

# A Validated High Performance Liquid Chromatography Method for the Simultaneous Analysis of Guaifenesin, Ambroxol and Loratidine in Bulk and Liquid Dosage form

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## ABSTRACT

A simple and sensitive HPLC method for simultaneous quantification of guaifenesin, ambroxol and loratidine in bulk and liquid dosage form was developed and fully validated. The separation and quantification was performed using a Kromasil C8 (250 × 4.6 mm, particles 5 μm) HPLC column. Isocratic elution mode with a flow rate of 1.2 mL/min was used, and the injection volume was 10 μL. The detector was set to a wavelength of 290 nm and the column oven was maintained at 30 °C. Orthophosphoric acid (0.1%) and acetonitrile in the ratio of 60:40 v/v was used as the mobile phase. Guaifenesin, ambroxol and loratidine were eluted with retention time of 3.045 min, 5.489 min and 13.981 min, respectively. The method was validated in accordance with ICH guidelines and the results of all the validation parameters were found to be within the acceptable limits. The calibration plots were linear over the concentration ranges from 50-150 μg/mL, 30-90 μg/mL and 5-15 μg/mL for guaifenesin, ambroxol and loratidine, respectively. Developed method was successfully applied for the quantification of the above three drugs in liquid dosage form. The excipient did not interfere with drug peaks.

## INTRODUCTION

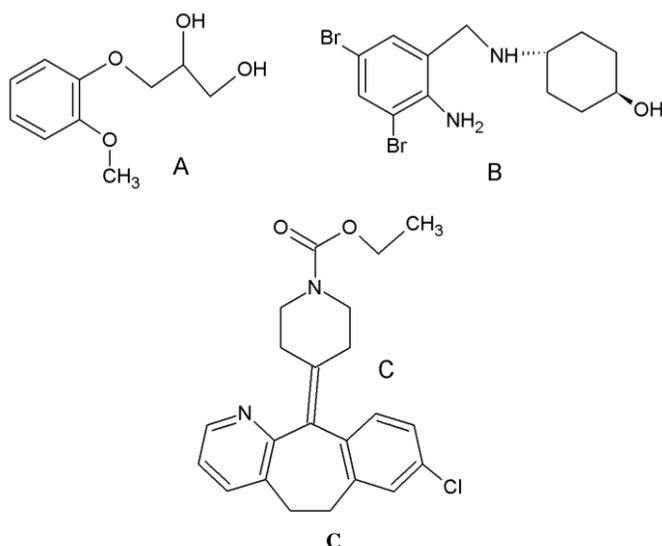
Guaifenesin (Dicpinigaitis and Gayle, 2003; Dicpinigaitis *et al.*, 2009; Storms and Farrar, 2009), glyceryl ether of guaiacol, is an expectorant used to lessen chest congestion caused by the common cold, infections, or allergies. Guaifenesin clears chest congestion by loosening and reducing the viscosity of phlegm, increasing the volume of phlegm and making coughs more productive. Chemically Guaifenesin is known as 3-(2-Methoxyphenoxy)-1,2-propanediol. Analytical methods for the determination of guaifenesin, either alone or in combination with other drugs, include spectrophotometry (Bhattacharyya *et al.*, 2013; Harika *et al.*, 2012), gas chromatography (Sharaf and Stiff, 2004; Harsono *et al.*, 2005), HPLC (Aluri and Stavchansky, 1993; Amer *et al.*, 2008; Galli and Barbas, 2004; Stavchansky, *et al.*, 1995; Shervington, 1997;

Vasudevan *et al.*, 2000; Wilson *et al.*, 1993; Wilcox and Stewart, 2000), capillary electrophoresis-mass spectrometry (Tanaka *et al.*, 1998), X-ray diffraction (Grygar *et al.*, 2008), voltammetry (Tapsoba *et al.*, 2005). Ambroxol hydrochloride (Beeh *et al.*, 2008; Chenot *et al.*, 2014; Gupta, 2010), chemically known as trans-4-((2-amino-3, 5-dibromobenzyl) amino)-cyclohexanol hydrochloride, is a potent mucolytic and mucokinetic, capable of inducing bronchial secretion. Ambroxol is used in the treatment of a variety of respiratory disorders including chronic bronchitis. It is also used in the treatment of cough. Literature survey revealed that several methods that have been reported for the estimation of ambroxol hydrochloride either alone or in combination with other drugs by using colorimetry (Levent and Şentürk, 2010; Pai *et al.*, 2006), atomic absorption spectrometry (Levent and Şentürk, 2010), spectrophotometry (Gunawan and Ratna, 2008; Nagras *et al.*, 2012; Ponnillavasaran *et al.*, 2012), conductometric titration (Ashour and Khateeb, 2013), high performance thin layer chromatography (Agrawal *et al.*, 2010; Jain, 2010; Mehta *et al.*, 2013; Sharma and Shah, 2010) and high performance liquid chromatography (Arora *et al.*, 2012; Buchupalli and Medidi, 2015;

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Gopalakrishnan *et al.*, 2012; Kumar *et al.*, 2012; Moses *et al.*, 2013; Patel *et al.*, 2011; Raja *et al.*, 2012; Venkateshwari *et al.*, 2012). Loratadine (Day *et al.*, 1998; Lupià *et al.*, 2003; Prenner *et al.*, 2009), chemically known as ethyl 4-(8-chloro-5,6-dihydro-11H-benzo(5,6)cyclohepta(1,2-b)pyridin-11-ylidene)-1-piperidine carboxylate, is a second-generation piperidine histamine H<sub>1</sub>-receptor antagonist with anti-allergic properties. It is used in the treatment of allergic rhinitis, urticaria and reduce the symptoms of hay fever for the short term. The review of the literature has revealed that several methods have been reported for the quantification of loratadine alone or in combination with other drugs. These methods included spectrophotometry (Bushra, 2013; Mabrouk *et al.*, 2003; Radhakrishna *et al.*, 2003; Singhvi and Bhatia, 2006), high performance liquid chromatography (Bushra, 2013; El-Sherbiny *et al.*, 2007; Gajjela *et al.*, 2011; Mabrouk *et al.*, 2003; Lu *et al.*, 2010; Radhakrishna *et al.*, 2003; Singhvi and Bhatia, 2006), voltammetry (Norouzi and Ganjali, 2008) and high performance liquid chromatography with mass spectrometry detection (Patel *et al.*, 2010; Salem *et al.*, 2004; Vlase *et al.*, 2007). The chemical structures of guaifenesin, ambroxol and loratadine are shown in Fig. 1.



**Fig. 1:** Chemical structure of A) Guaifenesin B) Ambroxol C) Loratadine.

The combination of guaifenesin, ambroxol and loratadine is used to treat cough, cold, allergy and other related conditions. The combination of these three drugs is not official in any pharmacopeias. As per the thorough literature review only one spectrophotometry (Patel and Chaudhri, 2013) and two HPLC (Sameena *et al.*, 2014; Vani *et al.*, 2014) methods are reported for the simultaneous estimation of guaifenesin, ambroxol and loratadine in bulk and liquid dosage form. The reported methods suffers from one or more drawbacks like use of triple solvent system as mobile phase, less precise, less accurate, preparation of buffer, greater tailing factor (>1.25), less resolution factor and less sensitive. Hence, the present investigation is aimed to develop and validate a simple, sensitive and accurate HPLC

method for the simultaneous quantification of guaifenesin, ambroxol and loratidine in bulk and in its liquid dosage form.

## MATERIALS AND METHODS

### Apparatus

The Waters HPLC system, consisted of a binary HPLC pump model 2695, photodiode-array (PDA) detector model 2998 and a vacuum degasser, all controlled by a Waters Empower2 software was used in the present investigation.

### Chromatographic conditions

Kromasil C8 (250 × 4.6 mm; 5 μm particle size) analytical column was used for separation and analysis of guaifenesin, ambroxol and loratidine. The column temperature was maintained at 30 ± 1°C. Mobile phase consisted of 0.1% orthophosphoric acid and acetonitrile in the ratio of (60:40 v/v, respectively). The separation was done under isocratic elution with flow rate maintained at 1.2 mL/min. The injection volume was 10 μL. The guaifenesin, ambroxol and loratidine were analyzed using a PDA detector set at 290 nm.

### Standard solutions

Reference standard of guaifenesin, ambroxol and loratidine were obtained from Lara Drugs Private Limited, Telangana. A combined standard stock solution of accurately weighted guaifenesin (50 mg), ambroxol (30 mg) and loratidine (5 mg) was prepared in 100 mL volumetric flask and dissolved in mobile phase. 5 mL aliquot of guaifenesin, ambroxol and loratidine stock solution were added to a 25 mL volumetric flask, and diluted in mobile phase, yielding a final concentration of 100, 60 and 10 μg/mL, respectively.

### Sample solution

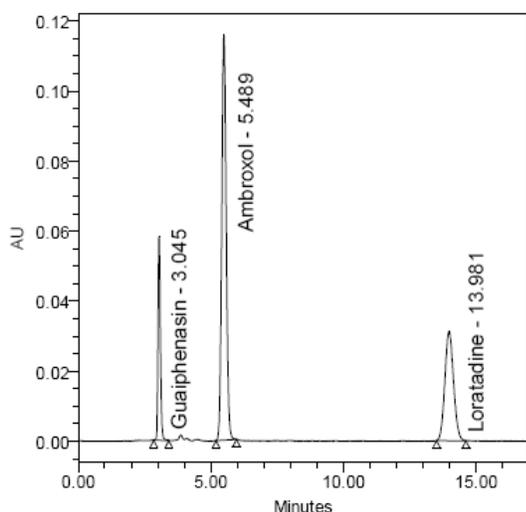
Commercial syrup (Lorfast AM Syrup, Cadila Pharmaceuticals Ltd., Ahmadabad: labeled to contain 50 mg guaifenesin, 30 mg ambroxol and 5 mg loratidine per 5 mL of syrup) was purchased from local pharmacy store. The syrup was shaken thoroughly to make homogenous mixture. A volume of the syrup equivalent to 50 mg guaifenesin, 30 mg ambroxol and 5 mg loratidine was transferred accurately into a 100 mL volumetric flask containing 30 mL of mobile phase. The contents of the flask was shaken for about 10 min and diluted to volume with the mobile phase. The solution was then filtered through a 0.45 μm millipore filter. The above solution was appropriately diluted with the mobile phase to get a final concentration of 100, 60 and 10 μg/mL of guaifenesin, ambroxol and loratidine, respectively.

## RESULTS AND DISCUSSION

### Method development

In the present work, we proposed a simple, sensitive, precise and accurate high performance liquid chromatographic method for simultaneous estimation of guaifenesin, ambroxol and

loratidine. For optimization of the chromatographic conditions and to obtain symmetrical peaks with better resolution and with acceptable system suitability results, various chromatographic conditions such as composition of mobile phase, flow rate and two different analytical columns were applied to guaifenesin, ambroxol and loratidine combination. Among the tested analytical columns [ACE C8 (150 mm x 4.6mm, 5 µm particle size) and Kromasil C8 (250 × 4.6 mm; 5 µm particle size)] during preliminary investigations, Kromasil C8 (250 × 4.6 mm; 5 µm particle size) was the most appropriate column for simultaneous analysis of guaifenesin, ambroxol and loratidine. In the preliminary trials different compositions of mobile phases consisting of 0.1 M dipotassium hydrogen phosphate/acetonitrile and 0.1% orthophosphoric acid/acetonitrile, different ratios and different flow rates of these solutions were employed to achieve the best system suitability results. Finally, the mobile phase composition of 0.1% orthophosphoric acid: acetonitrile in the ratio of 60:40 v/v with a flow rate of 1.2 mL/min was shown to have good resolution with minimal tailing factor in acceptable range. The column temperature of 30 °C and detector wavelength set at 290 nm was chosen as suitable condition. Under the mentioned chromatographic conditions highly symmetrical and sharp peaks of guaifenesin, ambroxol and loratidine were obtained at retention times of 3.045 min, 5.489 min and 13.981 min, respectively (Fig. 2).



**Fig. 2:** Chromatogram of guaifenesin, ambroxol and loratidine combination standard solution under optimized chromatographic condition.

### Method validation

The developed method was validated for system suitability, linearity, sensitivity, precision, accuracy and robustness following the ICH guidelines (International Conference on Harmonization, 2005).

### System suitability

Earlier to each analysis, the chromatographic system must satisfy suitability test requirements. System suitability test was performed from five replicate injections of a standard solution

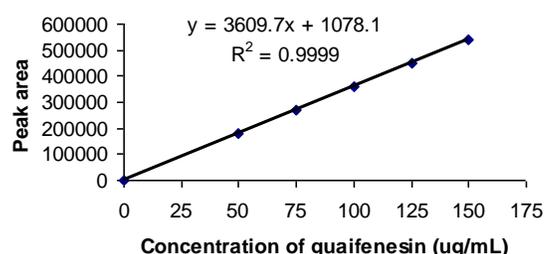
containing 100, 60 and 10 µg/mL of guaifenesin, ambroxol and loratidine, respectively. All peaks were well resolved. The precision of injections for all peaks were acceptable. The percent relative standard deviations of the peaks area responses were measured. The USP tailing factor, USP resolution and USP plate count were also calculated. The results of system suitability in association with the required limits are presented in Table 1. The developed method met requirements within the accepted limits.

**Table 1:** System suitability.

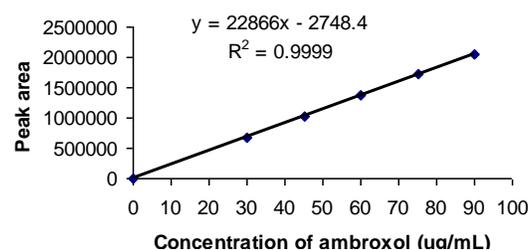
Parameters	Results			Recommended limits
	Guaifenesin	Ambroxol	Loratidine	
Retention time	3.045	5.489	13.981	-
Peak area	360940	1363778	710371	RSD ≤1
	(%RSD - 0.8)	(%RSD - 0.4)	(%RSD - 0.3)	
USP resolution	25.03	10.38	18.30	> 1.5
USP plate count	5517	5236	8467	> 2000
USP tailing factor	1.22	1.06	1.10	≤ 2

### Linearity

The linearity test was performed using five different amounts of guaifenesin, ambroxol and loratidine in the range 50-150 µg/mL, 30-90 µg/mL and 5-15 µg/mL, respectively. Solutions corresponding to each concentration level were injected in duplicate and linear regression analysis of the guaifenesin, ambroxol and loratidine peak area vs guaifenesin, ambroxol and loratidine concentration were calculated. The results are summarized in Fig. 3, 4 & 5. The results show a good correlation between the peak area of drugs and their concentrations with  $R^2$  value > 0.9998.



**Fig. 3:** Linearity and regression equation of guaifenesin.



**Fig. 4:** Linearity regression equation of ambroxol.

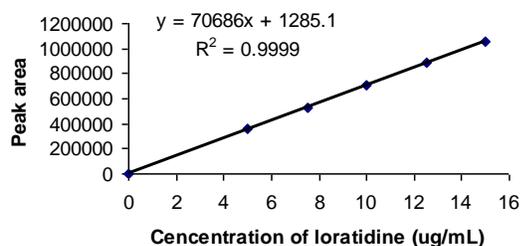


Fig. 5: Linearity regression equation of loratidine.

### Sensitivity

The sensitivity of the developed method was assessed by determining Limit of quantification (LOQ) and detection (LOD). The LOQ and LOD were predicted by the following formulae

$$(a) \text{ LOQ} = 10 \sigma / S$$

$$(b) \text{ LOD} = 3.3 \sigma / S$$

Where  $\sigma$  = standard deviation of response; S = slope of the calibration curve.

The LOD was found to be 0.754  $\mu\text{g/mL}$ , 0.231  $\mu\text{g/mL}$  and 0.145  $\mu\text{g/mL}$ , whereas LOQ was found to be 2.513  $\mu\text{g/mL}$ , 0.769  $\mu\text{g/mL}$  and 0.483  $\mu\text{g/mL}$  for guaifenesin, ambroxol and loratidine, respectively. The results reveal satisfactory sensitivity of the developed method.

### Precision

The precision of the developed method was demonstrated by intra-day variation studies. For this purpose, six repeated injections of standard solutions (guaifenesin-100  $\mu\text{g/mL}$ ; ambroxol-60  $\mu\text{g/mL}$ ; loratidine-10  $\mu\text{g/mL}$ ) were made. The response of guaifenesin, ambroxol, loratidine and their percentage relative standard deviation (%RSD) were calculated. From the results, the developed method was considered to be precise (Table 2).

Table 2: Results of precision of the method.

Guaifenesin		Ambroxol		Loratidine	
Peak area	%RSD	Peak area	%RSD	Peak area	%RSD
364354		1369971		712382	
363644		1377191		714875	
361943	0.29	1359782	0.41	711901	0.16
362672		1371184		713348	
363559		1368971		713069	
361704		1367314		711824	

### Accuracy

The accuracy of the method was determined via recovery experiments. The accuracy of the proposed method was demonstrated by preparing samples spiked with 50%, 100%, and 150% of the test concentration of guaifenesin, ambroxol and loratidine. Each concentration level was analyzed thrice.

Mean percent recovery and percent RSD were calculated for each concentration. Recovery of individual components was well within the acceptable limit (Table 3). From the data obtained, added recoveries of drugs were found to be accurate.

Table 3: Results of accuracy of the method.

Accuracy level	$\mu\text{g/mL}$ added	Peak area	$\mu\text{g/mL}$ found	% Recovery	% Mean
<b>Guaifenesin</b>					
50%	50.00	181685	50.03	100	100
	50.00	180916	49.82	100	
	50.00	181188	49.90	100	
100%	100.00	363957	100.23	100	100
	100.00	361611	99.58	100	
	100.00	364536	100.39	100	
150%	150.00	543535	149.69	100	100
	150.00	545074	150.11	100	
	150.00	544511	149.95	100	
<b>Ambroxol</b>					
50%	30.00	683406	29.92	100	100
	30.00	682872	29.89	100	
	30.00	682683	29.88	100	
100%	60.00	1373533	60.13	100	100
	60.00	1369581	59.95	100	
	60.00	1358886	59.49	99	
150%	90.00	2057259	90.06	100	100
	90.00	2047357	89.62	100	
	90.000	2061957	90.26	100	
<b>Loratidine</b>					
50%	5.00	354211	4.98	100	100
	5.00	356071	5.00	100	
	5.00	355322	4.99	100	
100%	10.00	714041	10.03	100	100
	10.00	712498	10.01	100	
	10.00	713146	10.02	100	
150%	15.00	1072341	15.07	100	100
	15.00	1068522	15.01	100	
	15.00	1067093	14.99	100	

### Robustness

Robustness of the method was determined by making slight changes in the chromatographic conditions. In all the deliberate varied chromatographic conditions, the parameters like tailing factor, peak area and theoretical plates were not much affected, which shows that the method is robust. The results are shown in Table 4.

Table 4: Results of robustness.

Sample. No	Parameter	Retention time	Peak area	USP plate count	USP Tailing
<b>Guaifenesin</b>					
1	Temp-1	3.263	385392	6262	1.23
2	Temp-2	2.564	283126	5611	1.21
3	Flow-1	3.213	381517	6547	1.25
4	Flow-2	2.555	290572	5489	1.22
<b>Ambroxol</b>					
1	Temp-1	5.975	1489174	5725	1.07
2	Temp-2	4.698	1099458	4734	1.05
3	Flow-1	5.939	1473039	5665	1.08
4	Flow-2	4.703	1112064	4818	1.04
<b>Loratidine</b>					
1	Temp-1	15.205	786656	8873	1.08
2	Temp-2	11.955	567326	8074	1.07
3	Flow-1	15.167	766862	9136	1.11
4	Flow-2	11.951	580928	7842	1.08

### CONCLUSION

The optimal chromatographic conditions for separation and simultaneous quantification of guaifenesin, ambroxol and loratidine were achieved on an Kromasil C8 (250  $\times$  4.6 mm; 5  $\mu\text{m}$

particle size) analytical column with a isocratic elution at a flow rate of 1.2 mL/min, using 0.1% orthophosphoric acid:acetonitrile (60:40 v/v) as mobile phase and detection set to a wavelength of 290 nm. The method was simple and does not require preparation of buffer. The proposed method has the advantages of being sensitive, high resolution factor and less tailing factor than the reported HPLC methods (Sameena *et al.*, 2014; Vani *et al.*, 2014). All measured parameters of the validation reveal the suitability of developed HPLC method for the simultaneous analysis of guaifenesin, ambroxol and loratadine in bulk and liquid pharmaceutical preparation.

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