3. Drug(s) Profile

The drugs for present study were selected on the basis of market survey. The selected drugs were Ambroxol hydrochloride, Cetirizine hydrochloride, Chlorpheniramine maleate, Guaiphenesin, Paracetamol, Phenylephrine hydrochloride and Salbutamol sulphate. Combination of these drugs has profound applications in analgesic, antipyretic, anti-tissue, cough and cold remedies. Important characteristics of these drugs are as follows:

3.1. Ambroxol Hydrochloride

3.1.1. Description\textsuperscript{1,2,3}

Ambroxol hydrochloride, is N-desmethyl metabolite of bromhexine (alkaloid vasicine derivative obtained from plant Vasaka-\textit{Adhatoda vasica}) is a potent mucolytic agent, capable of inducing thin copious bronchial secretion thus facilitating expectoration.

\textbf{Chemical name:} 4-(2-Amino-3,5-dibromo-benzylamino)cyclohexanol hydrochloride.

\textbf{Structural formula}

![Ambroxol hydrochloride](image)

\textbf{Molecular formula:} \(C_{13}H_{18}Br_2N_2O\). HCl

\textbf{Molecular weight:} 378.1

\textbf{Standards:} It contains 99.0–101.0 %, 4-(2-Amino-3, 5-dibromo-benzylamino)-cyclohexanol on dried basis.

\textbf{pKa:} The pKa values are pKa\textsubscript{1} 7.16, pKa\textsubscript{2} 4.19.

\textbf{Melting range:} 346.23°C

\textbf{Solubility:} Sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride.

\textbf{Storage:} Store protected from light.

\textbf{Category:} Mucolytic expectorant and bronchoscopicolytic.
3.1.2. Pharmacopoeial Specifications

Specifications for ambroxol hydrochloride are not reported in United State Pharmacopoeia (USP) as the drug in not officially approved in United States. Pharmacopoeial specifications of ambroxol hydrochloride as per IP and BP are given in Table 3.1\(^4\,5\,6\).

**Table 3.1 Pharmacopoeial specifications of ambroxol hydrochloride**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IP</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>White or yellowish crystalline powder</td>
<td>White or yellowish crystalline powder</td>
</tr>
<tr>
<td>Identification by UV</td>
<td>_</td>
<td>Sample scan between 200 to 350 nm shows two absorption maxima at 245 nm and 310 nm.</td>
</tr>
<tr>
<td>Identification by I.R.</td>
<td>Sample spectrum corresponds to that of reference standard</td>
<td>Sample spectrum corresponds to that of reference standard</td>
</tr>
<tr>
<td>pH (1 % w/v solution in CO(_2) free water)</td>
<td>4.5 to 6.0</td>
<td>4.5 to 6.0</td>
</tr>
<tr>
<td>Loss on Drying (1 gm 100-105 °C)</td>
<td>NMT 0.5 %</td>
<td>NMT 0.5 %</td>
</tr>
<tr>
<td>Sulphated Ash (on 1.0 gm)</td>
<td>NMT 0.1 %</td>
<td>NMT 0.1 %</td>
</tr>
<tr>
<td>Assay</td>
<td>99.0 to 101 % w/w on dried basis</td>
<td>99.0 to 101 % w/w on dried basis</td>
</tr>
</tbody>
</table>

‘-’ indicates that test is not mention in the respective pharmacopoeia.

3.1.3. Pharmacology \(^7\,10\)

**Mechanism of action**

Ambroxol hydrochloride facilitates expectoration of excessive secretions by virtue of mucolytic and mucokinetic action via depolymerization of long mucopolysaccharide chains which ultimately results in their fragmentation. Ambroxol hydrochloride also acts as tissue protective due to its inhibitory effect on release of destructive mediators and free oxygen radicals by phagocytosis.
### Pharmacokinetics

Absorption: It is rapidly absorbed (70-80%) from gastro intestinal tract after oral administration. The time to reach peak plasma concentration is approximately 2 hours.

Distribution: It is rapidly distributed through blood to lung, liver and kidney. The distribution half-life is around 90 minutes. Plasma protein binding was 90 for orally administered drug.

Metabolism: It undergoes hepatic metabolism. CYP 450 enzyme acts over ambroxol hydrochloride and initiates its metabolism and urinary excretion. Major metabolite of is dibromoanthranilic acid.

Excretion: Excretion is primarily takes place via kidneys. Renal clearance (rate) is approximately 53 ml/minute; approximately 5-6% of a dose is excreted unchanged in the urine. The elimination half-life is biphasic, with an alpha half-life of 1.3 hours and a beta half-life of 8.8 hours\textsuperscript{10,11}.

#### 3.1.4. Adverse Effect

Common side effects associated with long term use are rhinorrhoea, lacrymation, gastric irritation and hypersensitivity\textsuperscript{12}.

#### 3.1.5. Drug Interaction

Drug interactions of are not well known. It is mainly excreted in the urine therefore dosage adjustment may be required in patients with impaired renal function. Ambroxol hydrochloride has not been shown any teratogenic or toxic effects on the foetus\textsuperscript{13,14}.

#### 3.1.6. Doses

It is administered as hydrochloric salt in daily doses of 30–120 mg using mostly oral formulations like tablets and syrups. The prescribed daily dose in adults is 30 mg to 120 mg to be taken in 2 to 3 divided doses. In children up to 2 years of age half teaspoonful syrup is taken twice daily and in children 2 to 5 years of age group half teaspoonful ambroxol hydrochloride syrup 3 times daily is prescribed. Children over 5 years of age require one teaspoonful syrup 2-3 times daily\textsuperscript{15,16}.

#### 3.1.7. Brand Name

Ambril, Ambrolite, Ambrodil 30 mg tab, Respira tab, Salmucolyte tab\textsuperscript{17}.
3.2. Cetirizine Hydrochloride

3.2.1. Description \(^1,2,3\)

Cetirizine hydrochloride, an antihistamine is a major metabolite of hydroxyzine. It is a racemic compound. It acts as selective H\(_1\) receptor inverse agonist and also inhibits release of cytotoxic mediators from platelets as well as eosinophil chemotaxic during the secondary phase of the allergic response. Its use is indicated in the treatment of hay fever, angioedema and urticaria, due to its structural similarity to hydroxyzine and derivation from piperazine.

**Chemical name:** \((\pm)\) - \([2- [4- [(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy]acetic acid, dihydrochloride

**Structural formula**

\[
\text{Cetirizine hydrochloride} \quad \cdot 2 \text{ HCl}
\]

**Molecular formula:** \(\text{C}_{21}\text{H}_{25}\text{ClN}_{2}\text{O}_{3}\)

**Molecular weight:** 388.89

**State:** Solid

**Category:** Antihistamine

**Solubility:** Freely soluble in water, practically insoluble in acetone and in methylene chloride.

**Storage:** To be protected from light

3.2.2. Pharmacopoeial Specifications

Pharmacopoeial specifications of cetirizine hydrochloride as per IP are shown in Table 3.2\(^4,5,6\).
Table 3.2: Pharmacopoeial specifications of cetirizine hydrochloride

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characters</td>
<td>White, almost white powder</td>
</tr>
<tr>
<td>Melting range</td>
<td>140°C to 143°C</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>0.5% determined on 1.00g by drying in an oven at 100 to 105°C.</td>
</tr>
<tr>
<td>pH</td>
<td>1.2 to 1.8</td>
</tr>
</tbody>
</table>

3.2.3. Pharmacology

The active metabolite of the cetirizine hydrochloride is piperazine H₁-receptor antagonist hydroxyzine. It is used to treat chronic idiopathic urticaria, perennial allergic rhinitis, seasonal allergic rhinitis, allergic asthma, physical urticaria and atopic dermatitis. Cetirizine hydrochloride crosses the blood-brain barrier only slightly eliminating the sedative side-effect common with older antihistamines; however it still causes mild drowsiness⁷⁻¹².

**Mechanism of action**

It competes with histamine for binding at H₁-receptor sites on the effector cell surface resulting in suppression of histaminic edema, flare and pruritus. The low incidence of sedation can be attributed to reduced penetration into the CNS as a result of the less lipophilic carboxyl group on the ethylamine side chain.

**Pharmacokinetics**

Absorption: It is rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour after oral administration of tablets, chewable tablets or syrup in adults.

Distribution: The mean plasma protein binding is 93%.

Metabolism: It is metabolized up to limited extent by oxidative o-dealkylation.

Elimination: The mean elimination half-life is 8.3 hours and the apparent total body clearance is approximately 53 mL/min.
3.2.4. Interaction Studies
Pharmacokinetic interaction studies with cetirizine hydrochloride in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine hydrochloride (20 mg once daily for 3 days) a 16% decrease in the clearance of cetirizine was observed\(^{13}\).

3.2.5. Toxicity
Somnolence (sleepiness or unusual drowsiness), restlessness, irritability.

3.2.6. Side Effects

*Side effects in adults may include*
Drowsiness, dry mouth and fatigue

*Side effects in children aged 6 to 11 may include*
Abdominal pain, coughing, diarrhea, headache, sleepiness, sore throat, wheezing

3.2.7. Adverse Effects
It induces signs and symptoms associated with ocular dryness, including increased corneal and conjunctival staining increased ocular discomfort in healthy individuals\(^ {14,15}\).

3.2.8. Dosage and Safety\(^ {16,17,18}\)

*Adults and children ≥*
The usual starting dose is 5 or 10 milligrams once a day depending on the severity of symptoms. If patient have a kidney or liver problem, 5 milligrams daily is prescribed.

*Children 6 to 11 years*
The usual starting dose is 5 or 10 milligrams (1 or 2 teaspoonfuls of syrup) once a day. If child has a kidney or liver problem, doctor will probably prescribe the lower dose.

*Children 2 to 5 years*
The usual starting dose is 2.5 milligrams (one-half teaspoonful) once a day. Dosage may be increased to a maximum of 5 milligrams (1 teaspoonful) once daily or 2.5 milligrams (one-half teaspoonful) every 12 hours.

*Children 6 to 23 months*
The usual starting dose is 2.5 milligrams (one-half teaspoonful) once a day. In children 12 to 23 months old the dose can be increased to a maximum of 5 milligrams a day given as 2.5 milligrams (one-half teaspoonful) every 12 hours.
3.2.9. Brand Names

Alerlisin, Cetryn, Formistin, Hitrizin Film Tablet, Reactine, Setir, Virlix, Ziptek, Zirtek, Zyrlex, Zyrtec.
3.3. Chlorpheniramine Maleate

Chlorpheniramine maleate is histamine H1 antagonist used in allergic reactions, hay fever, rhinitis, urticaria and asthma. It has also been used in veterinary applications. One of the most widely used classical antihistaminic, it generally causes less drowsiness and sedation than promethazine\(^1\).

3.3.1. Description\(^2,3\)

**Chemical name:** \[(RS)-3-(4-chlorophenyl)-3-(2-pyridyl) propylmethylamine hydrogen maleate.\]

**Structural formula**

![Structural formula of Chlorpheniramine maleate]

**Molecular formula:** \(C_{16}H_{19}ClN_2\). \(C_4H_4O_4\)

**Molecular weight:** 390.87

**State:** Solid

**Category:** Antihistaminic (H1 antagonist)

3.3.2 Pharmacopoeial Specifications\(^4,5,6\)

Pharmacopoeial specifications of chlorpheniramine maleate as per IP, BP and USP are shown in Table 3.3.

**Table 3.3: Pharmacopoeial specifications of chlorpheniramine maleate**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IP</th>
<th>BP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characters</strong></td>
<td>White or almost white, crystalline powder</td>
<td>White or almost white, crystalline powder</td>
<td>White or almost white, crystalline powder</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td>Freely soluble in water, soluble in acetone, ethanol (95%), chloroform, slightly soluble in ether.</td>
<td>Freely soluble in water, soluble in ethanol (96%)</td>
<td>—</td>
</tr>
</tbody>
</table>
Chapter 3

Drug(s) Profile

<table>
<thead>
<tr>
<th>Melting Range</th>
<th>132 -135˚ C</th>
<th>132 -135˚ C</th>
<th>132 -135˚ C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage</td>
<td>Store in tightly-closed, light-resistant containers</td>
<td>Protected from light</td>
<td>Preserve in tight and light-resistant container</td>
</tr>
<tr>
<td>Standards</td>
<td>98.0 to 101.0% with reference to the dried substances</td>
<td>98.0 to 101.0% with reference to the dried substances</td>
<td>98.0 to 100.5% with reference to the dried substances</td>
</tr>
<tr>
<td>Sulphated Ash</td>
<td>Not more than 0.1%</td>
<td>Not more than 0.1%</td>
<td>Not more than 0.2%</td>
</tr>
<tr>
<td>LOD</td>
<td>Not more than 0.5%, determined on 1gm by drying in an oven at 105˚C for 4 hours.</td>
<td>Maximum 0.5%, determined on 1gm by drying in an oven at 100-105˚C for 4 hours.</td>
<td>Maximum 0.5%, determined on 1gm by drying in an oven at 105˚C for 3 hours.</td>
</tr>
<tr>
<td>pH</td>
<td>4.0 to 5.0 determined in a 1.0% w/v solutions.</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>pKa</td>
<td>9.2</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

‘–’ indicates that test is not mentioned in the respective Pharmacopoeia

3.3.3. Pharmacological Action

In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. It is a histamine H1 antagonist (an inverse histamine agonist) of the alkylamine class. It competes with histamine for the normal H1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. It provides temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever.

Mechanism of Action

It binds to the histamine H1 receptor. This blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought by histamine.

Pharmacokinetics
Absorption: It is well absorbed from oral and parenteral route, reach their peak effect in 1-2 hours and effective for 3-6 hours.

Distribution: It is widely distributed throughout the body but does not penetrate the blood brain barrier and peak plasma half life is 23 hours. It is well distributed after IV injection, the highest distribution of the drug occurs in the lungs, heart, kidneys, brain, small intestine and spleen. It is about 70% bound to plasma proteins.

Metabolism: It is metabolized in the liver by cytochrome P 450.

Elimination: Its metabolites and unchanged form is excreted through urine.

**3.3.4. Indications and Usage**

It is used in treatment of rhinitis, urticaria, allergy, common cold, asthma and hay fever. Temporary relief is also provides in sneezing, itchy, watery eyes, itchy nose or throat and runny nose caused by hay fever (allergic rhinitis) or other respiratory allergies.

**3.3.5. Adverse Effects**

Most commonly seen adverse effects are CNS depression (lethargy, somnolence) and GI effects (diarrhea, vomiting and anorexia). The sedative effects of antihistamines may diminish with time.

**3.3.6. Drug Interactions**

Drug interaction of chlorpheniramine maleate with others drugs is presented in table 3.4.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Possible antagonism of action</td>
</tr>
<tr>
<td>Ethotoin</td>
<td>Increases the effect of hydantoin</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Increases the effect of hydantoin</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Possible antagonism of action</td>
</tr>
<tr>
<td>Mephenytoin</td>
<td>Increases the effect of hydantoin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Increases the effect of hydantoin</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Possible antagonism of action</td>
</tr>
</tbody>
</table>

**3.3.7. Doses**

Oral: 4 to 16 mg daily, in divided doses.
Subcutaneous or intramuscular injection: 10 to 20 mg, repeated if required maximum 40 mg in 24 hours.

Intravenous injection: 10 to 20 mg diluted in the syringe with 5 to 10 ml blood.

**3.3.8. Dosage Forms**

It presents in various dosage forms like tablet, injection and oral solution.

**3.3.9. Brand Names**

Chlor-hist, Chlor-tripolon, Qdall AR, Piriton, Polaramine, Chlorate, Chloropiril, Cloropiril, Aller-Chlor, Allergican, Allergisan, Antagonate, Polaronil, Pyridamal 100, Telachlor
3.4. Guaiophenesin

Guaiophenesin is derivative of guaicol (obtained from wood creosote or synthetically prepared) used as expectorants. Guaiophenesin increases bronchial secretion thus reduces viscosity and facilitate the removal of deposited cough in air way pathway.

3.4.1. Descriptions\(^1\)\(^3\)

**Chemical name:** 3-(2-Methoxy phenoxy) propane-1, 2-diol

**Chemical structure**

![Chemical Structure](image)

**Molecular formula:** \(C_{10}H_{14}O_4\)

**Molecular weight:** 198.2

**Standards**- Guaiophenesin contains 98-102.0 % 3-(2-MethoxyPhenoxy) propane-1, 2-diol on dried basis.

**State** : Solid

**Appearance** : White or almost white crystalline powder

**Category** : Expectorant

**Solubility** : Sparingly soluble in water, soluble in alcohol.

**pKa** : 7.9

**Storage** : Preserve in tight container.

3.4.3. Pharmacopoeial Specifications\(^4\)\(^-\)\(^6\)

Pharmacopoeial specifications of guaiophenesin as per IP, BP and USP are shown in Table 3.5.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IP</th>
<th>BP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>White or almost white crystalline powder; odorless or with a slight characteristic odor.</td>
<td>White or almost white crystalline powder</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 3.5: Pharmacopoeial specifications of guaiophenesin
Melting point | 79 °C to 83°C | 79°C to 83°C | 78°C to 82°C
---|---|---|---
Loss on Drying (vacuum dry in 60 °C, 10 mm Hg Pressure) | NMT 0.5 % | NMT 0.5 % | NMT 0.5 %
Sulphated Ash (on 1.0 gm) | NMT 0.1 % | NMT 0.1 % | –
Assay | 98.0 to 101.5 % w/w on dried basis | 98.0 to 102.0 % w/w on dried basis | 98.0 to 102.0 % w/w on dried basis

‘–’ indicates that test is not mentioned in the respective Pharmacopoeia

3.4.3. Pharmacology

Mode of Action
It stimulate the bronchial glands lining of airway to produce a thin secretion that lubricates any thick mucous and making it easier to expel with coughing\(^7\)-\(^10\).

Pharmacokinetics
Absorption: It is rapidly absorbed with time to maximum concentration (\(t_{\text{max}}\)) of approximately 60 minutes for oral administration by tablets, chewable tablets or syrup dosage forms.
Distribution: The mean plasma protein binding is 93%, independent of concentration in the range of 25–1000 µg/ml.
Metabolism: It metabolized to a limited extent by oxidative o-dealkylation to metabolite with negligible antihistaminic activity using CYP 450 enzyme.
Elimination: The mean elimination half-life is 8.3 hours and the apparent total body clearance is approximately 53 ml/min.

3.4.4. Adverse Effect
In general gastric upset and rashes are minor side effects reported after use of guaiphenesin\(^{11}\).

3.4.5. Drug Interaction
Avoid the use of guaiphenesin when furazolidone, sodium oxybate, or an MAO inhibitor such as isocarboxazid, phenelzine, rasagiline, selegiline or tranylcypromine
when taken in last 14 days. Serious life threatening adverse effects can happen if these drugs are not eliminated completely from body before use of guaiphenesin\textsuperscript{12-15}.

3.4.6. Dose

General prescription dose of guaiphenesin is 100 to 200 mg. Specific indications for dose and frequency to use drug is as follows; for children below 2 years of age consultation with doctor is recommended, for age group 2 to 6 years 50-100 mg every 4 hr but not exceeding 600 mg in 24 hr, for age group 6 to 12 years 100-200 mg every 4 hr but not to exceed 1,200 mg in 24 hr, for children over 12 years of age & adults 200–400 mg every 4 hr, not to exceed 2,400 mg in 24 hr is prescribed from USFDA\textsuperscript{16-17}.

3.4.7. Brand Names

Abcof Syr, Adcold-G Liqd, Bromcough Syr, Cheston Exp Expectorant, X-Lcf Extentab, Xpar Expectorant Liqd, Xpar Tabs Tab, Viscodyne Syr\textsuperscript{18-20}.
3.5. Paracetamol

Acetaminophen or paracetamol is a popular analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. It is a major ingredient in numerous cold and flu medications and many prescription analgesics\textsuperscript{1}.

3.5.1. Description

**Chemical name:** N-(4-hydroxyphenyl) acetamide

**Chemical structure**

![Paracetamol chemical structure]

**Molecular formula** : C\textsubscript{8}H\textsubscript{9}NO\textsubscript{2}

**Molecular weight** : 151.2

**State** : Solid

**Category** : Analgesics, Non-Narcotic, Antipyretics.

3.5.2. Pharmacopoeial Specifications\textsuperscript{4-6}

Pharmacopoeial specifications of paracetamol as per IP, BP and USP are shown in table 3.6.

**Table 3.6: Pharmacopoeial specifications of paracetamol**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IP</th>
<th>BP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characters</td>
<td>White, crystalline powder</td>
<td>White, crystalline powder</td>
<td>White, crystalline powder</td>
</tr>
<tr>
<td>Solubility</td>
<td>Freely soluble in acetone, ethanol (95%). Sparingly soluble in water, very slightly soluble in dichloromethane and in ether</td>
<td>Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride</td>
<td>_</td>
</tr>
<tr>
<td>Melting range</td>
<td>168 -172 °C</td>
<td>168 -172 °C</td>
<td>168 -172 °C</td>
</tr>
<tr>
<td>Storage</td>
<td>Store in tightly- closed, light-resistant containers</td>
<td>Protected from light</td>
<td>Preserve in tight and light resistant container</td>
</tr>
<tr>
<td>Standards</td>
<td>99.0 to 101.0% with reference to the dried substances</td>
<td>99.0 to 101.0% with reference to the dried substances</td>
<td>98.0 to 101.0% with reference to the dried substances</td>
</tr>
</tbody>
</table>
### Sulphated ash

<table>
<thead>
<tr>
<th>LOD</th>
<th>Not more than 0.1%</th>
<th>Not more than 0.1%</th>
<th>Not more than 0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not more than 0.5%, determined on 1gm by drying in an oven at 100-105˚C for 4 hours</td>
<td>Maximum 0.5%, determined on 1gm by drying in an oven at 100-105˚C for 4 hours</td>
<td>–</td>
</tr>
</tbody>
</table>

‘−’ indicates that test is not mentioned in the respective Pharmacopoeia

#### 3.5.3. Pharmacological Action

Paracetamol, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties or effects on platelet function, so it is not a member of the class non-steroidal anti-inflammatory drugs or NSAIDs. In normal doses paracetamol does not irritate the lining of the stomach nor affect blood coagulation, the kidneys, or the fetal ductus arteriosus. (as NSAIDs can). Paracetamol and NSAIDs have the benefit of being completely free of problems with addiction, dependence, tolerance and withdrawal.

**Mechanism of Action**

It is act primarily on CNS, increasing the pain threshold by inhibiting both iso forms of cyclooxygenase, COX-1 and COX-2, enzymes involved in prostaglandin (PG) synthesis. It does not inhibit cyclooxygenase in peripheral tissues, thus, has no peripheral anti-inflammatory affects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site. Studies have found that paracetamol indirectly blocks COX, and this blockade is ineffective in the presence of peroxides. This might explain why paracetamol is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides.

**Pharmacokinetics**

Absorption: It is rapidly and completely absorbed from the gastrointestinal tract after oral administration with peak plasma levels occurring 30 to 60 minutes. Food intake delays its absorption. Plasma half life is 2-3 hours.

Distribution: It is uniformly distributed throughout the body. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increased concentrations.
Metabolism: It is metabolized by cytochrome P450 enzyme pathways (primarily by conjugation with glucuronic acid, sulfuric acid, and cysteine). Its main metabolite is N-acetyl-p-benzoquinoneimine (NABQI).
Elimination: It can cross the placenta and is excreted in milk. It is rapidly excreted through urine.

3.5.4. Indications and Usage
Paracetamol has good analgesic and antipyretic properties. It is suitable for the treatment of pains of all kinds (headaches, dental pain, postoperative pain, pain in connection with colds, post-traumatic muscle pain). Migraine headaches, dysmenorrhea and joint pain can also be influenced advantageously. In cancer patients, paracetamol is used for mild pain or it can be administered in combination with opioids.

3.5.5. Adverse Effects
Skin rashes and other allergic reactions may occur occasionally. The rashes are usually erythematous or urticarial but sometimes more serious and may be accompanied by drug fever and mucosal lesions. In a few cases the use of paracetamol has been associated with the occurrence of thrombocytopenia, neutropenia, pancytopenia, leucopenia and agranulocytosis. The dose should be reduced in renal functional impairment. It should also be given with care to patients taking other drugs that affect the liver such as the barbiturates. The absorption of paracetamol may be accelerated by metoclopramide. Excretion may be affected and plasma concentrations altered when administered with probenecid. Prolonged excessive use may cause irreversible kidney damage.

3.5.6. Drug Interactions
Barbiturates and prolonged alcohol ingestion may increase the metabolism of paracetamol. Certain hypnotics, antiepileptics (Phenobarbital, phenytoin and carbamazepine) and rifampicin when administered concomitantly with paracetamol products may increase the metabolism of paracetamol which can result in liver damage. Paracetamol may considerably slow down the excretion of chloramphenicol, resulting in toxicity. Concurrent use of paracetamol and zidovudine increases the tendency for neutropenia. Paracetamol may increase the risk of bleeding in patients taking warfarin and other coumarin derivatives.
3.5.7. Doses

The recommended dose of paracetamol is for;

1-3 year - 50mg

4-12 year - 240-320mg

Above 12 year - 300-600mg

3.5.8. Dosage Forms

Paracetamol present in various dosage forms like tablet, capsules, oral solution, oral suspension and suppositories\textsuperscript{17}.

3.5.9. Brand Names

Pacemo, Painex, Paldesic, Tempra, Tencon, Crocin, Metacin, Paracin, Ultragin, Pyrigesic, Calpol, Neomol, Fevastin, Fbrinil etc\textsuperscript{18-20}. 
3.6. Phenylephrine Hydrochloride

Phenylephrine hydrochloride is α-adrenergic agonist used as a mydriatic, nasal decongestant, and cardio tonic agent.

3.6.1. Description

Chemical name: 3-[(1R)-1-hydroxy-2-methylaminoethyl] phenol hydrochloride

Chemical structure

![Chemical structure of Phenylephrine Hydrochloride]

Molecular formula: C_{9}H_{13}NO_{2}.HCl

Molecular weight: 203.67

Category: Sympathomimetic

3.6.2. Pharmacopoeial Specifications

Pharmacopoeial specifications of phenylephrine hydrochloride as per IP, BP and USP are shown in Table 3.7.

Table 3.7: Pharmacopoeial specifications of phenylephrine hydrochloride

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IP</th>
<th>BP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characters</td>
<td>White or almost white, crystalline powder</td>
<td>White or almost white, crystalline powder</td>
<td>White or almost white, crystalline powder</td>
</tr>
<tr>
<td>Solubility</td>
<td>Freely soluble in water, ethanol (95%), practically insoluble in chloroform</td>
<td>Freely soluble in water, ethanol (96%)</td>
<td>–</td>
</tr>
<tr>
<td>Melting Range</td>
<td>171 - 176°C</td>
<td>171 - 176°C</td>
<td>140 - 145°C</td>
</tr>
<tr>
<td>Storage</td>
<td>Store in well closed, light-resistant containers</td>
<td>–</td>
<td>Preserve in tight and light resistant container</td>
</tr>
<tr>
<td>Standards</td>
<td>98.5 to 101.0% with reference to the dried substances</td>
<td>98.5 to 101.0% with reference to the dried substances</td>
<td>90.0 to 115.0% with reference to the dried substances</td>
</tr>
<tr>
<td>Sulphated Ash</td>
<td>Not more than 0.1%</td>
<td>Not more than 0.1%</td>
<td>Not more than 0.2%</td>
</tr>
</tbody>
</table>
3.6.3. Pharmacological Action

Phenylephrine hydrochloride is a powerful vasoconstrictor. It is used as a mydriatic, nasal decongestant, and cardiotonic agent. Phenylephrine is a postsynaptic α-receptor stimulant with little effect on the β-receptors of the heart. Parenteral administration of Phenylephrine hydrochloride causes a rise in systolic and diastolic pressures, cardiac output is slightly decreased and peripheral resistance is considerably increased, most vascular beds are constricted; renal, splanchnic, cutaneous, and limb blood flows are reduced but coronary blood flow is increased. Pulmonary vessels are constricted, and pulmonary arterial pressure is raised. This α-receptor sympathetic agonist is also used locally because its vasoconstrictor and mydriatic action.

Mechanism of Action

It produces its ophthalmic and systemic actions by acting on α-1 adrenergic receptors in the pupillary dilator muscle and the vascular smooth muscle, resulting in contraction of the dilator muscle and contraction of the smooth muscle in the arterioles of the conjunctiva and peripheral vasoconstriction. It decreases nasal congestion by acting on α-1 adrenergic receptors in the arterioles of the nasal mucosa to produce constriction.

Pharmacokinetics

Absorption: It is not absorbed by oral route. Its oral bioavailability is around 38%.
Distribution: It is distributed throughout the body but it gets 95% protein binding.
Metabolism: It metabolizes in the liver by monoamine oxidase enzymes. It metabolized in phenylephrine-glucuronide and phenylephrinesulfate.
Elimination: It is eliminated through renal route.

3.6.4. Indications and Usage

It acts as a mydriatic. It is sometimes used in open-angle glaucoma, to reduce intraocular pressure. It has been used to treat hypotension and shock. Its use to treat hypotension resulting from barbiturate or other CNS depressant agents is contro-
versial. It is also used to increase blood pressure to terminate attacks of paroxysmal supraventricular tachycardia, particularly when the patient is also hypotensive. It has been applied intranasally in an attempt to reduce nasal congestion. Temporary relief of symptoms of upper respiratory tract disorders such as sinusitis, vasomotor rhinitis, and hay fever, pharyngitis, bronchitis, and asthma when tenacious mucus and/or mucus plugs and congestion complicate these conditions.

3.6.5. Adverse Effects
Adverse effects of phenylephrine hydrochloride at usual doses, a reflex bradycardia CNS effects (excitement, restlessness, headache) and arrhythmias are seen. Extravasation injuries with phenylephrine can be very serious.

3.6.6. Contraindications
Phenylephrine is contraindicated in patients with severe hypertension, ventricular tachycardia. It should be used with extreme caution in geriatric patients, patients with hyperthyroidism, bradycardia, and partial heart block disease.

3.6.7. Overdose
Over dosage of phenylephrine can cause hypertension, seizures, vomiting, paresthesias, ventricular extrasystoles and cerebral hemorrhage.

3.6.8. Drug Interactions
Higher dosages of phenylephrine may be required to attain a pressor effect if phenothiazines or α-blocking agent (phentolamine) have been used prior to therapy. Phenylephrine may induce cardiac arrhythmias when used with halothane anesthesia or in digitalized patients. When used concurrently with oxytocic agents, pressor effects may be enhanced. Monoamine oxidase inhibitors should not be used with phenylephrine because of pronounced pressor effect.

3.6.9. Doses
Subcutaneous or intramuscular injection: 2-5mg
Slow intravenous injection: 100-500µg
Intravenous infusion: 5-20mg in 500ml

3.6.10. Dosage Forms
Tablet, Syrup, Capsule etc.

3.6.11. Brand Names
Neo-Synephrine, Metasympatol, M-sympathol, AK-nefrin, Alconefrin, Dionephrine, Adrianol, Metsatonum, Dimetane.
3.7. Salbutamol Sulphate

Salbutamol sulphate is more selective $\beta_2$ agonist. In United States salbutamol is marketed with the name of albuterol. Drug is used for treatment of reversible airway obstruction. Racemic (R, S) - salbutamol is 1:1 mixture of R- enantiomer (having bronchodilatory and anti-inflammatory effects) and S- enantiomer (which is associated with increased airway hyperreactivity and pro-inflammatory effect).

3.7.1. Descriptions\textsuperscript{1-3}

**Chemical name:** 4-(2-tert-Butylamino-ethyl)-2-hydroxymethyl-phenol, sulphate

![Chemical structure of Salbutamol sulphate]

*Salbutamol sulphate*

**Molecular formulae:** $C_{13}H_{21}NO_3$

**Molecular weight:** 239.3

**Standards:** Salbutamol sulphate contains 98.0- 101.0 % 4-(2-tert-Butylamino-ethyl)-2 hydroxymethyl-phenol, sulphate on dried basis.

**pKa:** 4.67

**Solubility:** Sparingly soluble in water, soluble in ethanol (96 percent).

**Category:** $\beta_2$ adrenoceptor agonist, bronchodilator.

**Storage:** Preserve in well-closed light resistant container.

3.7.2. Pharmacopoeial Specifications\textsuperscript{4-6}

Specifications for salbutamol sulphate are not included in Indian Pharmacopoeia, as the drug in not officially approved in India. Pharmacopoeial specifications of salbutamol sulphate as per BP and USP are as shown in table 3.8.

<table>
<thead>
<tr>
<th>Table 3.8: Pharmacopoeial specifications of salbutamol sulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Identification by UV</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Identification by I.R.</td>
</tr>
<tr>
<td>Melting point</td>
</tr>
<tr>
<td>Loss on Drying (1 gm 100-105 °C)</td>
</tr>
<tr>
<td>Sulphated Ash (on 1.0 gm)</td>
</tr>
<tr>
<td>Assay</td>
</tr>
</tbody>
</table>

‘–’ indicates that test is not mentioned in the respective Pharmacopoeia

### 3.7.3. Pharmacology

**Mechanism of Action**

Salbutamol sulphate acts by activation of β2 adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and increase in intracellular concentration of cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation of bronchial smooth muscles from trachea to terminal bronchioles. It acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway pathway.7-11

**Pharmacokinetics**

Absorption: It is readily absorbed from the gastrointestinal tract, maximum plasma concentrations occurring within 2.5 hours. It is subject to first pass metabolism in the liver. The plasma half-life ranges from 2.7-7.0 hours.
Distribution: Systemic availability is 0.50 ± 0.04 with oral administration and apparent volume of distribution is 156 ± 381. After inhalation therapy systemic absorption is low and maximum serum concentrations occur within 2-4 hours.

Metabolism: About 50% of administered salbutamol sulphate metabolized to its sulphate conjugate. Unlike isoprenaline, it is not inactivated by catechol-o-methyltransferase (COMT) or sulphatase enzymes. It does not appear to be metabolised in the lung.

Elimination: Elimination occurs by both metabolism and urinary excretion. 76% of an oral dose is excreted over 3 days with the majority of the dose excreted within the first 24 hours. With oral administration, systemic availability was 0.50 ± 0.04, and urinary excretion of unchanged drug and sulphate conjugate were 31.8 ± 1.9% and 48.2 ± 7.3% of the dose, respectively. The drug eliminated on the first-pass could be accounted for entirely as sulphate conjugate formed, presumably, in the intestinal wall. With intravenous administration, total plasma clearance was 480 ± 123 ml min⁻¹, elimination half-life was 3.86 ± 0.83 h. Urinary excretion of unchanged drug and sulphate conjugate were 64.2 ± 7.1% and 12.0 ± 3.1% of the dose, respectively. Renal clearance of salbutamol sulphate was 291 ± 70 ml min⁻¹ after intravenous and 272 ± 38 ml min⁻¹ after oral administration. The renal clearance of the sulphate conjugate was 98.5 ± 23.5 ml min⁻¹ after oral administration. Urinary studies indicate an elimination half-life of approximately four hours. It does not pass the blood-brain barrier.

3.7.4. Adverse Effects
Most common adverse reactions (incidence ≥3%) are throat irritation, viral respiratory infections, upper respiratory inflammation, cough, and musculoskeletal pain. Muscle tremors are the dose related side effect associated with use of salbutamol sulphate. Palpitation, restlessness, nervousness, throat irritation and ankle edema can also occur. The reported events included myocardial ischaemia, myocardial infarction, chest pain and ECG abnormalities indicative of myocardial ischaemia. Rare cases of hypersensitivity reactions including urticaria, angioedema, and rash have been reported after the use of salbutamol sulphate ¹².

3.7.5. Drug Interactions
Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with salbutamol sulphate. β₂ adrenergic receptor blocking agents not
only block the pulmonary effect of beta agonists, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of β adrenergic blocking agents in patients with asthma. In this setting, cardio selective beta-blockers should be considered, although they should be administered with caution. The ECG changes or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the co-administration of β agonists with non potassium-sparing diuretic. It would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol13-14.

3.7.6. Contraindications
It should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action on the vascular system may be potentiated. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants15.

3.7.7. Doses
The preparation is intended for oral administration only with dose range from 2 to 4 mg. The lowest effective dose of inhaled salbutamol sulphate is 100-200 µg to be used in the treatment of asthma. In adults for relief of acute asthma or before exercise 100-400 µg doses is useful. The recommended dose for maintenance treatment or prophylactic therapy is 100-400 µg three to four times a day with maximum dose 1.6mg/ day. The recommended dose for maintenance treatment or prophylactic treatment is 100-200 µg three to four times a day with maximum dose 0.8mg/day. For treatment or prevention of bronchospasm in adults and children 4 years of age, 2 inhalations every 4 to 6 hours is recommended16-17.

3.7.8. Brand Names
Asththalin tab, Cryosal , Salol , Ventorlin syr., Salmucolyte tab, Respira tab18-20.
References


18. *Current Index of Medical Specialties (CIMS)*, Medimedia Health Private Ltd., Bangalore, India, 2006; pp 392-394.
