Journal of Applied Pharmaceutical Science Vol. 5 (02), pp. 074-080, February, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.50211
ISSN 2231-3354 

# RP-HPLC Method for the Simultaneous Estimation of Ambroxol Hydrochloride and Fexofenadine Hydrochloride In bulk and in a Tablet Mixture

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**ARTICLE INFO**

*Article history:*
Received on: 08/12/2014
Revised on: 30/12/2014
Accepted on: 24/01/2015
Available online: 27/02/2015

***Key words:***
Ambroxol hydrochloride, Fexofenadine hydrochloride, HPLC, Validation.

**ABSTRACT**

A simple, rapid and precise reverse phase liquid chromatographic (RP-HPLC) method was developed and subsequently validated for simultaneous estimation of Ambroxol hydrochloride and Fexofenadine hydrochloride in bulk drug and in a synthetic mixture. The method is based on High Performance Liquid Chromatography (HPLC) on a reversed – phase column, Hypersil ODS C18 (Hypersil ODS 250 x 4.6 mm, 5µ, Make: Thermo Scientific) prepacked column. The separation was carried out using a mobile phase containing a buffer and acetonitrile (56:44 v/v), was pumped at a flow rate of 0.8 mL/min, column temperature at 35º C using UV-detection at 225 nm. Both the drugs were well resolved on the stationary phase and the retention times were around 2.424 minute for Ambroxol hydrochloride and 3.753 minute for Fexofenadine hydrochloride. The method was validated and shown to be linear for both the drugs. The correlation coefficients for Ambroxol hydrochloride and Fexofenadine hydrochloride are 0.9994 and 0.9992 respectively.

## INTRODUCTION

Ambroxol hydrochloride (AMB) chemically known as 1 ({[2-amino-3, 5 dibromo phenyl]-methyl} amino) cyclohexanol monohydrochloride **(Fig 1)** and is a semi synthetic derivative of Vasicine obtained from Indian shrub "*Adhatoda vascia*" and acts as a broncho secretolytic and expectorant drug. It stimulates the transportation of the viscous secretions in the respiratory organs and reduces the accumulation of the secretions (Maithan *et al.*, 2010; Pradeep *et al.*, 2012). Recently, the inhibition of nitric oxide dependent activation of sodium guanylate cyclase was suggested as one of the molecular mechanism of the therapeutic action of Ambroxol hydrochloride. AMB is also used in pulmonary alveolar protreinosis in pulmonary distress and infant respiratory distress syndrome (Nagavalli *et al.*, 2011).

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It is official in Martin Dale the Extra Pharmacopoeia (Sweetman *et al.*, 2005), Indian Pharmacopoeia (Indian Pharmacopoeia, 2007), British Pharmacopoeia (British Pharmacopoeia, 2009), European Pharmacopoeia (European Pharmacopoeia, 2005), and Merck Index (Merck Index, 2006). Fexofenadine hydrochloride (FEX), chemically known as (RS)-2-[4-[1-Hydroxy-4-[4- (hydroxy-diphenyl-methyl)-1-piperidyl] butyl] phenyl]-2-methyl-propanoic acid **(Fig 2)** is an orally administered non sedating antihistamine with selective peripheral $H_1$ receptor antagonist activity. It is used to relieve the allergy symptoms of seasonal allergic rhinitis (hay fever), including runny nose; sneezing; and red, itchy, or watery eyes; or itching of the nose, throat, or roof of the mouth in adults. It is a carboxylic acid metabolite of terfenadine, a non-sedating selective histamine $H_1$ receptor antagonist (Markham *et al.*, 1998; Simpson *et al.*, 2000). Fexofenadine, like other second and third generation antihistamines, does not readily cross the blood–brain barrier, and so causes less drowsiness than first generation histamine receptor antagonists. It works by being an antagonist to the $H_1$ receptor (Katagiri *et al.*, 2006).

It also exhibits anticholinergic, antidopaminergic, alpha1-adrenergic or beta adrenergic receptor blocking effects (Nagaraju *et al*., 2013). Fexofenadine hydrochloride is the subject of monograph in the Indian Pharmacopoeia (Indian Pharmacopoeia, 2010), United States Pharmacopoeia (United States Pharmacopoeia, 2011) and British Pharmacopoeia (British Pharmacopoeia, 2010).

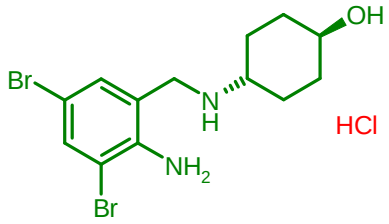


**Fig. 1:** Chemical structure of Ambroxol hydrochloride.

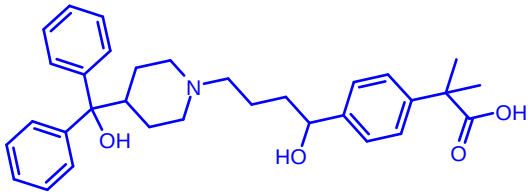


**Fig. 2:** Chemical structure of Fexofenadine hydrochloride.

The combination of Ambroxol hydrochloride with Fexofenadine hydrochloride used clinically for treatment and prophylaxis of allergic rhinitis, cold and flu. Literature survey reveals that Spectrophotometric (Polawar *et al*., 2008; Lata *et al*., 2012; Narayana *et al*., 2010; Vekaria *et al*., 2011; Amrithraj *et al*., 2011; Rahul *et al*., 2013; Ponnilavasaran *et al*., 2011; Nagras *et al*., 2012), Conductometric (Asjour *et al*., 2013), HPTLC (Vekaria *et al*., 2012; Sharma *et al*., 2010; Tandulwadkar *et al*., 2012), Potentiometric (Rajan *et al*., 2013), RP- UPLC (Bhupendrasinh *et al*., 2012), HPLC (Prasanth *et al*., 2012; Tamilselvi *et al*., 2012; Krishna *et al*., 2013; Ravisankar *et al*., 2012; Hashem *et al*., 2013; Mounika *et al*., 2012; Moses *et al*., 2013; Nidhi *et al*., 2012; Kamarupa *et al*., 2010; Khedkar *et al*., 2012; Suresh *et al*., 2012; Manasa *et al*., 2013), methods have been reported for their individual analysis, along with other combinations in pharmaceutical formulation and biological fluids. To the best of our knowledge no HPLC method of analysis has yet been reported for simultaneous analysis of AMB and FEX. Hence, the aim of the present investigation was to develop and validate an economic, simple, feasible, rapid, sensitive, and specific RP-HPLC method for simultaneous estimation of Ambroxol hydrochloride and Fexofenadine hydrochloride in bulk drug and in the tablet mixture and validate according ICH guidelines (ICH Guidelines, 2005).

## MATERIALS AND METHODS

### Reagents and chemicals

Methanol and Water were of HPLC grade and were purchased from Rankem, Gujarat. Acetonitrile of HPLC grade purchased from Merck, Mumbai. Orthophosphoric acid purchased from Rankem, New Delhi. Triethylamine AR grade purchased from Sd fine chemicals, Mumbai. Potassium dihydrogen phosphate for Chromatography purchased from Merck, Mumbai. Ambroxol hydrochloride and Fexofenadine hydrochloride was received as gift samples from Vasudha Pharma Chem, Hyderabad, India, and Dots Lifesciences private Limited, Gujarat, India.

### Equipment and chromatographic conditions

A high-performance liquid chromatographic system (Younglin, software: Autochro 3000) equipped with UV detector. All pH measurements were performed on a pH meter (Digisun Electronics, Hyderabad). Chromatographic separation was carried out at room temperature with Hypersil ODS C18 (Hypersil ODS 250 x 4.6 mm, 5µ, Make: Thermo Scientific) column. For the mobile phase, accurately weighed 2.72gm of Potassium dihydrogen orthophosphate was dissolved in a 900 mL of HPLC grade water and sonicated to remove dissolved gases. The pH of the mobile phase was adjusted to 4.8±0.05 with orthophospharic acid. The buffer solution was shaked manually to mix and finally make the volume upto 1000 mL with water. A mixture of Buffer and Acetonitrile in the ratio of 56:44 was prepared. Finally the mobile phase was filtered through a 0.45 µm membrane filter and degassed for 10 minutes. The injection volumes for samples and standards were 20 µl and eluted at a flow rate of 0.8 mL/min at 35°C. The eluents were monitored at 225 nm.

### Preparation of standard stock solutions

A working standard solution containing Ambroxol hydrochloride and Fexofenadine hydrochloride was prepared by weighing 10 mg of both the drugs and transferred to a 10 mL volumetric flask; 10 mL of methanol are added, and the solution is sonicated for 10 min. the volume is made up to the mark with methanol to obtain a stock solution of 1000 µg/mL.

### Preparation of working standard solutions

1 mL from stock solution of AMB and 1 mL from stock solution of FEX were withdrawn from standard stock solutions and transferred to a 10mL of volumetric flask and the volume is made up to the mark with diluent to obtain a mixed working standard solution containing 100 µg/mL of both the drugs.

## METHOD VALIDATION

The developed analytical method was further subjected to validation in accordance to the ICH guidelines. The parameters evaluated were linearity, sensitivity, system suitability, precision, accuracy, robustness and stability. Coefficients of variation and relative errors <2% were considered acceptable

### *Linearity*

In order to check the linearity for the developed method, solutions of six different concentrations ranging from 25-150µg / mL were prepared for AMB and 25-150µg / ml for FEX,

respectively. The Chromatograms peak areas were recorded and calibration curve was plotted of peak area against concentration of drug. The chromatograms were recorded and the peak areas are given in Table 1.

**Table 1:** Linearity data for Ambroxol hydrochloride and Fexofenadine hydrochloride.

| FEX Conc. (µg/mL) | Mean Peak area of FEX | AMB Conc. (µg/mL) | Mean Peak area of AMB |
|---|---|---|---|
| 25 | 288521 | 25 | 464698 |
| 50 | 517843 | 50 | 1002380 |
| 75 | 1104899 | 75 | 1569746 |
| 100 | 1104899 | 100 | 1935900 |
| 125 | 1347922 | 125 | 2419748 |
| 150 | 1647391 | 150 | 2933891 |

A linear relationship between areas versus concentrations was observed in the above mentioned linearity range. This range was selected as the linear range for the development of the analytical method, for the estimation of AMB and FEX. The calibration curves for both drugs given in Fig. 4 and Fig. 5.

### *Sensitivity*

The sensitivity of the measurement of AMB and FEX using the proposed method was estimated as the limit of quantification (LOQ) and the lowest concentration detected under these chromatographic conditions as the limit of detection (LOD). The LOD and LOQ were calculated by using the equations LOD = 3.3 × σ / S and LOQ = 10 × σ / S, where σ was the standard deviation of the peak areas of the drug (n = 6), and S was the slope of the corresponding calibration plot. The limits of detection and quantification for FEX were 0.15µg/mL and 0.45 µg /mL, respectively, and those for AMB were 0.78 µg/mL and 2.37 µg/mL, respectively. The results are shown in Table 2.

### *System suitability*

The system suitability test is an integral part of chromatographic analysis. It is used to verify that the resolution and reproducibility of the system are adequate for the analysis. A system suitability test according to the United States Pharmacopeia Convention was performed on chromatograms obtained for standard and test solutions to check differences in the above mentioned parameters. The results obtained with six replicate injections of the standard solution are summarized in Table 3.

### *Precision*

Precision was measured by the analysis of sample solutions of 6 replicates, to check the intraday and inter day variations of the method. The results are furnished in Tables 4 and 5.

### *Accuracy*

The accuracy of the method was determined by the analysis of standard additions at three levels, that is, multiple-level recovery studies. The reference standard, at three different concentrations (50, 100, and 150 %), was added to a fixed amount of the pre analyzed sample and the amounts of the drug were analyzed by the proposed method. Results from the recovery studies are given in Tables 6 and 7.

### *Robustness*

The robustness of the method was determined by making slight changes in the chromatographic conditions like flow rate (±0.1), temperature (±5), and organic phase of the mobile phase (±10%). It was observed that there were no marked changes in the chromatograms, which demonstrated that the RP-HPLC method developed was robust.

## RESULTS AND DISCUSSION

### Calibration curve

The coefficient correlation *r*, slope and intercept were 0.9994, 19493 and 4627.6 for AMB and 0.9992, 10926 and 487.54for FEX with UV detection with absorbance maxima at 225 nm (Fig. 3). The retention times were 2.424 for AMB and 3.753 for FEX (Fig. 6). Linear regression of data from the calibration curve indicated a linear response over the concentration range of both drugs. The curve can be therefore be used for determination of Fexofenadine and Ambroxol in tablet mixture.

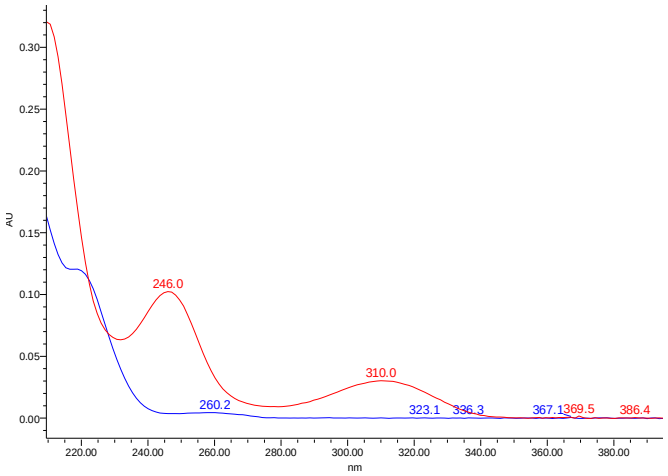


**Fig. 3:** UV spectra of AMB & FEX with blank (methanol) (100µg/mL).

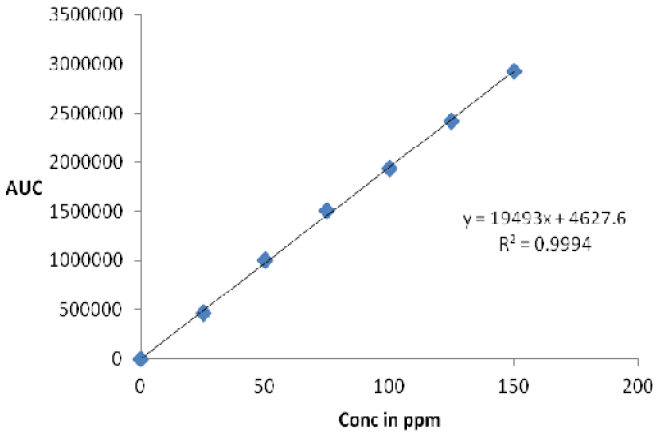


**Fig. 4:** Calibration curve for Ambroxol hydrochloride at 225 nm.

**Table 2:** Spectral and statistical data for determination of Fexofenadine and Ambroxol by proposed RP-HPLC method.

| Analyte | | | |
|---|---|---|---|
| **Ambroxol hydrochloride** | | **Fexofenadine hydrochloride** | |
| Absorption maxima,λ (nm) | 225 | Absorption maxima, λ (nm) | 225 |
| Linearity range( µg/mL) | 25-150 | Linearity range( µg/mL) | 25-150 |
| Coefficient of determination ($r^2$) | 0.9994 | Coefficient of determination ($r^2$) | 0.9992 |
| Regression equation ($Y^a$) | y = 19493x + 4627.6 | Regression equation ($Y^a$) | y = 10926x + 487.54 |
| Slope (b) | 19493 | Slope (b) | 10926 |
| Intercept (a) | 4627.6 | Intercept (a) | 487.54 |
| Limit of detection, LOD ( µg/mL) | 0.15 | Limit of detection, LOD ( µg/mL) | 3.3 |
| Limit of quantitation, LOQ( µg/mL) | 0.45 | Limit of quantitation, LOQ( µg/mL) | 10 |

[a]$Y = mx + c$, where $x$ is the concentration ( µg/mL).

**Table 3:** System suitability parameters for Ambroxol hydrochloride and Fexofenadine hydrochloride.

| Parameter (*n=6) | AMB | FEX |
|---|---|---|
| Retention time | 2.424 | 3.753 |
| Plate count | 2240 | 6944 |
| USP Tailing | 1.64 | 1.25 |

***Six replicates, AMB**-Ambroxol hydrochloride; **FEX**-Fexofenadine hydrochloride.

**Table 4:** Results of the intraday precision.

| Ambroxol hydrochloride | | | Fexofenadine hydrochloride | | |
|---|---|---|---|---|---|
| **Conc (µg/mL)** | **Peak area Mean S.D (n=6)** | **RSD (%)** | **Conc (µg/mL)** | **Peak area Mean S.D (n=6)** | **RSD (%)** |
| 100 | 8709 | 0.47 | 100 | 5159.45 | 0.47 |

**Table 5:** Results of the interday precision.

| Ambroxol hydrochloride | | | Fexofenadine hydrochloride | | |
|---|---|---|---|---|---|
| **Conc (µg/mL)** | **Peak area Mean S.D (n=6)** | **RSD (%)** | **Conc (µg/mL)** | **Peak area Mean S.D (n=6)** | **RSD (%)** |
| 100 | 7106.3 | 0.39 | 100 | 3984.50 | 0.36 |

**Table 6:** Results of the recovery study of Ambroxol hydrochloride.

| Amount of AMB in Sample (µg) | Total amount of AMB found (µg) Mean ± S.D | Total amount recovered (µg) | % Recovery (n=3) |
|---|---|---|---|
| 50 | 50.005 | 50.005 | 100.01 |
| 100 | 99.52 | 99.52 | 99.52 |
| 150 | 150.195 | 150.195 | 100.13 |

**Table 7:** Results of the recovery study of Fexofenadine hydrochloride.

| Amount of FEX in Sample (µg) | Total amount of FEX found (µg) Mean ± S.D | Total amount recovered (µg) | % Recovery (n=3) |
|---|---|---|---|
| 50 | 49.75 | 49.75 | 99.90 |
| 100 | 100.14 | 100.14 | 100.14 |
| 150 | 149.38 | 149.38 | 99.59 |

**Table 8:** Determination of % assay for AMB and FEX.

| Tablet mixture | Drug | Label claim mg/tablet | Amount taken (mg) | Conc. estimated (mg) | Mean conc. Estimated (mg) | % Assay (w/w) | % RSD |
|---|---|---|---|---|---|---|---|
| AMB +FEX | AMB | 30 mg | 10 | 9.28 | 9.84 | 98.4 | 0.8 |
| | | | | 9.69 | | | |
| | | | | 9.73 | | | |
| | | | | 9.87 | | | |
| | | | | 10.22 | | | |
| | | | | 10.27 | | | |
| | FEX | 30 mg | 10 | 9.97 | 9.73 | 97.3 | 0.73 |
| | | | | 9.56 | | | |
| | | | | 9.40 | | | |
| | | | | 9.82 | | | |
| | | | | 9.70 | | | |
| | | | | 9.98 | | | |

% Assay of AMB or FEX = AMB or FEX conc estimated (mg)/ AMB or FEX input (mg) X 100 ± SD; % RSD = SD/mean X 100.

**Validation**

***Linearity***

The coefficient of determination ($r^2$) for both AMB and FEX was 0.999 (Table 1 and Figs. 4 and 5).

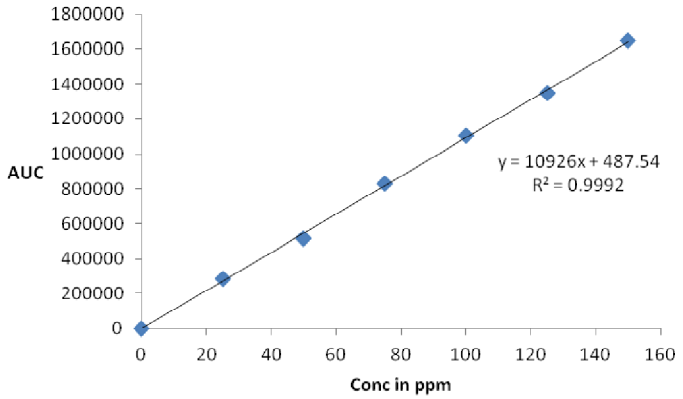


**Fig. 5:** Calibration curve of Fexofenadine hydrochloride at 225 nm.

**Sensitivity**

The limit of detection and the limit of quantification were determined from the calibration curve, according to the formulae 3.3 × SD/slope and 10 × SD/slope, respectively. The results are shown in Table 2.

***System suitability***

System suitability was evaluated by six replicate injections of 100 µg/mL standard solutions of Ambroxol hydrochloride and Fexofenadine hydrochloride. The parameters, such as tailing factor, percent relative standard deviation (RSD) and theoretical plates were studied and found satisfactory (Table 3).

***Precision***

The relative standard deviation was found to be<2.0% for both Ambroxol hydrochloride and Fexofenadine hydrochloride, indicating satisfactory precision (Tables 4 and 5). The intermediate precision of the expected results is expressed as a percentage.

***Accuracy***

Accuracy is the closeness of the test results to that of the true value, which can be determined in terms of percent recovery. To check the accuracy of the method, recovery studies were carried out by addition of standard drug solution to pre analyzed sample solution at three different levels 50, 100 and 150%. The results of recovery studies was tabulated and found satisfactory (Tables 6 and 7).

***Robustness***

Robustness determines the reproducibility of the test result with small and deliberate variations in the method parameters.

The experiment was carried out by slightly changing the chromatographic conditions like flow rate (±0.1), temperature (±5), and organic phase of the mobile phase (±10%). The retention times of the analytes did not change significantly when the flow rate, mobile phase ratio and temperature were changed. The statistical data gives no significant variations in the above parameters indicating that the method is robust.

***Solution stability***

The stability of AMB and FEX standard and sample solutions was determined by storing the solutions at an ambient temperature (30 ± 5°C).

The solutions were checked in triplicate after three successive days of storage and the data were compared with the freshly prepared samples. In each case, it could be noticed that the solutions were stable for 48 hours, as during this time the results did not decrease below 98%. This showed that AMB and FEX were stable in standard and sample solutions for at least two days, at ambient temperature.

***Assay***

The proposed method was successfully applied for the estimation of Ambroxol hydrochloride and Fexofenadine hydrochloride in bulk drug and in a tablet mixture. Ten tablets powdered equivalent were mixed in a ratio of 10 mg Ambroxol hydrochloride: 10 mg Fexofenadine hydrochloride. A quantity of this tablet mixture powder equivalent to 20 mg was taken up in a 10 mL volumetric flask, and methanol was added up to the mark. The solution was sonicated for 5 min.

This solution was further diluted to obtain a concentration of 100 µg/mL AMB and 100 µg/mL FEX. The assay results were compiled, found satisfactory and show that there is a no interference of tablet matrix with the drug and the results are summarized in Table 8, and the standard and test chromatograms are given in Fig. 6 and 7. Low % RSD shows that this method can be easily applied for the estimation of AMB and FEX in bulk drug and in the tablet mixture.

**CONCLUSIONS**

The proposed study describes a new and simple RP-HPLC method for the estimation of Ambroxol hydrochloride and Fexofenadine hydrochloride in bulk drug and in a tablet mixture. The method has been validated and found to be simple, rapid, sensitive, accurate, and precise. Moreover, the lower solvent consumption along with the short analytical run time of 5 minutes leads to an environmentally friendly chromatographic procedure that allows the analysis of a large number of samples in a short period of time. Therefore, the proposed method can be used for routine analysis of both drugs in the process control of bulk drug and formulated products without any interference from the excipients in laboratories and in the pharmaceutical industry.

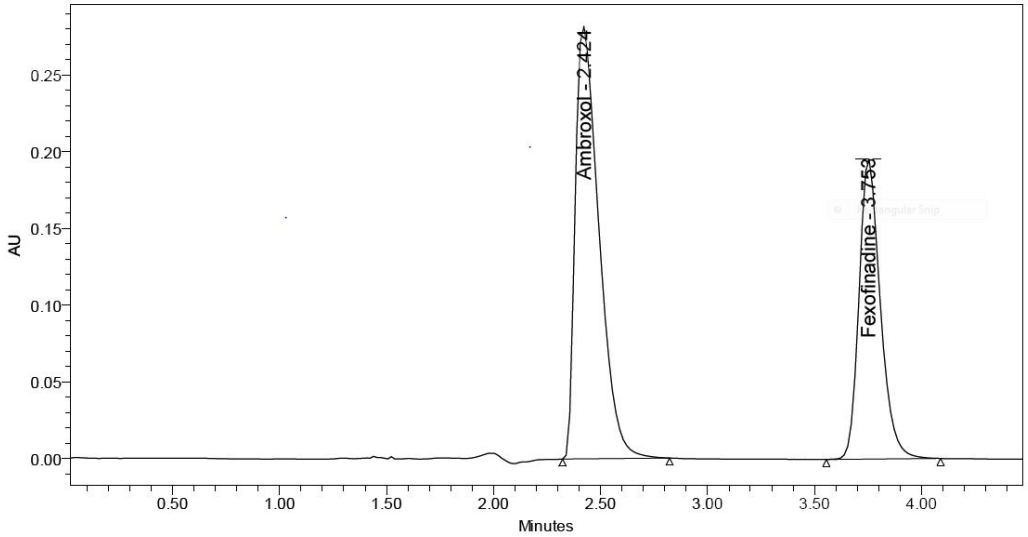


**Fig. 6:** Chromatogram of the standard preparation of Ambroxol hydrochloride and Fexofenadine hydrochloride.

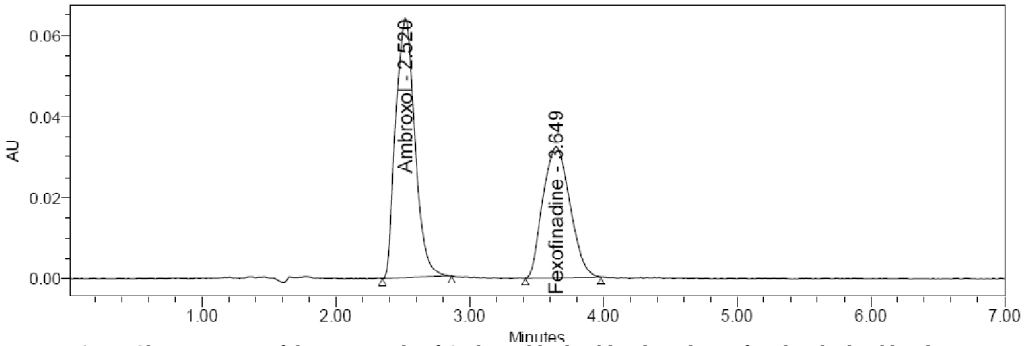


**Fig. 7:** Chromatogram of the test sample of Ambroxol hydrochloride and Fexofenadine hydrochloride.

## ACKNOWLEDGEMENTS

The authors are thankful to Vasudha Pharma Chem, Hyderabad, for providing Fexofenadine HCl and Dots Lifesciences Pvt. Ltd., Gujarat, for providing Ambroxol HCl , both free of charge. The authors are also thankful to Principal and Management of the Sri Venkateshwara College of Pharmacy and Research Centre, Madhapur, Hyderabad, for providing chemicals and equipment for this work.

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**How to cite this article:**

Prathyusha Buchupalli, Srinivas Medidi. RP-HPLC Method for the Simultaneous Estimation of Ambroxol Hydrochloride and Fexofenadine Hydrochloride In bulk and in a Tablet Mixture. J App Pharm Sci, 2015; 5 (02): 074-080.