium dihydrogen phosphate monohydrate and 0.046 M 1-octane sulfonic acid sodium salt monohydrate - pH 3.0 buffer adjusted with OPA Mobile phase A - pH 3.0 buffers: ACN (90:10 v/v). Mobile phase B - pH 3.0 buffer: ACN: MET (10:10:80 v/v/v)	0.8	224	Tablet	[16]
4	GUA+ CHL+ BRO	Spherisorb CNRP C_{18} (25cm x 4.6mm and 5µm)	ACN : 0.01 M Potassium dihydrogen phosphate pH -3 buffer adjusted with 1% of OPA) - 60:40 % v/v	1.5	254	Tablet	[17]
5	GUA+ DEX+ SBT	Zorbax CN (25cm x 4.6mm)	500 ml ACN, 1ml formic acid, 1ml methanesulfonic acid and 500 ml distilled water – pH 3.5 adjusted with a 10% sodium hydroxide solution	1.0	290	Syrup	[18]
6	GUA+PPL+ DIP	Shimpak C_8 (25cm x 4.6mm and 10µm)	ACN: Triethylamine (pH adjusted to 3.5 using OPA; 0.5%), (35:65v/v). Diphenhydramine was used as internal standard.	1.2	210	Syrup	[19]
7	GUA+DEX+ PES	25 cm underivatized silica column	6.25 mM phosphate buffer (pH 3.0) : ACN -60:40% v/v	1	216	Capsule	[20]
8	GUA+PSE+ PRM+PYM+DEX+CHL	Kromasil LC 18 (15cm x 4.6mm and 5µm)	Methanol : 0.1 mol/L KH_2PO_4 buffer (pH adjusted with OPA or sodium hydroxide)	1	220	Tablet and capsule	[21]
9	GUA+PSE+ DCP	Phenomenex C_{18} (25cm x 4.6mm and 5µm)	MET : ACN : 10m M sodium pentansulphonate at pH 4.0 ± 0.1(55:5:40 v/v/v)	1	218	Syrup	[22]
10	GUA+ BRO+ TER	ODS C_{18} (25cm x 4.6mm and 5µm)	ACN : MET : pH 4.2 buffer adjust with GAA - (300:250:450 v/v/v)	1.2	220	Syrup	[23]

11	GUA+ PAR+ PHE+ CHL+BRO	Symmetry C_8 (15cm x 4.6mm and 3.5µm)	Mobile phase A – pH 4 buffer (10 mM KH_2PO_4 and 3.7 mM octane 1-sulphonic acid) adjusted with OPA . Mobile phase B - MET : ACN - 3 : 2	1	220	Tablet	[24]
12	GUA	Symmetry C_{18} (15cm x 4.6mm and 5µm)	Solvent A – 0.02M KH_2PO_4 (pH 3.2 adjusted with OPA) : MET (90 : 10 v/v) Solvent B – 0.02M KH_2PO_4 (pH 3.2 adjusted with OPA) : MET (10 : 90 v/v)	0.8	273	Tablet	[25]
13	GUA+ AMB+LOR	Kromasil (25cm x 4.6mm and 5µm)	0.1% OPA : ACN - 60 : 40 v/v	1.2	290	Syrup	[26]
14	GUA+ACE + PHE+ DEX	Altima C_{18} (15cm x 4.6mm and 5µm)	Solvent A – 1 ml of Conc.OPA in a 1000 ml of water Solvent B – CAN	1	272	Tablet	[27]
15	GUA+ DOX+ PPL+ CHL+ DEX+ PAR	Partisil 5 CCS/C (25cm x 4.6mm)	7 mM sodium dioctyl sulfosuccinate in an ACN / MET/Tetrahydrofuran/water/phosphoric acid (370/300/300/30/0.7 v/v/v/v/v/v). pH adjusted to 4.0 with ammonium hydroxide	2	258	Syrup	[28]
16	GUA + PSE	Hidrosorb C_{18} (25cm x 4.6mm and 5µm)	Deionized water : MET (50 : 50 v/v) pH adjusted with OPA	1	210	Syrup	[29]
17	GUA+ OXO+ SBT+ PAR	Lichrosorb C_{18} (25cm x 4.6mm and 10µm)	MET : ACN : 35mM KH_2PO_4 pH adjusted with 2.9 ± 0.1 with phosphoric acid (5:20:75 v/v/v)	1.5	220	Syrup	[30]
18	GUA+ PSE	Prontosil C_{18} (25cm x 4.6mm and 5µm)	ACN : MET : Phosphate buffer (pH 5.0) – (72 : 8:20 v/v/v)	1.2	218	Tablet	[31]
19	GUA	Greece C_{18} (25cm x 4.6mm and 5µm)	Solvent A : MET : Water – 80 : 20 v/v Solvent B : pH 3.0 adjusted with OPA	0.8	225	Bulk	[32]
20	GUA+ AMB + SAB	Phenomenex Luna C_8 (15cm x 4.6mm and 5µm)	Methanol : Ammonium acetate buffer (50mM) - (45 : 55 v/v)	1	236	Syrup	[33]
21	GUA+ AMB+ DEX	Hibar C_{18} (25cm x 4.6mm and 5µm)	ACN : MET : 10mM Phosphate buffer – 0.3 % Triethyl amine (pH 3.0 adjusted with OPA) – 25:15:60 v/v/v	1	205	Syrup	[34]
22	GUA+ AMB	Bondapack C_{18} (25cm x 4.6mm and 5µm)	Methanol : Water (20 :80, containing 1% triethylamine, pH 2.9 ± 0.1 adjusted with OPA)	1.5	220	Syrup	[35]
23	GUA+AMB+LOR	Hypersil, ODS C_{18} (25cm x 4.6mm and 5µm)	Phosphate buffer : CAN (20:50:30) pH-5.5	1	245	Syrup	[36]
24	GUA+AMB+SAL	Princeton sphere C8 (25cm x 4.6mm x 5µm)	Phosphate buffer:methanol (40:60) pH-4.5	1	220	Tablet	[37]
25	GUA+TER+ BRO	Wakosil II	Phosphate buffer pH 3.0 and acetonitrile (80:20 v/v for 18 mins and then changed to 60:40 v/v for	1	248 and 280	Syrup	[38]

			next 12 mins and equilibrated back to 80:20v/v for 10 mins)				
27	GUA+PPL+ DEX+ SBT	PPL and DEX(Silica based SCX column) GUA and SBT (Reversed phase C_{18})	Mobile phase A – 0.1 M(NH_4) (H_2PO_4):MeOH (30:70,v/v); pH 6.2 Mobile phase B – Water : diethylamine : glacial acetic acid : acetonitrile (739:1:10:250,v/v); pH 4.1	2 PPL-DEX &1.3 GUA -SBT	263 and 273	Syrup	[39]
28	GUA+DEX+BT+ SAC	Varian Prostar HPLC: i.(25cm x 4.6mm; 5µm) ii.(5cm x 4.6mm, 2.6µm)	Phosphate buffer (pH=2.8) : acetonitrile (75:25)	1	250 and 290	Syrup	[40]
29	GUA+AMB+CET	Phenomenax C_{18} (25cm x 4.6mm; 5µm)	0.1% OPA : acetonitrile (60:40, v/v, 30^0C)	1	290	Tablet	[41]
30	GUA	Supelco L_7 (25cm x 4.6mm; 5µm)	Methanol:acetonitrile:water (80:10:10; v/v/v)	1	254	Syrup	[42]
31	GUA+BRO+CET	Qualisil C_{18} (25cm x 4.6mm; 5µm)	0.05M KH_2PO_4:1%HCl (62:38) pH adjusted to 2.5 by TEA	1	254	Syrup	[43]
32	GUA+ PHE+ PPL+ SBT	C_{18} column (18cm x 2mm)	Water : Ethanol (80:20)	1.5	254	Tablet/capsule	[44]
33	GUA+ COD+ PRM+ PPL	Octadecylsilane trichlorosilane (30cm x 4mm)	0.02M KH_2PO_4 in methanol-water	2	254	Syrup	[45]
34	DIC+ MTC+GUA	Symmetry waters C_{18} column (15cm x 4.6mm; 5 µm)	Phosphate buffer (pH-8) and Acetonitrile	1	274 and 282	Tablet	[46]
35	GUA+ DIP+ GCS+ CBPC	Shimadzu LC-MS System LC-20AD Pump - C_{18} (15cm x 4.6mm) RP column	Water : ACN (60:40 v/v)	0.8	190-300	Syrup	[47]
37	GUA+ DEX+BT	C_{18} Column (Supelco, Alcobendar, Madrid,Spain) (25cmx4.6mm)	Phosphate buffer(pH2.8) : ACN (75:25;v/v)	1	250 and 290	Syrup	[48]
38	GUA+ MHB+PHB	Phenomenex (15cm x 4.6mm; 5 µm)	Eluent A: Aq. Phosphate buffer (pH 3.0; 10mm) : Acetonitrile (25:75; v/v) Eluent B: Methanol A:B - 85:15;v/v	1	254 and 276	Syrup	[49]
39	GUA+PHE+ PPL	A.C_8 column B.C_{18} column	A. 300 ml methanol, 675 ml water and 25 ml pentasulfonic acid sodium salt in GAA B. 350ml methanol, 625 ml water and 25 ml pentasulfonic acid sodium salt in GAA	2	254, 270 and 280	Tablet	[50]
40.	GUA+ACE+ PSE+	Octadecylsilane column	Methanol : Water : Acetic acid (45:55:2)	2.5	254 and	Syrup	[51]

	PHO+ MHB/ PHB	(30cm x 4mm)			280		
41.	GUA+THP+ BA	Stainless steel column (25cm x 4.6mm; 5 µm)	0.001M sodium citrate - citric acid buffer : Acetonitrile (9:1; v/v)	2	230	Tablet and Syrup	[52]

Challenges

Guaifenesin is act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. Guaifenesin belongs to BCS class-I, it means guaifenesin has high permeability and high solubility. However, for successful treatment a uniform and constant supply of drug is to be needed. To overcome those challenges and problems an important strategy is considered. Commonly, hydrophilic matrices are use to achieve slow release of drug over an extended period. Onset of its pharmacological action is delay and duration of its therapeutic effect has sustained. In development of hydrophilic matrix, there is a chance to interference of excipients to drug. It becomes necessary to analysis of drugs and selection of solvent is greater challenges for the analysis. From this review of literature, reveals that commonly used diluents are methanol, acetonitrile, phosphate buffer and distilled water in HPLC methods, which extended the run time with greater tailing factor. For spectrophotometric estimation, presence of excipients includes complexity with includes complexity with multi–component dosage forms, which produce significant challenge to the analyst during the development of assay. Estimation of individual drugs in multicomponent dosage forms becomes difficult. For multicomponent dosage forms, chemo-metric methods can be preferred to routine spectrometric methods.

CONCLUSION

A systematic review of various analytical methods for determination of Guaifenesin and its combined pharmaceutical dosage forms. Wide ranges of instrumental methods for quantitative estimation of Guaifenesin have developed successfully. However, the methods repoted are time consuming and complex. A vast number of HPLC methods have developed for analysis of Guaifenesin and its combination with other drugs. Guaifenesin is an important pharmaceutical ingredient used in infants, children, and adults to relieve cough and congestion. For analysis of Guaifenesin in pharmaceuticals, HPLC with UV detection is applicable because this method provides simple, precise, rapid, accurate, and economical analytical methods for estimation of this drug.

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REFERENCES

1. https://www.drugs.com
2. https://www.drugbank.ca
3. Rahul,S., Hemendra, K.S., Vinod,S., Shruti,T., & Nilesh, J. (2011). Spectrophotometric determination of Guaifenesin and Pseudoephedrine. *International Journal of Research in Pharmacy and Science*, 1(3), 41-49.
4. Pushpalatha, E., Tejaswini, P., Najboonbi, M., Vineesha, S., Madhanna, MD., Anil, K.T., & Raju, M. (2015). Development of UV Spectroscopic method for the determination of Guaifenesin in bulk and formulation. *International Journal of Pharmaceutical Research and Analysis*, 5(2), 90-95.
5. Attia, K.A.S., Nassar, M.W., & Olemy, A.E. (2014). Simultaneous spectrophotometric determination of Guaifenesin and Pseudoephedrine HCl using derivative of ratio spectra and ratio difference methods.*European Journal of Biomedical and Pharmaceutical Sciences*, 1(2), 1-12.
6. Koteswara,R.B.,Jyothsna, K.I., Nageswara, M., & Ram, B.C. (2015). A new and sensitive UV Spectrophotometric method for the determination of Guaifenesin in dosage forms. *International Journal of Pharmacy and Pharmaceutical Research*, 3(4), 140-148.
7. Bhattacharya, S.P., Kyal, C., Choudhury, P., Dhakal, B., & DR.Ghosh, S.K. (2013). Estimation and validation of stability indicating UV spectrophotometric method for the determination of guaifenesin in presence of its degradant products. *International Journal of Pharmacy and Pharmaceutical Sciences*, 5(1), 262-268.
8. Tunica, A.K. (2014). Quanititative analysis of paracetamol, acetylcysteine, and guaifenesin in commercial cold medicines by UV spectroscopy. *SOP Transactions on Analytical Chemistry*, 1(1), 40-48.
9. Prasanthi, N.L., Krishna, M.C., Manikiran, S.S., & Rao, N.R. (2010). Estimation of Ambroxol HCl and Guiaphensin in tablet dosage form by simultaneous equation method. *International Journal of Research in Ayurveda and Pharmacy*, 1(1), 140-146.
10. Kimbahune, R.K., Sunil, P.K., Delvadiya, K., & Surani, S. (2011). Spectrophotometric simultaneous analysis of Ambroxol HCl, guaifenesin and

terbutaline sulphate in liquid dosage form. *International Journal of Pharmaceutical Sciences Review and Research*, 8, 24-28.

11. Deshpande, S.D., Deosarkar, A.V., & Walode, S.G. (2012). Absorption Ratio, Derivative spectroscopy and RP-HPLC methods for estimation of Guaifenesin and Ambroxol HCl in tablet. *Der Chemica Sinica*, 3, 759-765.
12. Arora., Ritika, M., & Sarma, G.S. (2013). Development and validation of chemometrics assisted spectrophotometric multipurpose methods for simultaneous estimation of Ambroxol Hcl, Guaiphensin, Cetirizine Hcl and Phenylephirine Hcl for binary, tertairy or quaternary combinations. *Inventi Rapid: Pharm Analysis and Quality Assurance*, 4, 1-11.
13. Ladmeera.,Raj, H., & Jain. (2015). Development and validation of analytical method for bromhexine HCl, chlorpheniramine maleate and guaifenesin by simultaneous equation method. *Asian Journal of Pharmaceutical Sciences*, 5(2), 76-82.
14. Jain, V., & Mukesh, C.S. (2016). Validated RP-HPLC method for determining the levels of bromhexine HCl, chlorpheniramine maleate, dextromethorphan Hbr and guaiphenesin in their pharmaceutical dosage forms. *Journal of Taibah University for Science*, 10(1), 38-45.
15. Rao, K.L.N.,Krishnaiah, Ch., Sudheer Babu, K., & Padmaja Reddy, K. (2014). Development and validation of a stability indicating LC method for simultaneous determination of related compounds of guaifenesin, terbutalinesulfate and ambroxol HCl in cough syrup formulation. *Journal of Saudi Chemical Society*, 18(5), 593-600.
16. Raju, T.V.R., Anil, K.N., Raja, K.S., Malleswara, R.A., Someswara Rao, N., & Mrutyunjaya, R.I. (2013). Development and Validation of a Stability-Indicating RP-HPLC Method for the Simultaneous Estimation of Guaifenesin and Dextromethorphan Impurities in Pharmaceutical Formulations. *Chromatography Research International*, 1-12.
17. Chaudhary, A.B., Bhadani, S.M., & Shah, C.M. (2015). Development and Validation of RP-HPLC Method foesimultaneous Estimation of Bromhexine Hydrochloride, Guaiphenesin and Chlorpheniramine maleate in Tablet. *World Journal of Pharmacy and Pharmaceutical Sciences*, 4(5), 1679-1694.
18. Chen, T.M., Pacifico, J.R., Daly, R.E. (1988). High-Pressure Liquid Chromatographic Assay of Dextromethorphan Hydrobromide, Guaifenesin, and Sodium Benzoate in an Expectorant Syrup. *Journal of Chromatographic Science*, 26, 636-639.
19. Vasudevan, M., Ravisankar, S., Sathiyanarayanan, A., & Chandan, R.S. (2000). Simultaneous estimation of phenylpropanolamine HCl, guaiphenesin and diphenylpyraline HCl in syrups by LC. *Journal of Pharmaceutical and Biomedical Analysis*, 24, 25-31.
20. Wilcox, M.L., & Stewart, J.T. (2000). HPLC determination of guaifenesin with selected medications on underivatized silica with an aqueous-organic mobile phase. *Journal of Pharmaceutical and Biomedical Analysis*, 23, 909-916.
21. Louhaichia, M.R., Jebali, S., Loueslatia, M.H., Adhoumb, N., & Monser, L. (2009). Simultaneous determination of pseudoephdrine, pheniramine, guaifenisin, pyrilamine, chlorpheniramine and dextromethorphan in cough and coldmedicines by high performance liquid chromatography. *Talanta*, 78, 991-997.
22. Yolanda, M., Martono, S., & Rohman, A. (2016). Validation of an Ion-Pair High Performance Liquid Chromatography for the Determination of Pseudoephedrine HCl, Guaifenesin and Dexchlorpheniramine Maleat in Cough and Cold Medicines. *International Journal of Pharmaceutical and Clinical Research*, 8(5), 476-480.
23. Senthilraja, & Giriraj, P. (2011). Reverse Phase Method for the Simultaneous Estimation of tertbutaline sulphate, bromhexine HCl and Guaifenesin in Cough Syrup. *Asian Journal of Pharmaceutical and Clinical Research*, 4(2), 13-15.
24. Nalini, K., Narmada, P., Vijaya Lakshmi, G., Gowtham, Y., & Jogi, K.V. (2014). Simultaneous Estimation of Paracetamol, Guaiphenesin, Phenylephrine HCl, Chlorpheniramine maleate and Bromohexine HCl in combined tablet dosage form by Reverse Phase High Performance Liquid Chromatography. *International Journal of Pharmaceutical Sciences and Research*, 5(2), 410-416.
25. Reddy, S.P., Sudhakar Babu, K., Kumar, N., & Sasi Sekhar, Y.V.V. (2011). Development and validation of stability indicating the RP-HPLC method for the estimation of related compounds of Guaifenesin in pharmaceutical dosage forms. *Pharmaceutical Methods*, 2(4), 229-234.
26. Sailaja, G., & Hari Babu, B. (2015). A Validated High Performance Liquid Chromatography Method for the Simultaneous Analysis of Guaifenesin, Ambroxol and Loratidine in Bulk and Liquid Dosage form. *Journal of Applied Pharmaceutical Science*, 5(12), 061-066.
27. Kumar, V.R., & Vinay, U.R. (2015). A novel stability RP-HPLC method development and validation for simultaneous estimation of phenylephrine, acetaminophen, guaifenesin and dextromethorphan in tablet dosage form. *Scholars Research Library*, 7(7), 329-339.
28. Sasa, S.I., Momani K.A., & Jalal I.M. (1987). Chromatographic Behavior of Doxylamine Succinate, Phenylpropanolamine Hydrochloride, Chlorpheniramine Maleate, Dextromethorphan Hydrobromide, Paracetamol and Guaifenesin in Ion

Pair Reverse-Phase High Performance Liquid Chromatography. *Microchemical Journal*, 36, 391-398.
29. Nada, S.A., & Eglal A.A. (2013). Stability indicating RP-HPLC method for simultaneous determination of Guaifenesin and Pseudoephedrine hydrochloride in presence of syrup excepients. *Arabian Journal of Chemistry*, 1-13.
30. Nehal, F.F., Nariman, A.E.R., Maha, A.H., Mohamed, A., & Fadia, H.M. (2014). Simultaneous determination of a quaternary mixture of oxomemazine, sodium benzoate, guaifenesin and paracetamol by chromatographic methods. *Beni – Suef University Journal of Basic and Applied Sciences*, 3, 260-268.
31. Rahul, S., Sengar, N.P.S., Parul, D.M., & Lodhi, N.S. (2012). A validated RP-HPLC method for determination of guaifenesin and pseudoephedrine HCl in tablet dosage form. *International Pharmacy of Journal*, 2(2), 317-321.
32. Pandurang, H.P., Bhimraj, L.R., Dattatatraya, B.R., & Mhasu, M.M. (2016). A validated RP-HPLC method for estimation of Guaifenesin in bulk dosage form. *Indo American Journal of Pharmaceutical Sciences*, 3(1), 44-51.
33. Nirav, C.P., Dipti, B.P., & Pruthviraj K.C. (2013). Development and validation of reverse phase HPLC method for simultaneous estimation of ambroxol HCl, guaifenesin and levosalbutamol in syrup. *Pharm Analysis and Quality Assurance*, 2, 1-6.
34. Sagathiya, K., & Bagada, H. (2014). Development and validation of RP-HPLC and HPTLC methods of analysis for simultaneous estimation of ambroxol HCl, dextromethomorphan HBr and guaifenesin in pharmaceutical cough cold preparation and statistical comparision of developed methods. *International Journal of Pharmacy and Pharmaceutical Sciences*, 6(2), 312-316.
35. Abdelkawy, M., Metwaly, F., Raghy, N.E., Hegazy, M., & Fayek, N. (2011). Simultaneous determination of ambroxol HCl and guaifenesin by HPLC, TLC-spectrodensitometric and multivariate calibration methods in pure form and in cough cold formulations. *Journal of Chromatography Separation Techniques*, 2(3), 1-9.
36. Mehveen,S., Basha, S.A.A.,& Fatima.A. (2014). Stability indicating method development and validation for simultaneous estimation of loratadine, ambroxol HCl and guaiphenesin in bulk drug and liquid dosage form using RP-HPLC method. *International Journal of Pharmacy and Technology*, 6(2), 6536-6551.
37. Nidhi, D., Sandeep, S., & Singh, G.N. (2012). Development of HPLC method for simultaneous estimation of ambroxol, guaifenesin and salbutamol in single dosage form. *Indian Journal of Chemistry*, 15, 1633-1636.
38. Porel, A., Haty, S., & Kundu, A. (2011). Stability-indicating HPLC method for simultaneous determination of terbutaline sulphate, bromhexine HCl and guaifenesin. *Indian Journal of Pharmaceutical Sciences*, 46-56.
39. Wilson, T.D., Jump, W.G., Neumann, W.C., & Martin, T.S. (1993). Validation of improved methods for HPLC determination of phenylpropanolamine, dextromethomorphan, guaifenesin and sodium benzoate in a cough –cold formulation. *Journal of Chromatography*, 641, 241-248.
40. Adjekum, A., & Kebede, R., (2011). Analysis of dextromethorphan, guaifenesin, benzoate and saccharin in cough syrup using HPLC. *Concordia College Journal of Analytical Chemistry*, 2, 1-5.
41. Rao, A.S.,Kumar, K.L.P., Satyanarayana, P., & Sastry. G.S. (2015). A validated RP-HPLC method for the simultaneous estimation of guaifenesin, ambroxol, and levo cetirizine in pharmaceutical dosage forms. *World Journal of Pharmacy and Pharmaceutical Sciences*, 4(9), 1735-1747.
42. Ahmed, N.R., & Lottfi, S.N. (2013). HPLC method for the determination of guaifenesin in pharmaceutical syrups and in environmental samples. *Baghdad Science Journal*, 10(3), 1014-1022.
43. Sheikh, S., Asghar, S., & Ahmad,S. (2013). RP-HPLC method for simultaneous estimation of phenylepherine HCl, guaifenesin, bromhexine HCl, Cetirizine HCl in pharmaceutical liquid formulation. *International Journal for Pharmaceutical Research Scholar*, 2(4), 448-457.
44. Schieffer, G.W., Smith, W.O., Lubey G.S. & Newby, D.J. (1984). Determination of the Structure of a Synthetic Impurity in Guaifenesin: Modification of a High-Performance Liquid Chromatographic Method for Phenylephrine Hydrochloride, Phenylpropanolamine Hydrochloride, Guaifenesin, and Sodium Benzoate in Dosage Forms. *Journal of Pharmaceutical Sciences*, 73(12), 1856-1858
45. Gupta, V.D., & Ghanekar, A.G. (1977). Quantitative Determinations of Codeine Phosphate, Guaifenesin, Pheniramine Maleate, Phenylpropanolamine Hydrochloride, and Pyrilamine Maleate in an Expectorant by High-pressure Liquid Chromatography. *Journal of Pharmaceutical Sciences*, 66(6), 895-897.
46. Ehab, F.E. (2010). Simultaneous determination of diclofenac potassium and methocarbamol in ternary mixture with guaifenesin by reversed phase liquid chromatography. *Talanta*, 82, 1604-1607.
47. Ozlem, A.D., Burge, A., Abdurrezzak, B.G., & Sidika, S. (2013). Simultaneous determination of potassium guaiacolsulfonate, guaifenesin, diphenhydramine HCl and carbetapentane citrate in syrups by using HPLC-DAD coupled with partial

least squares multivariate calibration.*Talanta*, 83, 1601-1605.

48. Galli, V., & Barbas, C. (2004). High-performance liquid chromatographic analysis of dextromethorphan, guaifenesin and benzoate in a cough syrup for stablity testing. *Journal of Chromatography*, 1048 (2), 207-211.
49. Grosa, G., Grosso, E.D., Russo, R., & Allegrone, G. (2006). Simultaneous stability indicating, HPLC-DAD determination of guaifenesin and methyl and propyl paraben in cough syrup. *Journal of Pharmaceutical and Biomedical Analysis*, 41, 798-803.
50. Gary, W.S., & David, E.H. (2013). Simultaneous stability - indicating determination of phenylephrine Hcl, phenyl propanolamine HCl and guaifenesin in dosage forms by RP-paired-ion high performance liquid chromatography. *Journal of Pharmaceutical Sciences*, 72(1), 55-59.
51. Laura, C. (1983). Simultaneous determination of Acetaminophen, Guaifenesin, Pseudoephedrine, Pholcodine, and Paraben Preservatives in Cough Mixture by High-Performance Liquid Chromatography. *Journal of Pharmaceutical Sciences*, 7(2), 196-198.
52. Heidemann, D.R. (1979). Rapid, Stability-Indicating, HPLC Determination of Theophylline, Guaifenesin, and Benzoic Acid in Liquid and Solid Pharmaceutical Dosage Forms. *Journal of Pharmaceutical Sciences*, 68(4), 530-532.