Drugs And Excipients Profile
3.1 DRUGS PROFILE

3.1.1 Metoprolol Tartrate

Chemical structure

![Chemical structure of Metoprolol Tartrate](image)

- **Chemical formula**: \((C_{15}H_{25}NO_3)_2, C_4H_6O_6\)
- **Molecular weight**: 684.8
- **Category**: \(\beta_1\)-adrenoreceptor antagonist
- **Chemical name**: 1-[4-(2-Methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanolol-tartrate
- **Description**: White crystalline powder
- **Melting point**: About 120°C
- **Dissociation constant \(pK_a\)**: 9.7
- **Partition coefficient**
  - **Log P (octanol/water)**: 1.9
- **Solubility**: Very soluble in water, soluble in ethanol and chloroform, practically insoluble in ether

**Mechanism of action**: Metoprolol works by competing for \(\beta_1\) receptor sites on cardiac muscle with no intrinsic sympathomimetic activity and membrane stabilizing activity is detectable only at plasma concentrations much greater than required for \(\beta\)-blockade.

**Disposition in the body**: Well absorbed after oral administration, although the bioavailability is low because of extensive first-pass metabolism. Metoprolol crosses the
blood-brain barrier and placental barrier, it is also excreted into breast milk. About 95% of a dose is excreted in the urine within 48 h, with about 65% of the dose as the inactive metabolite, 4-(2-hydroxy-3-isopropylaminopropoxy)-phenylacetic acid and about 10% as a further inactive metabolite, 2-hydroxy-3-[4-(2-methoxyethyl)-phenoxy]-propionic acid. Two active metabolites, α-hydroxymetoprolol and o-desmethyelmeproprolol are also excreted in the urine in amounts equivalent to about 10% and less than 1% of the dose, respectively. Up to about 10% of a dose is excreted as unchanged drug.

**Pharmacokinetic parameters**

**Bioavailability:** About 40 to 50% (about 70% after modified-release preparations).

**Half life:** Plasma half-life, metoprolol 3 to 4 h in fast hydroxylators and about 7 h in slow hydroxylators.

**Volume of distribution:** About 4 L/kg.

**Plasma clearance:** 15 ml/min/kg.

**Distribution in blood:** Plasma: whole blood ratio- 0.77.

**Protein binding:** about 12%.

**Indications, dosage and administration**

**Dosage**

Hypertension: 50-450 mg orally daily or divided twice daily.

Acute myocardial infarction: IV bolus of 5-50 mg

Acute myocardial infarction: 100 mg orally twice daily for up to 3 year

Angina: 100 to 400 mg orally daily (divided doses)

Cardiac dysrhythmia: 25 to 100 mg orally daily

Congestive heart failure: 6.25-50 mg orally twice daily

Migraine, Prophylaxis: 50 to 200 mg orally daily

**Administration:** It should be taken with or immediately following meals

**Indications**

FDA labeled indications

- Acute myocardial infarction
- Angina
Non-FDA labeled indications

- Cardiac dysrhythmia
- Congestive heart failure
- Migraine, Prophylaxis

**Contraindications**

- Bradycardia
- Cardiac failure (patients with hypertension and angina)
- Cardiogenic shock (patients with hypertension and angina)
- Heart block, second and third degree
- Heart block, 1st degree heart block (patients with myocardial infarction)
- Hypersensitivity to metoprolol, related derivatives and other beta-blockers
- Pheochromocytoma
- Sick-sinus syndrome
- Systolic blood pressure less than 100 mmHg (patients with myocardial infarction)

**Adverse effects**

**Common**

- Cardiovascular: Bradyarrhythmia (3-16%), Heart block (5%), Heart failure (27%), Hypotension (1-27%)
- Dermatologic: Pruritus (5%), Rash (5%)
- Gastrointestinal: Constipation (1%), Diarrhea (5%), Indigestion (1%), and Nausea (1%)
- Neurologic: Dizziness (10%), Fatigue (10%), Headache
- Psychiatric: Depression (5%)
- Respiratory: Dyspnea (1-3%), Wheezing (1%)

**Serious**

Respiratory: Bronchospasm (1%)

**Drug interactions**

Catecholamine depleting drugs-Additive effect
Risk of anaphylactic reaction—Patients with a history of severe anaphylactics to a variety of allergen may be more reactive to repeated challenge, accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction (MICROMEDEX, 2006).

3.1.2 Carvedilol

Chemical structure

![Chemical structure of carvedilol](image)

Chemical formula: $C_{24}H_{26}N_2O_4$

Molecular weight: 406.5

Category: Alpha/Beta-Adrenergic Blocker

Chemical name: 1-(9H-Carbazol-4-yl)oxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol

Description: A white to off-white powder

Melting point: 114-115°C

Dissociation constant (pKₐ): 7.8

Partition coefficient

Log P (octanol/water): 4.19

Solubility: It is practically insoluble in water, freely soluble in dimethyl sulfoxide, soluble in methylene chloride and in methanol, sparingly soluble in ethanol and in isopropyl alcohol, slightly soluble in ethyl ether.
Mechanism of action: Carvedilol is a nonselective beta-adrenergic blocking agent with alpha-1 blocking activity, moderate membrane stabilizing activity (MSA), no intrinsic sympathomimetic activity (ISA), and high lipid solubility.

Disposition in the body: Carvedilol is rapidly and well absorbed after oral administration but is subject to considerable first-pass metabolism in the liver. The drug is widely distributed and extensively metabolised, primarily by aromatic ring oxidation and glucuronidation. The metabolites are excreted mainly via bile into faeces. Approximately 16% of a dose is detected in urine with less than 2% as the unchanged drug. Some of the metabolites have beta-blocking and vasodilating activity. The o-demethyl-p-hydroxyl and m-hydroxyl metabolites possess beta–blocking activity. Its metabolism is stereoselective and plasma concentrations of R(+)carvedilol are about 2 to 3 times higher than S(-)-carvedilol. The principal enzymes involved are CYP2D6 and CYP2C9.

Pharmacokinetic parameters

Bioavailability: Absolute bioavailability- 25 to 35%.

Half-life: Plasma- 4 to 7 h

Volume of distribution: 1.5 to 2.0 L/kg.

Clearance: Plasma clearance -0.52 L/h/kg.

Protein binding: 98%.

Indications, dosage and administration

Adult

(a) Hypertension 6.25-25 mg orally twice daily

(b) Congestive heart failure: 3.125-25 mg orally twice daily

(c) Angina pectoris: 25-50 mg orally twice daily

(d) Impaired left ventricular function; Myocardial infarction: 6.25-25 mg orally twice daily

Administration: Carvedilol tablets should be taken with food orally.

Indications

FDA approved indications
➢ Congestive heart failure
➢ Hypertension
➢ Impaired left ventricular function - Myocardial infarction

Non-FDA approved indications

Chronic angina pectoris

Contraindications

➢ Atrioventricular block, second or third degree
➢ Bronchial asthma or related bronchospastic condition.
➢ Cardiogenic shock
➢ Decompensated cardiac failure, with IV inotropic therapy
➢ Hepatic impairment
➢ Hypersensitivity to carvedilol or any component of the product
➢ Sick sinus syndrome
➢ Sinus bradycardia

Serious adverse effects

➢ Aplastic anemia
➢ Asthma with status asthmaticus
➢ Atrioventricular block
➢ Erythema multiforme
➢ Heart failure, Worsening
➢ Stevens-Johnson syndrome
➢ Toxic epidermal necrolysis

Storage: Tablets should be stored below 30°C and protected from light and moisture.

Drug interactions:

CYP2D6 inhibitors and poor metabolizers: These drugs would be expected to increase blood levels of the \( R \) (+)-enantiomer of carvedilol and produce dizziness due to vasodilating effects of the higher concentrations of the \( \alpha \)-blocking \( R \) (+)-enantiomer.

Hypotensive agents: Patients taking both agents with \( \beta \)-blocking properties and a drug that can deplete catecholamines (e.g. reserpine and monoamine oxidase inhibitors) should
be observed closely for signs of hypotension and/or severe bradycardia.

**Digitalis glycosides**: Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

**Amiodarone**: Amiodarone, and its metabolite desethyl amiodarone, inhibitors of CYP2C9 such as fluconazole increased concentrations of the S (-)-enantiomer of carvedilol by at least 2-fold and may enhance the β-blocking properties of carvedilol resulting in further slowing of the heart rate or cardiac conduction.

**Calcium channel blockers**: If carvedilol is to be administered with calcium channel blockers such as verapamil or diltiazem, it is recommended that ECG and blood pressure should be monitored.

**Insulin or oral hypoglycemics**: Agents with β-blocking properties may enhance the blood sugar reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended (MICROMEDEX, 2006).

### 3.2 Excipients/Polymers profile

#### 3.2.1 Hydroxypropyl methylcellulose (HPMC)

The PhEur 2005 describes hypromellose (hydroxypropyl methylcellulose) as a partly O-methylated and O-(2-hydroxypropylated) cellulose.

**Structural formula**

```
Where R is H, CH₃, or CH₃CH(OH)CH₂
```
**Functional category:** Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder and viscosity-increasing agent.

**Applications in pharmaceutical formulations:** Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets.

**Description:** Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

**Solubility:** Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol.

**Viscosity:** Typical viscosity values for 2% (w/v) aqueous solutions of methocel (Dow Chemical Co.). Viscosities measured at 20°C.

<table>
<thead>
<tr>
<th>Methocel product</th>
<th>USP28 designation</th>
<th>Nominal viscosity (cp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methocel K100 Premium LVEP</td>
<td>2208</td>
<td>100</td>
</tr>
<tr>
<td>Methocel K4M Premium</td>
<td>2208</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel K15M Premium</td>
<td>2208</td>
<td>15 000</td>
</tr>
<tr>
<td>Methocel K100M Premium</td>
<td>2208</td>
<td>100 000</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>2910</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel F50 Premium</td>
<td>2906</td>
<td>50</td>
</tr>
<tr>
<td>Methocel E10M Premium CR</td>
<td>2906</td>
<td>10 000</td>
</tr>
<tr>
<td>Methocel E3 Premium LV</td>
<td>2906</td>
<td>3</td>
</tr>
<tr>
<td>Methocel E5 Premium LV</td>
<td>2906</td>
<td>5</td>
</tr>
<tr>
<td>Methocel E6 Premium LV</td>
<td>2906</td>
<td>6</td>
</tr>
</tbody>
</table>
Methocel E15 Premium LV    2906    15
Methocel E50 Premium LV    2906    50
Metolose 60SH     2910    50, 4000, 10 000
Metolose 65SH     2906    50, 400, 1500, 4000
Metolose 90SH     2208              100, 400, 4000, 15 000

Stability and storage conditions: Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities: Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety: Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.

Handling precautions: Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Regulatory status: GRAS listed. Included in the FDA inactive ingredients guide (Rowe et al., 2006).

3.2.2 Hydroxypropyl Cellulose (HPC)

The PhEur 2005 and USPNF 23 describe hydroxypropyl cellulose as partially substituted poly (hydroxypropyl) ether of cellulose. Molecular weight has a range of 50000-1250 000.
**Functional category:** Coating agent, emulsifying agent, stabilizing agent, suspending agent, tablet binder, thickening agent and viscosity-increasing agent.

**Applications in pharmaceutical formulations:** Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations. In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating and extended-release matrix former. Concentrations of hydroxypropyl cellulose of 2-6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes. Concentrations of 15-35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Low-substituted hydroxypropyl cellulose is used as a tablet disintegrant.

**Description:** Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

**Moisture content:** Hydroxypropyl cellulose absorbs moisture from the atmosphere.

Moisture content of Klucel (Aqualon).
<table>
<thead>
<tr>
<th>Grade</th>
<th>Molecular weight</th>
<th>Moisture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klucel EF</td>
<td>80 000</td>
<td>0.59</td>
</tr>
<tr>
<td>Klucel LF</td>
<td>95 000</td>
<td>2.21</td>
</tr>
<tr>
<td>Klucel JF</td>
<td>140 000</td>
<td>1.44</td>
</tr>
<tr>
<td>Klucel GF</td>
<td>370 000</td>
<td>1.67</td>
</tr>
<tr>
<td>Klucel MF</td>
<td>850 000</td>
<td>1.52</td>
</tr>
<tr>
<td>Klucel HF</td>
<td>1 150 000</td>
<td>4.27</td>
</tr>
</tbody>
</table>

**Solubility:** Practically insoluble in aliphatic hydrocarbons, aromatic hydrocarbons, carbon tetrachloride, petroleum distillates, glycerine and oils. Hydroxypropyl cellulose is freely soluble in water below 38°C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45°C.

**Viscosity (dynamic):** A wide range of viscosity types are commercially available.

Viscosity of aqueous solutions of Klucel (Aqualon) at 25°C.

<table>
<thead>
<tr>
<th>Grades</th>
<th>Viscosity (cp) of various aqueous solutions of stated concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Klucel HF</td>
<td>1500–3000</td>
</tr>
<tr>
<td>Klucel MF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel GF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel JF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel LF</td>
<td>-</td>
</tr>
<tr>
<td>Klucel EF</td>
<td>-</td>
</tr>
</tbody>
</table>

**Stability and storage conditions:** Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0-8.0. Hydroxypropyl cellulose powder should be stored in a well closed container in a cool, dry place.
**Incompatibilities:** Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methyl paraben and propyl paraben.

**Safety:** Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material. Excessive consumption of hydroxypropyl cellulose may have a laxative effect.

**Regulatory status:** GRAS listed and included in the FDA inactive ingredients guide (Rowe et al., 2006).

### 3.2.3 Ethylcellulose (EC)

Ethylcellulose with complete ethoxyl substitution (DS=3) is \( \text{C}_{12}\text{H}_{23}\text{O}_6 \) \( (\text{C}_{12}\text{H}_{22}\text{O}_5)_n \) \( \text{C}_{12}\text{H}_{23}\text{O}_5 \). Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages.

**Structural formula**

![Structural formula of ethylcellulose](image)

**Functional category:** Coating agent, flavoring fixative, tablet binder, tablet filler and viscosity-increasing agent.

**Applications in pharmaceutical formulations:** Ethylcellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified release tablet formulations may also be produced using...
ethylcellulose as a matrix former. An aqueous polymer dispersion of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents. Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

**Description:** Ethylcellulose is a tasteless, free-flowing and white to light tan colored powder.

**Moisture content:** Ethylcellulose absorbs very little water from humid air or during immersion and that small amount evaporates readily.

**Solubility:** Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol and toluene.

**Viscosity:** The viscosity of ethylcellulose is measured typically at 25°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene :20% ethanol (w/w). Grades of ethylcellulose with various viscosities ranging from 7 to 100 cp commercially available.

**Stability and storage conditions:** Ethylcellulose is a stable, slightly hygroscopic material. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. Ethylcellulose should be stored at a temperature not exceeding 32°C in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

**Incompatibilities:** Incompatible with paraffin wax and microcrystalline wax.

**Safety:** Ethylcellulose is generally regarded as a nontoxic, nonallergenic and non irritating material.

**Regulatory status:** GRAS listed and included in the FDA inactive ingredients guide (Rowe et al., 2006).
3.2.4 Lactose Monohydrate

**Empirical formula and molecular weight:** C$_{12}$H$_{22}$O$_{11}$, H$_2$O, 360.31

**Structural formula (α-Lactose Monohydrate)**

![Structural formula of α-Lactose Monohydrate]

The Ph Eur 2005 describes lactose monohydrate as the monohydrate of O-β-D-galactopyranosyl-(1 → 4)-α-D-glucopyranose.

**Functional category:** Binding agent, diluent for dry-powder inhalers, tablet binder, tablet and capsule diluent.

**Applications in pharmaceutical formulations:** Lactose is widely used as a filler or diluent in tablets and capsules and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar-coating solutions. Direct-compression grades of lactose monohydrate are available containing small amounts of anhydrous lactose.

**Description:** Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-taste.

**Typical properties**

- **Angle of repose:** 33° for Pharmatose DCL 15, 32° for Tablettose 70 and Tablettose 80.
- **Moisture content:** Lactose monohydrate contains approximately 5% w/w water of crystallization.
Solubility of lactose

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility at 20ºC unless otherwise stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform</td>
<td>Practically insoluble</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Practically insoluble</td>
</tr>
<tr>
<td>Ether</td>
<td>Practically insoluble</td>
</tr>
<tr>
<td>Water</td>
<td>1 in 5.24</td>
</tr>
<tr>
<td></td>
<td>1 in 3.05 at 40ºC</td>
</tr>
<tr>
<td></td>
<td>1 in 2.30 at 50ºC</td>
</tr>
<tr>
<td></td>
<td>1 in 1.71 at 60ºC</td>
</tr>
<tr>
<td></td>
<td>1 in 0.96 at 80ºC</td>
</tr>
</tbody>
</table>

**Stability and storage conditions:** Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Lactose should be stored in a well-closed container in a cool, dry place.

**Incompatibilities:** A maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, aminophylline, amphetamines and lisinopril.

**Safety:** Lactose is widely used in pharmaceutical formulations as a filler and filler-binder in oral capsule and tablet formulations. Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase. This results in lactose being undigested and may lead to cramps, diarrhea, distension and flatulence. Lactase hydrolyzes lactose in the small intestine to glucose and galactose, which are then absorbed.

**Regulatory status:** Included in the FDA inactive ingredients guide (Rowe et al., 2006).

### 3.2.5 Citric acid

**Empirical formula and molecular weight:** C$_6$H$_8$O$_7$  192.12
2-hydroxypropane-1,2,3-tricarboxylic acid.

**Functional category:** Acidifying agent, antioxidant, buffering agent, chelating agent and flavour enhancer.

**Applications in pharmaceutical formulations:** Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions (0.1-2%). It has also been used experimentally to adjust the pH of tablet matrices in enteric coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets. Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations. It is also a component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

**Description:** Odorless or almost odorless, colorless crystals or a white crystalline powder. Crystal structure is monoclinic holohedral.

**Acidity/alkalinity:** pH = 2.2 (1% w/v aqueous solution)

**Dissociation constants:**

- pKa₁: 3.128 at 25°C
- pKa₂: 4.761 at 25°C
- pKa₃: 6.396 at 25°C.

**Hygroscopicity:** At relative humidities between about 25-50%, anhydrous citric acid absorbs insignificant amounts of water at 25°C. However, at relative humidities between 50% and 75%, it absorbs significant amounts, with the monohydrate being formed at
relative humidities approaching 75%. At relative humidities greater than 75% substantial amounts of water are absorbed by the monohydrate.

**Melting point:** 151-153°C

**Solubility:** Soluble 1 in 1 part of ethanol (95%) and 1 in 1 of water, sparingly soluble in ether.

**Viscosity (dynamic):** 6.5 cp for a 50% w/v aqueous solution at 25°C.

**Stability and storage conditions:** Citric acid monohydrate loses water of crystallization in dry air or when heated to about 40°C. It is slightly deliquescent in moist air. The bulk monohydrate or anhydrous material should be stored in airtight containers in a cool, dry place.

**Incompatibilities:** Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents and nitrates. It is potentially explosive in combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.

**Safety:** Orally ingested citric acid is absorbed and is generally regarded as a nontoxic material when used as an excipient. However, excessive or frequent consumption of citric acid has been associated with erosion of the teeth.

**Handling precautions:** Eye protection and gloves are recommended. Direct contact with eyes can cause serious damage (Rowe *et al.*, 2006).

### 3.2.6 Talc

Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg₆(Si₂O₅)₄(OH)₄. It may contain small, variable amounts of aluminum silicate and iron.

**Functional category:** Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

**Applications in pharmaceutical formulations:** Talc is used as a lubricant, glidant (1-10%) in tablet formulations, in a novel powder coating for extended-release pellets and as an adsorbent. It is widely used as a dissolution retardant in the development of
controlled-release products. In topical preparations, talc is used as a dusting powder (90-99%), although it should not be used to dust surgical gloves. Talc is a natural material, it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

**Description:** Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

**Typical properties**

Acidity/alkalinity: pH 7-10 for a 20% w/v aqueous dispersion.

Moisture content: Talc absorbs insignificant amounts of water at 25ºC and relative humidities up to about 90%.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents, and water.

**Stability and storage conditions:** Talc is a stable material and should be stored in a well-closed container in a cool, dry place

**Incompatibilities:** Incompatible with quaternary ammonium compounds.

**Safety:** Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas. Inhalation of talc causes irritation and may cause severe respiratory distress in infants. Talc contaminated with asbestos has been proved to be carcinogenic in humans and asbestos-free grades should therefore be used in pharmaceutical products.

**Handling precautions:** Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis. Eye protection, gloves and a respirator are recommended.

**Regulatory status:** Accepted for use as a food additive in Europe. Included in the FDA inactive ingredients guide (Rowe et al., 2006).

### 3.2.7 Magnesium Stearate

**Empirical formula and molecular weight**

C_{36}H_{70}MgO_{4} \quad 591.34
**Structural formula:** \([\text{CH}_3(\text{CH}_2)_{16}\text{COO}]_2\text{Mg}\)

**Functional category:** Tablet and capsule lubricant.

**Applications in pharmaceutical formulations:** It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

**Description:** Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

**Typical properties**
Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
Flowability: Poorly flowing, cohesive powder.
Melting range: 117-150ºC
Solubility: Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol (95%).

**Stability and storage conditions:** Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

**Incompatibilities:** Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

**Safety:** Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

**Handling precautions:** Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, and coughing.

**Regulatory acceptance:** GRAS listed and included in the FDA inactive ingredients guide (Rowe *et al.*, 2006).