



## A REVIEW ON BROMHEXINE HYDROCHLORIDE AND THE DIFFERENT ANALYTICAL METHODS USED FOR ITS DETERMINATION

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### ABSTRACT

Bromhexine hydrochloride is a mucolytic agent (expectorant) used in the treatment of respiratory disorders associated with viscid or excessive mucus. The active ingredient Bromhexine hydrochloride is an expectorant which works by loosening mucus in the chest, making it easier to cough up secretions. It is also used to treat productive, chesty coughs. It is chemically named 2-amino-3,5-dibromobenzyl (cyclohexyl) methylamine hydrochloride. According to IUPAC it is 2,4-dibromo-6-[[cyclohexyl (methyl) amino] methyl] aniline; hydrochloride. Bromhexine hydrochloride is a synthetic substance obtained as a synthetic analog of vasicine, a substance found in plants called *Adhoda vasica*. The mechanism of action is based on phlegm degradation, thereby easing coughs. The different analytical methods used to quantify the drug as a single active pharmaceutical ingredient includes 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 hydrochloride, mucolytic, respiratory, expectorant, analysis*



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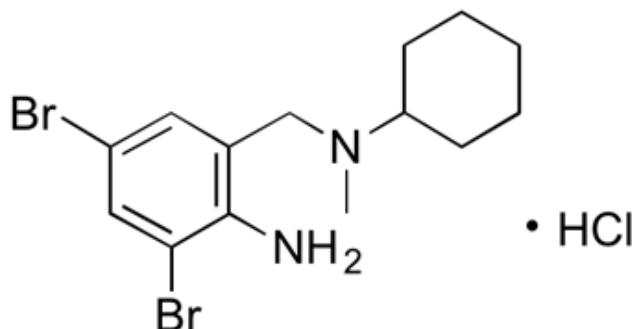


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## INTRODUCTION

Bromhexine hydrochloride is a mucolytic agent rendering the sputum less viscous thereby facilitating easy expulsion of it from the respiratory tract.<sup>1</sup>The drug is official in IP and BP.

## STRUCTURAL FORMULA<sup>2</sup>



Molecular formula : <sup>2</sup> C<sub>14</sub>H<sub>20</sub>Br<sub>2</sub>N<sub>2</sub>.HCl  
 Molecular weight : 412.594 g/mol  
 Monoisotopic mass: 409.976 g/mol  
 Exact mass : 411.974 g/mol  
 IUPAC name : 2,4-dibromo-6-[[cyclohexyl(methyl)amino]methyl]aniline;hydrochloride  
 Chemical name : 2-amino-3,5-dibromobenzyl(cyclohexyl)methylamine hydrochloride

## SYNONYMS

1. Benzenemethanamine, 2-amino-3,5-dibromo-N-cyclohexyl-N-methyl-, monohydrochloride
2. Toluene-a,2-diamine,3,5-dibromo-Na-cyclohexyl-Na-methyl-,monohydrochloride
3. 2-Amino-3,5-dibromo-N-cyclohexyl-N-methylbenzylamine monohydrochloride
4. Bromhexine chloride
5. Bromhexine monohydrochloride
6. Cyclohexylmethyl(2-amino-3,5-dibromobenzyl)ammonium chloride
7. N-Cyclohexyl-N-methyl-(2-amino-3,5-dibromobenzyl)ammonium chloride
8. N-Cyclohexyl-N-methyl-N-(2-amino-3,5-dibromobenzyl)ammonium chloride
9. Na-Cyclohexyl-Na-methyl-3,5-dibromotoluene-a,2-diaminehydrochloride

Category : Mucolytics

Dose : 8-16 mg (Tablets)

Description: White crystalline powder

## SOLUBILITY

Slightly soluble in alcohol and methylene chloride,

Sparingly soluble in water.

Melting point : 240-244 °C

Boiling point : 441.5 °C at 760 mmHg

Flash point : 220.8 °C

## PHARMACOLOGICAL ACTION

Bromhexine hydrochloride is a mucolytic expectorant which exhibits its action by increasing bronchial secretions and reducing their viscosity. In addition, it produces 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 a result in enhancing the bronchial penetration of antimicrobial drugs.<sup>3</sup>

## PHARMACOKINETICS

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 85-90% of a dose is excreted in the urine mainly as metabolites. It has a terminal elimination half life of up to about 6-8 hours. Bromhexine crosses the blood brain barrier and small amounts cross the placenta.<sup>4</sup>

## MECHANISM OF ACTION

It is secretolytic, increasing the production of serous mucus in the respiratory tract and makes the phlegm thinner and less viscous. This contributes to a secretomotoric effect by helping the cilia transport the phlegm out of the lungs. Bromhexine hydrochloride thins and loosens mucus to help clear stubborn chest congestion. For this reason it is often added to cough syrups.<sup>5</sup>

## USES

Bromhexine Hydrochloride is used in conditions where breathing is difficult because there are a lot of secretions (also referred to as mucus) in your air passages.<sup>6</sup> Such conditions include

- common cold
- flu
- infections of the respiratory tract
- Relieves chesty coughs and breathing difficulties due to excess mucus in cold, flu and respiratory tract infections

## USES OF BROMHEXINE HYDROCHLORIDE DURING PREGNANCY AND BREASTFEEDING

Bromhexine hydrochloride should be used during pregnancy only if the benefit to the mother outweighs

the risk to the foetus. Animal studies have shown adverse effects of Bromhexine inhaler, syrup and tablets on the unborn baby. It should not be used during the first three months of pregnancy unless recommended by a doctor. Bromhexine hydrochloride passes into breast milk. Avoid breastfeeding while using this medicine.<sup>7</sup>

### CONTRAINDICATIONS

- Galactose Intolerance: Do not take Bromhexine hydrochloride if you have galactose intolerance. Bromhexine hydrochloride tablets contain lactose as expensive.
- Antibiotics: Bromhexine hydrochloride may increase the amount of antibiotic penetration. Antibiotics are medicines used to treat infections.
- Pregnancy: The use of Bromhexine hydrochloride tablets during the first trimester is not recommended.
- Breastfeeding mothers: It is not recommended that Bromhexine hydrochloride tablets to be taken by women who are breastfeeding.
- Stevens-Johnson Syndrome: There have been very rare reports of severe skin reactions of Stevens Johnson Syndrome. Stevens-Johnson Syndrome (SJS) is a type of severe skin reaction. Together with toxic epidermal necrolysis (TEN) it forms a spectrum of disease, with SJS is less severe. Early symptoms include fever and flu-like symptoms. A few days later the skin begins to blister and peel forming painful raw areas.
- Lyell's syndrome: There have been very rare reports of severe skin reactions of Lyell's syndrome. Lyell's syndrome, or toxic epidermal necrolysis is a rare, potentially life-threatening mucocutaneous disease, usually provoked by the administration of a drug and characterised by acute necrosis of the epidermis.<sup>8</sup>

### SIDE EFFECTS

- Nausea
- Diarrhoea
- Vomiting
- Stomach Pain
- Mild stomach problems
- Headache
- Dizziness
- Sweating
- Temporary rise in some liver enzyme levels
- Skin rashes, including pinkish, itchy swellings (also called hives)
- Difficulty in breathing
- Swelling of the face, lips, mouth, tongue, or throat, which may cause difficulty swallowing or breathing

### LABEL INDICATIONS

The required label indication is 'Helps clear chest congestion'

### SIDE EFFECTS

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

### PRECAUTIONS

Bromhexine hydrochloride should be avoided in patients allergic to this medicine.<sup>9</sup>

### SPECIFICATIONS

Several animal studies of Bromhexine Hydrochloride that has been carried out and their respective specifications are as follows (Table 1)

Table 1  
Specifications of Bromhexine Hydrochloride

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect
Mouse	LD50	Intraperitoneal	2210mg/kg <sup>10</sup>	Cardiac: other changes
Mouse	LD50	Intravenous	44mg/kg	Behavioural: tremor
Mouse	LD50	Oral	3gm/kg <sup>11</sup>	Behavioural: tremor
Mouse	LD50	Subcutaneous	> 14gm/kg <sup>12</sup>	Behavioural: tremor
Rabbit	LD50	Oral	10gm/kg <sup>13</sup>	Cardiac: other changes Lungs, thorax or respiration: respiratory depression
Rat	LD50	Intraperitoneal	1680mg/kg <sup>14</sup>	Sense organs and special senses: lacrimation: eye Behavioural: tremor Behavioural: ataxia
Rat	LD50	Oral	6g/kg <sup>15</sup>	Sense organs and special senses: lacrimation: eye Behavioural: tremor Behavioural: ataxia
Rat	LD50	Subcutaneous	> 14g/kg	

### DOSAGE

Bromhexine Hydrochloride is available in various formulations such as tablets, inhalation, syrup. The various required dosages along with their respective doses are as shown (Table 2)

**Table 2**  
**Dosages of Bromhexine Hydrochloride**

<b>Bromhexine 2 mg / ml syrup<sup>16</sup></b>	
Patients above the age of 14	4-8 ml every 8 hours ( <i>three times a day</i> )
Children aged 6-14 years	4 ml every 8 hours ( <i>three times a day</i> )
Children aged 2-6 years	2.5 ml every 8 hours ( <i>three times a day</i> )
<b>Bromhexine 4 mg / 5 ml syrup</b>	
Patients above the age of 14	10ml-20ml three times a day ( <i>every 8 hours</i> )
Children aged 6 -14 years	10 ml three times a day ( <i>every 8 hours</i> )
Children aged 2 - 6 years	5 ml three times a day ( <i>every 8 hours</i> )
<b>Bromhexine inhalation</b>	
Adults	4 ml every 12 hours ( <i>twice a day</i> )
Patients above the age of 14	2 ml to every 12 hours ( <i>twice a day</i> )
Children aged 6-14 years	1 ml every 12 hours ( <i>twice a day</i> )
Children aged 2-6 years	10 drops, every 12 hours ( <i>twice a day</i> )
<b>Bromhexine tablets</b>	
Patients above the age of 14	8-16 mg, three times a day ( <i>every 8 hours</i> )
Children aged 6 - 14 years	Bromhexine 8 mg, three times a day ( <i>every 8 hours</i> )

## BRAND NAMES

Bromhexine Hydrochloride is available is different brand names as shown in Table 3

**Table 3**  
**Brand Names of Bromhexine Hydrochloride**

Constituents	Brand Name	Dosage Forms	Company
Bromhexine Hydrochloride 4mg/5ml	Bromhexine Sopharma	Syrup	Sopharma PLC
Bromhexine Hydrochloride 4mg/5ml	Bronchotussine	Syrup	Adelco Chromatourgia
Bromhexine Hydrochloride 4mg/5ml	Bisolvon	Oral solution	Boehringer Ingelheim
Bromhexine Hydrochloride 4mg/5ml	Bisolvon	Oral solution	Ecosse Ltd
Bromhexine Hydrochloride 4mg/5ml	Bisolvon	Oral solution	NeoFarma
Bromhexine Hydrochloride BP 8mg	Flecoxin 8 Tablets	Tablet	Remedica Ltd.
Bromhexine	Theosal PD	Syrup	Monichem Healthcare Pvt Ltd
Bromhexine	Bromex	Syrup	Hygeia Pharmaceuticals
Bromhexine 4mg	Bromex	Syrup	Cipla Ltd
Bromhexine Hydrochloride 8mg	Bromex	Tablet	Cipla Ltd
Bromhexine	Mucospel	Syrup	S R Pharmaceuticals
Bromhexine	Brohex	Syrup	Biochem Pharmaceutical Industries
Bromhexine	Ventex PD	Syrup	Cure Quick Pharmaceuticals
Bromhexine Hydrochloride 8mg	Bromhexine tablet	Tablet	Ipca Laboratories Ltd
Bromhexine 4mg	Bromhexine elixir	Syrup	Ipca Laboratories Ltd
Bromhexine	Bisolvon	Oral solution	Zydus Cadila
Bromhexine Hydrochloride 8mg	Bisolvon	Tablet	Zydus Cadila
Bromhexine 4mg	Pelkof	Syrup	PAX HEALTHCARE

## ANALYTICAL METHODS

Various analytical methods are present to determine Bromhexine hydrochloride. These methods are Compendial Methods (Table 4), Chromatographic Methods (Table 5), UV Spectroscopic Methods (Table 6)

## COMPENDIAL METHODS

**Table 4**  
**Compendial Methods for the analysis of Bromhexine Hydrochloride**

PHARMACOPOEIA	METHOD
IP	<b>Potentiometry</b> Weigh accurately about 0.3g, dissolve in 70 ml of ethanol(95%), add 1 ml of 0.1M hydrochloric acid and titrate with 0.1 M sodium hydroxide, Determine the end point potentiometrically. Record the volume added between the two inflections. <sup>17</sup> 1 ml of 0.1 M sodium hydroxide is equivalent to 0.04126 g of $C_{14}H_{21}Br_2ClN_2$
BP	<b>Potentiometric Titration</b> Dissolve 0.300 g in 70 ml of ethanol(95%) and add 1 ml of 0.1 M hydrochloric acid. Carry out a potentiometric titration using 0.1M sodium hydroxide. Read the volume added between the two points of inflexion. <sup>18</sup> 1 ml of 0.1 M sodium hydroxide is equivalent to 41.26 mg of $C_{14}H_{21}Br_2ClN_2$
EP	<b>Potentiometric Titration</b> Dissolve 0.300 g in 70 ml of ethanol (95%) and add 1 ml of 0.1 M hydrochloric acid. Carry out a potentiometric titration using 0.1M sodium hydroxide. Read the volume between the 2 points of inflexion. <sup>19</sup> 1 ml of 0.1 M sodium hydroxide is equivalent to 41.26 mg of $C_{14}H_{21}Br_2ClN_2$

**CHROMATOGRAPHIC METHODS****Table 5**  
**Chromatographic Methods for the analysis of Bromhexine Hydrochloride**

Title	Method	Mobile phase	Stationary phase	Wavelength (nm)
Bromhexine hydrochloride film content on High Performance Liquid Chromatography <sup>20</sup>	HPLC	Acetonitrile 0.05 mol·L <sup>-1</sup> :Phosphate buffer (containing 0.2% triethylamine)(30:70)	An Altima C18 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 <sup>21</sup>	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 <sup>22</sup>	HPLC	Phosphate buffer (0.05 M, pH 3): Acetonitrile (70:30 v/v)	ODS C8 column (length 250 mm and internal diameter 4.6 mm)	270 nm
Simultaneous Estimation of Amoxicillin Trihydrate and Bromhexine hydrochloride from Oily Suspension <sup>23</sup>	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 <sup>24</sup>	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 <sup>25</sup>	RP-ion pair HPLC	Water/Acetonitrile/Phosphoric acid/Triethylamine (78/22/0.1/0.1 v/v/v/v)	C18 Column (250 x 4.6mm internal diameter, 5 μm)	225 nm
Simultaneous Determination of Salbutamol Sulphate and Bromhexine Hydrochloride in Tablets <sup>26</sup>	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	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	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

**UV SPECTROSCOPIC METHODS****Table 6**  
**UV Spectroscopic Methods for the analysis of Bromhexine Hydrochloride**

Sl/No	Title	Method
1	Bioequivalence study of bromhexine by liquid chromatography–electrospray ionization-mass spectrometry after oral administration of bromhexine hydrochloride tablets <sup>27</sup>	LC-MS
2	Determination of Pseudoephedrine Hydrochloride and Bromhexine Hydrochloride in Pharmaceuticals <sup>28</sup>	Gas Liquid Chromatography & Ion Pair HPLC
3	Simultaneous Determination of Bromhexine and Amoxicillin in Pharmaceutical Formulations <sup>29</sup>	Capillary Electrophoresis
4	Bromhexine hydrochloride with morin as chemiluminescent reagent <sup>30</sup>	Chemiluminescence

## CONCLUSION

Bromhexine hydrochloride is a widely used mucolytic agent worldwide. It is a highly efficient drug and pharmacologically proven to render the sputum less viscous thereby facilitating its easy expulsion from the respiratory tract. Bromhexine hydrochloride has been discussed in all its aspects in this review. HPLC-HPTLC-UV methods were found to be the most widely used. Furthermore the analytical methods mentioned are time

saving, simple and do not require elaborate treatments associated with chromatographic methods. Without any doubt, there will be new types of Bromhexine hydrochloride formulations and also newer techniques for its analysis.

## CONFLICT OF INTEREST

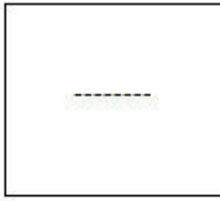
Conflict of interest declared none

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