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A Rapid and Simultaneous Determination of Ambroxol Hydrochloride, Methyl Parabene and Propyl Paraben in Mucol Ambroxol Syrup Dosage Form.

Aqib Zahoor[1], Hira Munir[1], Shafiquat Hussain[1], Zeeshan Ahmed Sheikh[1],Khan Usmanghani[1,2]

[1] Department of Research and Development, Herbion Pakistan (Pvt.) Limited, Plot 30, sector 28 Korangi Industrial Area, Karachi-74900, Pakistan

[2] Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

ABSTRACT

Ambroxol HCl is an active compound that improve the exploration and a mucolytic activity for the treatment of bronchial asthma and chronic bronchitis.A method is delineate ambroxol, trans-4-(2-amino-3,5-dibromobenzylamino) cyclohexanol, hydrochloride, methyl and propyl parabeneseparation by HPLC, with UV detection at 247 nm in a syrup as pharmaceutical presentation. The optimal conditions maintained were column symmetry shield RPC8, 5 microm 250 x 4.6 mm, and methanol/H3PO4 8.5 mM/triethylamine pH=2.8) 40:60 v/v. The validation was carried out using ICH guildlines. HPLC assay method was validated for linearity, precision, accuracy, specificity and robustness. The developed and validated method can be used extensively for quality control and assurance purposes of Ambroxol hydrochloride and Parabenes.

Keywords: *Ambroxol HCl, Analytical methods, HPLC spectrophotometry, Mucolytics.*

INTRODUCTION

Ambroxol hydrochloride (Fig. 1) is chemically a metabolite of bromohexine elaborated by Adhatodavasica that is a semi synthetic derivative of vasicine. Ambroxol is a an effective agents used as the treatment of chronic bronchitis and bronchial asthma [1].Ambroxol Pharmacological attributes are follows surfactant stimulatory, anti inflammatory, and anti-oxidant and local anesthetic and mucociliary effects. Ambroxol has been mentioned as an official drugs in British Pharmacopoeia 2005 [2], Indian Pharmacopoeia 2007 [3], and European Pharmacopoeia 2005[4].

Ambroxol is a clinically proven systemically active mucolytic agent. When administered orally onset of action occurs after about 30 minutes. The breakdown of acid mucopolysaccharide fibers makes the sputum thinner and less viscous and therefore more easily removed by coughing. Although sputum volume eventually decreases, its viscosity remains low for as long as treatment is maintained. Indications: All forms of tracheobronchitis, emphysema with bronchitis pneumoconiosis, chronic inflammatory pulmonary conditions, bronchiectasis, bronchitis with bronchospasm asthma. During acute exacerbations of bronchitis it should be given with the appropriate antibiotic. *Contraindications:* There are no absolute contraindications but in patients with gastric ulceration relative caution should be observed [5]. Side effects: Occasional gastrointestinal side effects may occur but these are normally mild. Precautions: It is advisable to avoid use during the first trimester of pregnancy.

Dosage: Adults: teaspoonful twice daily taken in 2 to 3 divided doses. Children up to 2 years:

Corresponding Author: aqib.zahoor@herbion.com

half a teaspoonful Ambroxol syrup twice daily. Children 2 - 5 years: half a teaspoonful Ambroxol syrup 3 times daily. Children over 5 years: One teaspoonful Ambroxol syrup 2-3 times daily. Storage: Store at a temperature not exceeding 30 degrees celsius. Keep all medicine out of reach of children.

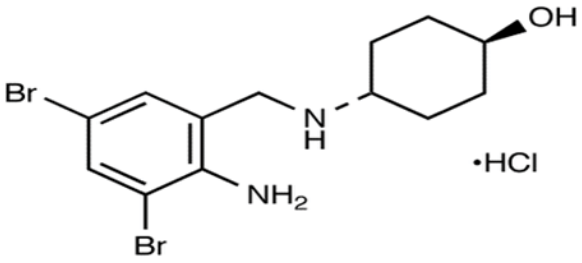

Fig. 1. Structure of Ambroxol

EXPERIMENTAL

Material and Method:

The purity of all chemicals was above 98%. Standards of Ambroxol HCl, methyl and propyl-parabenes from Sigma Aldrich were used for analysis and Ambroxol HCl from KORES (India) Ltd. was used for syrup formation.

HPLC-grade Methanol, reagent grade ortho-phosphoric acid and triethylamine were procured from Merck (Darmstadt, Germany). High purity water was prepared by using Milli Q plus water purification system (Millipore, Milford,MA, USA). Phenomenex RP-8 column was procured from Phenomenax USA.

Equipment

Chromatography was performed with Agilent 1260 HPLC system that consists of quaternary pump equipped with aN auto injector and photodiode array detector. The output signal was monitored and processed using Agilent Chem Station software. All solutions were degassed by ultra sonication (Power sonic 420, Labtech, Korea) and filtered through a 0.45 µm Millipore filters.

Mucol Ambroxol Syrup:

Research and development department of Herbion Pakistan Pvt. Limited was successfully developed the formulation of Ambroxol HCl for cough and cold which named Mucol Ambroxol HCl Syrup. Each 5 ml of solution contains ambroxol hydrochloride 15 mg, see table 1.

Table 1. Unit composition¬ –MucolAmbroxol Syrup

Each 5 ml of solution contains:

S.No	Ingredients	Quantity/5ml
ACTIVES		
01.	AmbroxolHcl	15 mg
EXCIPIENTS		
02.	Propylene glycol	100 mg
03.	Methyl paraben	5 mg
04.	Propyl paraben	0.6 mg
05.	Purified water	Q.S

Analytical Method:

The main objective of the RP-HPLC method development was to rapid and simultaneous determination of Ambroxol HCl, methyl parabene and propyl parabene in liquid pharmaceutical formulation. The method should be able to determine assay of three compounds in single run and should be accurate, reproducible, robust, stability indicating, filter compatible, linear, free of interference from blank / placebo / impurities / degradation products and straightforward enough for routine use in quality control laboratory.

Standard preparation

Take 45 mg of the standard in 50ml volumetric flask and make up the volume up to the mark by water R and sonicate for 20 minutes. Then take 1ml of this solution to 10 ml volumetric flask and make up the volume up to the mark with the mobile phase. Filter the obtained solution with HPLC filter (0.45µm) and proceed for

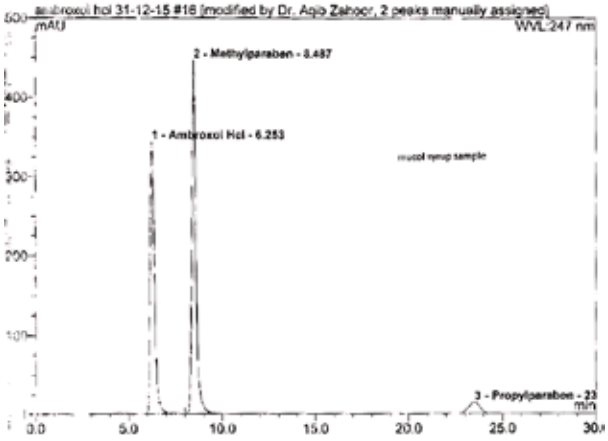

Fig. 1: Mucol Syrup

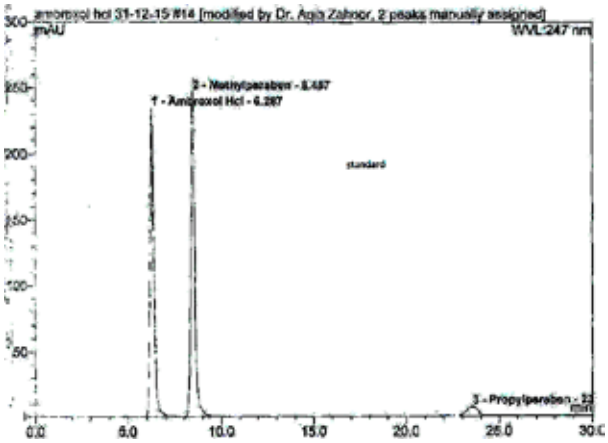

Fig. 2: Ambroxol HCL, Methyl parabene and Propyl parabene STD

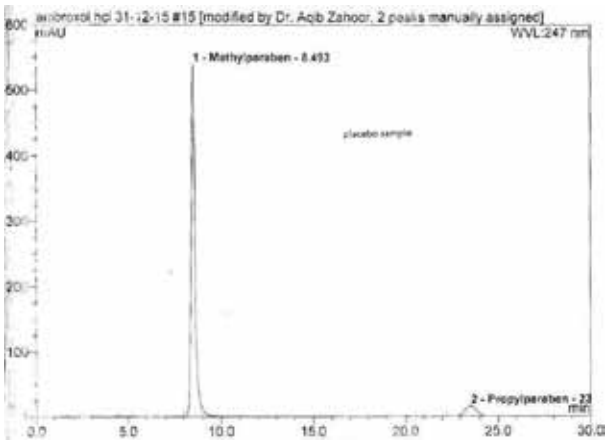

Fig. 3: Placebo for Ambroxol HCl.

HPLC analysis.

Sample preparation

Take 15 ml of syrup (note the weight) in 50ml volumetric flask and make up the volume up to the mark by water R and sonicate for 20 minutes.Then take 1ml of this solution to 10ml volumetric flask and make up the volume up to the mark with the mobile phase. Filter the obtained solution with HPLC filter (0.45µm) and proceed for HPLC analysis.

Analysis

Chromatograph 20 µL of test solution and Ambroxol HCl standard solutions alternately on liquid chromatography with UV detector or DAD detector obtaining not less than 3 chromatograms of each sample and standard solution in the following conditions

Chromatographic conditions

Mobile phase : A mixture of methanol / (H_3PO_4 8.5 Mm/triethylamine pH 2.8) 40:60v/v.
Column : Symmetry shieldRPC8, 5 micron 250 ×4.6 mm.
Temperature : 40°C
Flow rate : 1ml/min
Detection : Spectrophotometer at 247nm
Injection : 20 µL
Run time : 20 min

Ambroxol HCl content in Mucol Ambroxol syrup calculated by the following formula.

$$X = \frac{A_{SMP} \times Wt_{STD} \times D_{SPL} \times \%\ purity \times D \times 5 \times 100}{A_{STD} \times D_{STD} \times Wt_{SMP} \times 100 \times 15} = \ldots\ldots\ldots \text{ Percent}$$

Where,

A_{SMP} Mean value of peak area of tested solution samples
A_{STD} Mean value of peak area of standard solution samples
W_{SMP} Weight of sample, g
W_{STD} Standard weight, mg
D_{SPL} Dilution of sample .
D_{STD} Dilution of standard .
D Density of syrup .

For reference the chromatograms of sample, standard and ambroxolHCl placebo are present

in figure # 1, 2, and 3 respectively.

RESULTS AND DISCUSSION

In most pharmaceutical preparations, especially in syrups, preservation is essential because the excipients, and sometimes the drug itself, may be destroyed by different microorganisms and consequently the formulation breaks down. Synthetic preservatives constitute the largest and most commonly used group in the preservation of pharmaceutical products. The esters of p-hydroxybenzoic acid with different alcohols, known as hydroxybenzoates or parabens, and benzoic acid are widely used as antimicrobial preservatives in liquid pharmaceutical forms[6]. Several different methods have been used for the individual determination of ambroxol hydrochloride in pharmaceutical preparations including, spectrophotometry [7] and HPLC [8]. More complex methods have been reported for ambroxol determination in biological fluids [9]. Out of these only one of them [10] has been applied to a determination of ambroxol in presence of different preservatives.

The present study elaborate with the determination of ambroxol hydrochloride, methylparaben, and propylparaben in liquid pharmaceutical formulation using the developed and validated method. Liquid preparations are particularly susceptible to microbial growth because of the nature of their ingredients. Such preparations are protected by the addition of preservatives that prevent the alteration and degradation of the product formulation [11]. The finished product release specifications should include an identification test and a content determination test with acceptance criteria and limits for each antimicrobial preservative present in the formulation. The finished product self-life specification should also include an identification test and limits for the antimicrobial preservatives present [12]. Hence the antimicrobial and antifungal properties make them an integral part of the product formulation. This encourages the development of stability indicating method for simultaneous estimation of all compounds to provide driving force in today's pharmaceutical industry.

CONCLUSION

A simple reverse phase HPLC method was found to be accurate, precise, linear and robust. The method was specific for the determination of Ambroxol as well as methylparaben and propylparaben in the syrup formulation. All the criteria meet the ICH guidelines for method of validation. The peaks are well resolved. There were no interference peaks in the chromatogram. The method is rapid and sensitive enough to be used in the syrup dosage form.

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