

A Review of Analytical Methods for Determination Bromhexine Hydrochloride in Pharmaceutical and Biological Samples

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ABSTRACT

Bromhexine HCl (BRH) is a mucolytic agent used in the treatment of respiratory disorders associated with viscid or excessive mucus, chemically named 2-amino-3,5-dibromo-N-cyclohexyl-N-methylbenzenemethanamine hydrochloride. According to IUPAC it is 2,4-dibromo-6-[[cyclohexyl(methyl)amino]methyl] aniline hydrochloride. Because of its physiological importance, the drug has been quantified by exploiting its chemical and physical properties. Bromhexine is a weak base and its precipitate out at pH value above 6. Bromhexine is a synthetic benzyl amine derivative of vasicine. The different analytical methods used to quantify the drug as a single active pharmaceutical ingredient include flow injection analysis with ion selective electrodes, inductively coupled plasma mass spectrometry, electrokinetic chromatography, electrochemical oxidation at the glassy carbon electrode, liquid chromatography, liquid gas chromatography, GC with mass detection, and voltammetry. The drug has also been quantified in its combined formulations using HPLC, direct and derivative UV spectrophotometry.

Keywords: Bromhexine, UV Spectroscopic Method, Chromatography

INTRODUCTION ^[1-9]

Bromhexine hydrochloride is a mucolytic agent rendering the sputum less viscous thereby facilitating easy expulsion of it from the respiratory tract.

The drug is official in IP and BP.

CHEMICAL AND PHYSICAL INFORMATION OF BROMHEXINE HYDROCHLORIDE:

STRUCTURAL FORMULA:

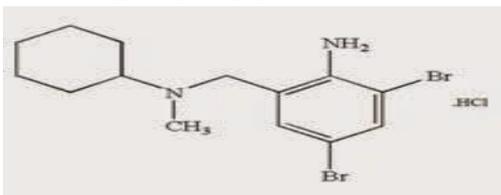


Figure 1: Chemical structures of Bromhexine Hydrochloride

MOLECULAR FORMULA: C₁₄H₂₀Br₂N₂.HCl

MOLECULAR WEIGHT: 412.59 g/mol

CHEMICAL NAME:

2-Amino-N-cyclohexyl-3,5-dibromo-N-methylbenzylamine hydrochloride

CATEGORY: Mucolytics

DOSE: 8 mg

DESCRIPTION: white crystalline powder

SOLUBILITY:

Slightly soluble in alcohol and methylene chloride,

Sparingly soluble in water.

How to cite this article: MV Lad, V Jain, R Hasumati; A Review of Analytical Methods for Determination Bromhexine Hydrochloride in Pharmaceutical and Biological Samples; PharmaTutor; 2014; 2(11); 35-41

PHARMACOLOGICAL ACTION ^[10]

Bromhexine hydrochloride (Figure 1) is a mucolytic expectorant which exhibits its action by increasing bronchial secretions and reducing their viscosity. In addition, it produces in an increase in immunoglobulin levels in airway secretions. This agent was recently recommended as a new therapy for pathological states, such as alcoholic chronic pancreatitis where there is an increased viscosity of the pancreatic juice. Bromhexine hydrochloride may be administered in combination with antimicrobial agents in the treatment of respiratory infections, due to its capacity to disrupt the mucopolysaccharides of bronchial secretion and as results in enhancing the bronchial penetration of antimicrobial drugs.

PHARMACOKINETICS ^[11]

On oral administration, Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver. Its oral bioavailability is stated to be only about 20%. It

is widely distributed to body tissues and is highly bound to plasma proteins. About 85 to 90% of a dose is excreted in the urine mainly as metabolites. It has a terminal elimination half-life of up to about 12 hours. Bromhexine crosses the blood brain barrier and small amounts cross the placenta.

SIDE EFFECTS ^[11]

Gastrointestinal side effects may occur occasionally with bromhexine and a transient rise in serum aminotransferase values has been reported.

Other reported side effects include headache, vertigo (dizziness), sweating and allergic reactions.

ANALYTICAL METHODS

This all are the methods which are used for the determination of Bromhexine Hydrochloride in marketed formulation and in biological fluids. This all analytical methods are reported which are seen during the literature survey. This article describes the review on the all reported analytical methods with specific conditions.

I. COMPENDIAL METHODS:

Table No.1: Summary of Compendial Methods of Bromhexine hydrochloride

PHARMACOPOEIA	METHOD
IP ^[3]	<p>Potentiometry:</p> <p>Weigh accurately about 0.3.g, dissolve in 70 ml of ethanol(95%), add 1 ml of 0.1. M hydrochloric acid and titrate with 0.1 M sodium hydroxide, determining the end point potentiometrically. Record the volume added between the two inflections.</p> <p>1 ml of 0.1 M sodium hydroxide is equivalent to 0.04126 g of $C_{14}H_{20}Br_2N_2, HCL$.</p>
BP ^[4]	<p>Potentiometric Titration:</p> <p>Dissolve 0.300 gm in 70 ml of alcohol R and add 1 ml of 0.1 M hydrochloric acid. Carry out a potentiometric titration, using 0.1 M sodium hydroxide. Read the volume added between the two points of inflexion.</p> <p>1 ml of 0.1 M sodium hydroxide is equivalent to 41.26 mg of $C_{14}H_{21}Br_2ClN_2$.</p>

EP ^[12]	Potentiometric Titration: Dissolve 0.300 g in 70 ml of alcohol R and add 1 ml of 0.1 M hydrochloric acid. Carry out a potentiometric titration, using 0.1 M sodium hydroxide. Read the volume between the 2 points of inflexion. 1 ml of 0.1 M sodium hydroxide is equivalent to 41.26 mg of $C_{14}H_{21}Br_2ClN_2$.
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II. CHROMATOGRAPHIC METHODS:^[13-21]

Various chromatographic methods are used for the determination of the Bromhexine Hydrochloride alone or combination with other drugs in various marketed formulation and in biological fluids like human plasma and urine. Chromatographic methods like High performance liquid chromatography (HPLC/ RP-HPLC), High performance thin layer chromatography (HPTLC), High performance liquid chromatography (HPLC) with Solid Extraction method, Thin Layer Chromatography (TLC) Densitometric method are used. In which the stationary phase commonly used is C_{18} column and mobile phase is commonly used is acetonitrile & phosphate buffer & methanol, its proportion is varies with condition of method and range of pH is 3 to 4. commonly used wavelength for detection is in the range of 250-270 nm. Below in table describes the summary of the various chromatographic methods are used with the method description.

Table No.2: Summary of Chromatographic Methods of Bromhexinehydrochloride

Title	Method	Mobile Phase	Stationary Phase	Wavelength (nm)
Bromhexine hydrochloride film content on High Performance Liquid Chromatography ^[13]	HPLC	Acetonitrile 0.05 mol·L ⁻¹ :Phosphate buffer (containing 0.2% triethylamine ,)(30:70)	an Altima C ₁₈ column (4.6 mm × 150 mm, 5 μm),	249 nm
Molecularly imprinted solid-phase extraction for the selective determination of bromhexine in human serum and urine ^[14]	Solid phase Extraction with HPLC	3× 1 mL Methanol/Acetic Acid (10/1, v/v)	Octadecylsilica column (55 mm × 4 mm , 3 μm particles)	270 nm
Estimation Of Bromhexine And Terbutaline In Bulk And Tablet Dosage Forms ^[15]	HPLC	Phosphate buffer (0.05 M, pH 3): Acetonitrile (70:30 v/v)	ODS C ₈ column (length 250 mm and internal diameter 4.6 mm)	270 nm

Simultaneous Estimation of Amoxicillin Trihydrate and Bromhexine Hydrochloride from Oily Suspension ^[16]	RP-HPLC	Methanol and Glacial Acetic Acid (50:50 v/v)	ODS C18 (250 X 4.5mm ID),	254 nm
Simultaneous determination of Terbutaline and Bromhexine in Combined Pharmaceutical Dosage Form ^[17]	RP-HPLC	Methanol: Acetonitrile: Ortho-Phosphoric acid in the ratio of 80:10:10 (v/v/v)	Inertsil ODS C-18 column 5µm column having 250 x 4.6mm internal diameter	270 nm
Simultaneous Determination of Bromhexine HCl and Baicalin in Chinese Compound Medicine ^[18]	RP-ion pair HPLC	Water/Acetonitrile/Phosphoric acid/Triethylamine (78/22/0.1/0.1 v/v/v/v)	C ₁₈ Column (250 x 4.6mm internal diameter , 5 µm)	225 nm
Simultaneous Determination of Salbutamol Sulphate and Bromhexine Hydrochloride in Tablets ^[19]	RP-HPLC	Acetonitrile, Methanol and Phosphate buffer, pH 4 in the ratio 60:20:20 v/v.	SS Wakosil-II C-18 column	224 nm
TLC Densitometric Determination of Bromhexine Hydrochloride in Pharmaceuticals ^[20]	TLC Densitometric Method	n-Butanol–Glacial Acetic Acid–Water (26:7.5:7.5)	Pre-coated silica gel plates	325 nm
Determination of Bromhexine hydrochloride in Human Plasma ^[21]	HPTLC	a mixture of n-Butyl acetate: Methanol : GAA: Water(HPL grade) in the ratio of 5:2.5:2.5:1v/v/v/v.	TLC plates precoated with silica gel 60 F254	246 nm

II. UV SPECTROSCOPIC METHOD:^[22-25]

A simple, precise and economical spectrophotometric method for the estimation of Bromhexine Hydrochloride in pharmaceutical bulk and tablet dosage form was developed and validated. Identification was carried out using a UV- visible double beam spectrophotometer detector with working wavelength in the range of 250-270 nm in methanol medium. The method was validated with respect to its specificity, linearity range, accuracy, and precision in analytical media. Bromhexine Hydrochloride shows the maximum absorbance (λ_{max}) at 248nm. Simple UV spectroscopy, first derivative spectroscopy, AUC method and simultaneous equation methods are reported for determination of the Bromhexine

Hydrochloride in marketed formulation. Below in table describes the various spectroscopic methods with the method description and condition which are reported on review literature.

Table No.3: Summary of Miscellaneous methods of Bromhexine Hydrochloride

Sr.No.	Title	Method
1	Bioequivalence study of bromhexine by liquid chromatography–electrospray ionization-mass spectrometry after oral administration of bromhexine hydrochloride tablets ^[26]	LC-MS
2	Determination of Pseudoephedrine Hydrochloride and Bromhexine Hydrochloride in Pharmaceuticals ^[27]	Gas Liquid Chromatography & Ion Pair HPLC
3	Simultaneous Determination of Bromhexine and Amoxicillin in Pharmaceutical Formulations	Capillary Electrophoresis
4	bromhexine hydrochloride with morin as chemiluminescent reagent ^[28]	Chemiluminescence

SR NO.	BRAND NAME	COMPANY NAME	FORMULATION	DOSE(mg)
1.	Bromhexine (8 mg)	Intima(IPCA Laboratories Ltd)	TABLET	8 mg
2	Bisolvon(8 mg)	German Remedies (Zydus Cadila Healthcare Ltd)	TABLET	8 mg
3.	Bromex (8 mg)	Cipla Limited	TABLET	8 mg
4.	RTMox Kid (4+125)	Fourrts Laboratories Pvt Ltd	TABLET	Brom-4 mg Amoxi-125 mg
5.	Etoxin B	Ind-Swift Limited	TABLET	Brom-8 mg Ter-2.5 mg

(Brom-Bromhexine, Amoxi- Amoxicillin, Ter- Terbutaline)^[29]

CONCLUSION

The presented review highlights on various analytical methods reported on Bromhexine Hydrochloride and in combination with other drug. HPLC-HPTLC-UV methods were found to be most widely used. Various chromatographic conditions are presented in under Table. The faster time, high sensitivity; specificity and better separation efficiency enable HPLC to be used frequently for the determination of Bromhexine Hydrochloride in the comparison

with the other methods. There is no doubt on the fact that these chromatographic methods are rapid and far more economical. Other methods are also useful. In this way various analytical methods for the estimation of Bromhexine Hydrochloride in bulk or in various matrixes like plasma, alone or in combination with other drugs is discussed. The presented information is useful for the researchers especially those involved in the formulation development of Bromhexine Hydrochloride in

individually and combination with other drug because there are various marketed formulation of Bromhexine Hydrochloride and

with other combination. No method reported for degraded product of Bromhexine hydrochloride.

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