3.1 DRUG PROFILE

1) Tramadol Hydrochloride \(^{[1-7]}\)

IUPAC-(1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride

**Synonym** - Tramadol HCl, Tramadol hydrochloride, Tramadolum [INN-Latin]

**Molecular weight** - 299.8

**Molecular Formula** - C\(_{16}\)H\(_{26}\)ClNO\(_2\)

**Solubility** - Freely soluble in water.

**pKa** - 9.41

**Melting Point** - 180-181\(^\circ\)C

**Dose of drug** - 50mg, 75mg and 100mg

**Assay** –
Dissolve 0.180 g in 25 ml of anhydrous acetic acid R and add 10 ml of acetic anhydride. Titrate with 0.1 M perchloric acid. 1 ml of 0.1 M perchloric acid is equivalent to 29.28 mg of C\(_{16}\)H\(_{26}\)ClNO\(_2\)

**Pharmacodynamics**
Tramadol, a centrally-acting analgesic, exists as a racemic mixture of the trans isomer, with important differences in binding, activity, and metabolism associated with the two enantiomers. Although Tramadol is a synthetic analog of codeine, it has a significantly lower affinity for opioid receptors than codeine.
Pharmacokinetics
The analgesic activity is due to both parent drug and the M1 metabolite. Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Linear pharmacokinetics has been observed following multiple doses of 50 and 100 mg to steady-state.

Mechanism of action -
Tramadol acts as a µ-opioid receptor agonist, serotonin releasing agent, norepinephrine reuptake inhibitor, NMDA receptor antagonist, 5-HT\textsubscript{2C} receptor antagonist,\textsubscript{(α7)}nicotinic acetylcholine receptor antagonist, TRPV1 receptor agonist, and M\textsubscript{1} and M\textsubscript{3} muscarinic acetylcholine receptor antagonist. The analgesic action of tramadol has yet to be fully understood, but it is believed to work through modulation of serotonin and norepinephrine in addition to its mild agonism of the µ-opioid receptor.

Overdose-
Acute overdose with tramadol can be manifested by respiratory depression, somnolence progressing coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, seizures, bradycardia, hypotension, cardiac arrest and death. Deaths due to overdose have been reported with abuse and misuse of tramadol.

Absorption –
The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~10%) exist in the absolute amount of each enantiomer present. Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with four times per day dosing. There is no evidence of self-induction.
CHAPTER 3

Food Effects –
Oral administration of ULTRAM® (Tramadol HCl) with food does not significantly affect its rate or extent of absorption, therefore, ULTRAM® (Tramadol HCl) can be administered without regard to food.

Distribution–
The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism–
Tramadol is extensively metabolized after oral administration by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyltramadol, denoted M1) is pharmacologically active in animal models.

Side effects–
Nausea, vomiting, constipation, light headedness, dizziness, drowsiness, or headache may occur. To reduce the risk of dizziness and light headedness, get up slowly when rising from a sitting or lying position. Many people using this medication do not have serious side effects.

Drug Interactions –
Increase in anticoagulation with warfarin. Increased risk of seizures with SSRI, TCA. Increased risk of serotonin syndrome with mirtazapine, venlafaxine, SSRI and MAOI; tramadol should not be given to patients receiving MAOIs or within 14 days of their discontinuation. Reduced analgesic efficacy of tramadol with carbamazepine, 5-HT3-
receptor antagonist e.g. ondansetron. Increased respiratory and CNS depression with CNS depressants e.g. alcohol, opioids, anaesthetic agents, narcotics, phenothiazines, tranquillisers or sedative hypnotics.

2) Metoprolol Succinate

\[
\text{Chemical Name} - (\pm) 1-(\text{isopropylamino})-3-[p-(2\text{-methoxyethyl}) \text{phenoxy}]-2\text{-propanol Succinate}
\]

\[
\text{IUPAC Name} - \{2\text{-hydroxy}-3-[4-(2\text{-methoxyethyl}) \text{phenoxy}] \text{propyl}\} \text{ (propan-2-yl) amine}
\]

\[
\text{Molecular Formula} - (\text{C}_{15}\text{H}_{25}\text{NO}_{3})_2\cdot \text{C}_4\text{H}_6\text{O}_4
\]

\[
\text{Molecular weight} - 653
\]

\[
\text{Synonym} - \text{Metoprolol succinate}
\]

\[
\text{Metoprolol Tartrate}
\]

\[
\text{Solubility} - \text{Freely soluble in water}
\]

\[
\text{pK}_a - 9.68
\]

\[
\text{Melting point} - 136^\circ \text{c}
\]

\[
\text{Dose of drug} - 25\text{mg, 50mg, 100mg and 200mg}
\]

\[
\text{Assay} -
\]

Dissolve 0.25 gm in 40 ml anhydrous acetic acid R. Titrate with 0.1 M perchloric acid. Determine end point potentiometrically.

1 ml of 0.1 M perchloric acid is equivalent to 32.64 mg of \((\text{C}_{15}\text{H}_{25}\text{NO}_{3})_2\cdot \text{C}_4\text{H}_6\text{O}_4\)
Pharmacodynamics

Metoprolol, a competitive, beta1-selective (cardioselective) adrenergic antagonist, is similar to atenolol in its moderate lipid solubility, lack of intrinsic sympathomimetic activity (ISA), and weak membrane stabilizing activity (MSA).

Pharmacokinetics

Absorption of metoprolol approaches 95%, whereas systemic bioavailability is approximately 50% for IR metoprolol due to extensive first-pass metabolism. First-pass metabolism has an even greater impact on metoprolol succinate and systemic bioavailability of this preparation is 25-30% less than that of the IR product, likely due to maximum first-pass metabolism resulting from the slow rate of drug release.

Metoprolol is absorbed primarily through the small intestine and colon, not through the stomach. This may account for some decreased systemic availability with the ER preparation if the tablet is eliminated from the body before the entire drug is released. In addition, systemic bioavailability may be affected in patients with gastrointestinal motility impairment or in those receiving drug therapies to enhance gastrointestinal motility.

Metabolism

The agent is extensively metabolized by several oxidative pathways, primarily a-hydroxylation, O-demethylation and N-dealkylation. Metoprolol is also a substrate of the cytochrome P450 2D6 pathway and drugs that inhibit metabolism of that isoenzyme may affect the drug's plasma levels.

Mechanism of Action -

Hypertension - The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

Heart Failure - The precise mechanism for the beneficial effects of beta-blockers in heart failure has not been elucidated.
Overdose –

**Signs and Symptoms** - Overdosage of Metoprolol succinate may lead to severe bradycardia, hypotension and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

**Side Effects** -
Side effects, especially with higher dosages, include the following: dizziness, drowsiness, fatigue, diarrhea, unusual dreams, ataxia, trouble sleeping, depression, and vision problems. It may also reduce blood flow to the hands and feet, causing them to feel numb and cold; smoking may worsen this effect.

**Drug Interactions** –

**Catecholamine Depleting Drugs** - Catecholamine-depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents.

**CYP2D6 Inhibitors** - Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine and propafenone are likely to increase metoprolol concentration.

**Digitalis, Clonidine, and Calcium Channel Blockers** - Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate.

3) **Cyclobenzaprine Hydrochloride**[^13-16]

![Chemical structure of Cyclobenzaprine Hydrochloride](image)

**Chemical Name** - 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N, N-dimethyl-1-propanamine hydrochloride.

**Molecular formula** - C<sub>20</sub>H<sub>21</sub>N.HCl
Molecular weight - 311.85

Synonym - Cyclobenzaprine HCl

Solubility - Freely soluble in water

pKa – 8.47

Melting point - 216-218°C

Dose of drug – 5mg and 10mg

Assay –
Dissolve about 400 mg Cyclobenzaprine Hydrochloride, accurately weighed, in about 80 ml of glacial acetic acid and 15 ml of mercuric acetate TS and titrate with 0.1 N perchloric acid VS, determining end point potentiometrically. Perform a blank determination, and make any necessary correction.
Each ml of 0.1 N perchloric acid is equivalent to 31.19 mg of C_{20}H_{21}N.HCl

Pharmacodynamics
Cyclobenzaprine, closely related to the antidepressant amitriptyline, is used as a skeletal muscle relaxant to reduce pain and tenderness and improve mobility. Unlike dantrolene, cyclobenzaprine cannot be used to treat muscle spasm secondary to cerebral or spinal cord disease.

Pharmacokinetics –
Mean oral bioavailability of cyclobenzaprine ranges from 33% to 55%. Cyclobenzaprine exhibits linear pharmacokinetics over the dose range 2.5 mg to 10 mg, and is subject to enterohepatic circulation. It is highly bound to plasma proteins. Drug accumulates when dosed three times a day, reaching steady-state within 3-4 days at plasma concentrations about four-fold higher than after a single dose. At steady state in healthy subjects receiving 10 mg t.i.d. (n=18), peak plasma concentration was 25.9 ng/mL (range, 12.8-46.1 ng/mL), and area under the concentration-time (AUC) curve over an 8-hour dosing interval was 177 ng.hr/mL (range, 80-319 ng.hr/mL).
MECHANISM OF ACTION -

The mechanism of action for cyclobenzaprine is unclear. Studies from the 1980s in rats indicate that cyclobenzaprine activates the locus ceruleus in the brain stem, leading to an increased release of norepinephrine in the ventral horn of the spinal cord and the subsequent inhibitory action of norepinephrine on alpha motor neurons. Cyclobenzaprine has been considered structurally related to the first-generation tricyclic antidepressants. Such tricyclics, including amitriptyline, act to inhibit the uptake of norepinephrine, resulting in increased transynaptic norepinephrine concentration. They have been shown to exert analgesic effects in chronic nerve and muscle pain. Cyclobenzaprine may have a similar effect.

OVERDOSE –

The most common effects of overdose are drowsiness and tachycardia. Rare but potentially critical complications are cardiac arrest, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome.

SIDE EFFECTS –

- fast, pounding or uneven heartbeats;
- chest pain or heavy feeling, pain spreading to the arm or shoulder, nausea, sweating, general ill feeling;
- sudden numbness or weakness, especially on one side of the body;
- sudden headache, confusion, problems with vision, speech, or balance;
- feeling light-headed, fainting;

DRUG INTERACTIONS -

Cyclobenzaprine has major contraindications with monoamine oxidase inhibitors (MAOIs).

The following substances may interact with cyclobenzaprine:

- Alcohol
- Central nervous system (CNS) depressants (medicines that cause drowsiness)
- Tricyclic antidepressants may increase the chance of side-effects
4) Aceclofenac–[17-22]

Chemical Name – Glycolic acid, [o-(2,6-dichloroanilino)phenyl]acetate (ester)

IUPAC Name- 2-[2-[2-(2,6-dichlorophenyl)amino]phenyl]acetyl]oxyacetic acid

Molecular weight- 352.2

Molecular formula- C_{16}H_{13}Cl_{2}NO_{4}

Solubility – Insoluble in acetone, soluble in alcohol.

pKα – 4.7

Melting point – 150-154°C

Dose of drug - 100mg

Assay –
Dissolve 0.003 gm in 40 ml of methanol R. Titrate with 0.1 M NaOH, determining the end point potentiometrically.

1 ml of 0.1 M NaOH is equivalent to 35.42 mg of C_{16}H_{13}Cl_{2}NO_{4}

Pharmacodynamics-
Aceclofenac is a non-steroidal agent with marked anti-inflammatory and analgesic properties. The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Pharmacokinetics -
After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following
ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L. The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (> 99%). Aceclofenac circulates mainly as unchanged drug. 4'-Hydroxyaceclofenac is the main metabolite detected in plasma. Approximately two-thirds of the administered dose is excreted via the urine, mainly as hydroxyl metabolites. No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

Mechanism of Action –
Aceclofenac, a phenylacetic acid derivative, has antiinflammatory and analgesic properties. It is a potent inhibitor of cyclo-oxygenase which is involved in the production of prostaglandins.

Overdose –
Management: Gastric lavage and treatment with activated charcoal. Treatment is supportive and symptomatic. Dialysis, haemoperfusion unlikely to be useful.

Side Effects –
Gastrointestinal disorders – Stomach upset, Abdominal pain, Nausea, vomiting sometimes bloody diarrhoea, flatulence, constipation, mouth ulceration, stomatitis, dark stool, stomach ulcer and bleeding, pancreatitis.

Immune system disorders - Anaphylactic reaction, Drug allergic reaction

Skin disorders - Pruritus, Rash, Skin inflammation, Hives, Facial swelling, Purpura Eczema.

Hematological - Anaemia, Low white blood cells count, Low platelet counts, Cardiac disorders - Rapid and irregular heart rate

Respiratory disorders - Shortness of breath, Bronchospasm, Stridor (A whistling sound when breathing)

Liver - Hepatitis, Jaundice
Kidney disorders - Nephrotic syndrome, Kidney dysfunction

Drug Interactions –
Aceclofenac may increase plasma concentrations of lithium and digoxin. It showed increased nephrotoxicity when used with diuretics or ciclosporin. Monitor serum potassium when used with potassium-sparing diuretics and ACE inhibitors. It may enhance activity of anticoagulants. It may increase risk of methotrexate toxicity when administered within 24 hr of methotrexate admin. It showed increase risk of GI bleed with other NSAIDs.
3.2 POLYMERS AND EXCIPIENT

1) Hydroxypropyl methyl cellulose[23]

According to the European pharmacopoeia, Hydroxypropyl methyl cellulose (hypromellose) is partly α-methylated and α-(2-hydroxypropylated) cellulose. Hypromellose is an inert, odorless, tasteless, non-ionic, hydrophilic polymer. It is prepared from purified cellulose, which is obtained from cotton linters or wood pulp. The cellulose is treated with an alkali like sodium hydroxide to produce swollen alkali cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide due to which it gets converted to methylhydroxypropyl ethers of cellulose. The final product is then purified and ground to powders or granules.

1. Nonproprietary Names
   - BP: Hypromellose
   - JP: Hydroxypropylmethylcellulose

2. Synonyms
   - Benecel MHPC; E464; Hydroxypropyl methyl cellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl Hydroxypropylcellulose; Metolose; Tylopur.

3. Molecular Weight
   - Approximately 10000–1500000

4. Structural Formula

\[
\text{Where } R \text{ is } \text{H, CH}_3, \text{ or } \text{CH}_3\text{CH(OH)CH}_2
\]
5. Functional Category
Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

6. Applications in Pharmaceutical Formulation or Technology
- HPMC used as a tablet binder, in film-coating, 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.
- It is used as a suspending and thickening agent in topical formulations.
- It is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

7. Melting point:
Browns at 190–200°C; chars at 225–230°C.

8. Solubility:
It is practically insoluble in hot water, in absolute ethanol, in acetone, in ether, and in toluene. It dissolves in cold water forming a colloidal solution. Amongst the various hydrophilic polymers hypromellose is the most commonly used material used for the preparation of CR dosage forms because of the number of advantages it offers viz., non-toxicity, ease of compression, ability to accommodate a large percentage of drugs and low influence of processing variables on the drug release from the matrices. The mechanism of drug release through a hydrophilic matrix CR system involves polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution.
9. Viscosity:

Table 3.1: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel at 20°C

<table>
<thead>
<tr>
<th>Methocel product</th>
<th>USP 28 designation</th>
<th>Nominal viscosity (mPa s)</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>15000</td>
</tr>
<tr>
<td>Methocel K100M Premium</td>
<td>2208</td>
<td>100000</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>2910</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel F50 Premium</td>
<td>2910</td>
<td>4000</td>
</tr>
<tr>
<td>Methocel E10M Premium CR</td>
<td>2906</td>
<td>10000</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>
<tr>
<td>Methocel E15 Premium LV</td>
<td>2906</td>
<td>15</td>
</tr>
<tr>
<td>Methocel E50 Premium LV</td>
<td>2906</td>
<td>50</td>
</tr>
</tbody>
</table>

10. Stability and Storage Conditions
Hypromellose powder is a stable material, although it is hygroscopic after drying.

11. 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.

2) Xanthan Gum\(^{[24]}\)

Nonproprietary Names
BP : Xanthan gum
PhEur : Xanthaniumm
USPNF: Xanthan gum

Empirical Formula and Molecular Weight
\((C_{35}H_{59}O_{29})_n\) Approximately \(2 \times 10^6\)
The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

**Functional Category**
Stabilizing agent; suspending agent; viscosity-increasing agent

**Applications in Pharmaceutical Formulation or Technology**
Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range. Xanthan gum gels show pseudo plastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.

When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur. In general, mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1 : 2 and 1 : 9 produce the optimum properties. Similarly, optimum synergistic effects are obtained with xanthan gum : guar gum ratios between 3 : 7 and 1 : 9.

**Description**
Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

**Typical Properties**

**Acidity/alkalinity:**
pH = 6.0–8.0 for a 1% w/v aqueous solution.

**Freezing point:** 0°C for a 1% w/v aqueous solution.

**Melting point:** Chars at 270°C.

**Refractive index:** \( n^2_{D} = 1.333 \) for a 1% w/v aqueous solution.

**Solubility:** Practically insoluble in ethanol and ether; soluble in cold or warm water.

**Viscosity (dynamic):**
200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.
Stability and Storage Conditions
Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids, and bases.

The bulk material should be stored in a well-closed container in a cool, dry place.

Method of Manufacture
Xanthan gum is a polysaccharide produced by a pure-culture aerobic fermentation of a carbohydrate with Xanthomonas campestris. The polysaccharide is then purified by recovery with propan-2-ol, dried, and milled.

Safety
Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

3) Polyethylene oxide-[25]

1. Nonproprietary Names
   USPNF: Polyethylene oxide

2. Synonyms
   Polyox; polyoxirane; polyoxyethylene.

3. Chemical Name:
   Polyethylene oxide
Table 3.2: Empirical Formula and Molecular Weight of Polyethylene oxide

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polyox grade</th>
<th>Approximate molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>WSR N-10</td>
<td>100000</td>
</tr>
<tr>
<td>2</td>
<td>WSR N-80</td>
<td>200000</td>
</tr>
<tr>
<td>3</td>
<td>WSR N-750</td>
<td>300000</td>
</tr>
<tr>
<td>4</td>
<td>WSR N-3000</td>
<td>400000</td>
</tr>
<tr>
<td>5</td>
<td>WSR 205</td>
<td>600000</td>
</tr>
<tr>
<td>6</td>
<td>WSR 1105</td>
<td>900000</td>
</tr>
<tr>
<td>7</td>
<td>WSR N-12K</td>
<td>1000000</td>
</tr>
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<td>8</td>
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<tr>
<td>9</td>
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<td>4000000</td>
</tr>
<tr>
<td>10</td>
<td>WSR Coagulant</td>
<td>5000000</td>
</tr>
<tr>
<td>11</td>
<td>WSR 303</td>
<td>7000000</td>
</tr>
</tbody>
</table>

4. Structural Formula
The USPNF 23 describes polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula \((\text{CH}_2\text{CH}_2\text{O})_n\), where \(n\) represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide.

5. Functional Category
Mucoadhesive; tablet binder; thickening agent.

6. Applications in Pharmaceutical Formulation or Technology
Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach. The relationship between swelling capacity and molecular weight is a good guide when selecting products for use in immediate- or sustained-release matrix formulations. Polyethylene oxide films demonstrate good lubricity when wet. This property has been utilized in the development of coatings for medical devices. Polyethylene oxide can be radiation crosslinked in solution to produce a hydrogel that can be used in wound care applications.

7. Description:
White to off-white, free-flowing powder. Slight ammoniacal odor.
8. Melting point: 65–70°C

9. Solubility:
Polyethylene oxide is soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.²

10. Stability and Storage Conditions
Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.

4) Carbopol²⁶

Structural Formula
Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown below. It is chemically crosslinked with polyalkenyl alcohol or divinyl glycol.

![Acrylic acid monomer unit in carbomer resins.]

Description
Carbomer are white-colored, ‘fluffy’, acidic, hygroscopic powders with a slight Characteristic odor.
Carbopol 71G, Carbopol 971P, Carbopol 974P are used in sustained release preparation.

Typical Properties
Glass transition temperature: 100–105°C
Melting point:
Decomposition occurs within 30 minutes at 260°C.
Moisture content:
Normal water content is up to 2% w/w. However, carbomer are hygroscopic and a typical equilibrium moisture content at 25°C and 50% relative humidity is 8–10% w/w.
Solubility:
Carbomer do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally cross linked micro gels.

Viscosity (dynamic):
Carbomer disperse in water to form acidic colloidal dispersions of low viscosity that, when neutralized, produce highly viscous gels.

Functional Category
Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; Viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology
- Carbomer are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents.
- Carbomer having low residuals only of ethyl acetate, Such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets, sustained release tablet formulations.
- Carbomer are used in cosmetics.

![Fig. 3.3: Uses of Carbomer](image)

<table>
<thead>
<tr>
<th>Use</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifying agent</td>
<td>0.1–0.5%</td>
</tr>
<tr>
<td>Gelling agent</td>
<td>0.5–2.0%</td>
</tr>
<tr>
<td>Suspending agent</td>
<td>0.5–1.0%</td>
</tr>
<tr>
<td>Tablet binder</td>
<td>5.0–10.0%</td>
</tr>
</tbody>
</table>

5) Compritol 888 ATO.\(^{[27]}\)

1. Chemical Name:
*Docosanoic acid, monoester with glycerin* (glycerylbehenate)
*Docosanoic acid, diester with glycerin* (glyceryldibehenate)
*Docosanoic acid, triester with glycerin* (glyceryltribehenate)

2. Synonym:
Glycerylbehenate; glycerylmonobehenate.
3. Functional Category
Coating agent; tablet binder; tablet and capsule lubricant.

4. Applications in Pharmaceutical Formulation or Technology
Glyceryl behenate is used in cosmetics, foods, and oral pharmaceutical formulations. In cosmetics, it is mainly used as a viscosity-increasing agent in emulsions.
In pharmaceutical formulations, Glyceryl behenate is mainly used as a tablet and capsule lubricant and as a lipidic coating excipient. It has been investigated for the encapsulation of various drugs such as retinoids. It has also been investigated for use in the preparation of sustained release tablets; as a matrix-forming agent for the controlled release of water-soluble drugs; and as a lubricant in oral solid dosage formulations, and it can also be used as a hot-melt coating agent sprayed onto a powder.

5. Description
Glycerylbehenate occurs as a fine white powder or hard waxy mass with a faint odor.

6. Melting point: 70–73°C

7. Solubility:
Soluble, when heated, in chloroform and dichloromethane, practically insoluble in ethanol (95%), hexane, mineral oil, and water.

8. Stability and Storage Conditions
Glycerylbehenate should be stored in a tight container, at a temperature less than 35°C.

6) Precirol ATO 5-\(^\text{[28]}\)

1. Synonyms
Glycerin palmitostearate; glycerol palmitostearate; 2-[(1-oxohexadecyl)-oxy]-1,3-propanediyl dioctadecanoate and 1,2,3-propane triol.

2. Chemical Name:
Octadecanoic acid, 2,3-dihydroxypropyl ester mixed with 3-hydroxy-2-[(1-oxohexadecyl)-oxy] propyl octadecanoate.
3. **Functional Category**

Biodegradable material; coating agent; gelling agent; release modifying agent; sustained-release agent; tablet and capsule diluent; tablet and capsule lubricant; taste-masking agent.

4. **Applications in Pharmaceutical Formulation or Technology**

Glyceryl palmitostearate is used in oral solid-dosage pharmaceutical formulations as a lubricant. Disintegration times increase and a tablet strength decrease with increase in mixing time. It is used as a lipophilic matrix for sustained-release tablet and capsule formulations. Tablet formulations may be prepared by either granulation or a hot-melt technique, the former producing tablets that have the faster release profile. Release rate decreases with increased glyceryl palmitostearate content. Glyceryl palmitostearate is used to form microspheres, which may be used in capsules or compressed to form tablets, pellets, coated beads, and biodegradable gels. It is also used for taste-masking.

5. **Description**

Glyceryl palmitostearate occurs as a fine white powder with a faint odor.

6. **Melting point:** 55–58°C

7. **Solubility:**

Freely soluble in chloroform and dichloromethane; practically insoluble in ethanol (95%), mineral oil, and water.

8. **Stability and Storage Conditions**

Glyceryl palmitostearate should not be stored at temperatures above 35°C. For storage for periods over 1 month, glycerylpalmitostearate should be stored at a temperature of 5–15°C in an airtight container, protected from light and moisture.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix for sustained release</td>
<td>10.0 – 25.0</td>
</tr>
<tr>
<td>Tablet masking</td>
<td>2.0 – 6.0</td>
</tr>
<tr>
<td>Tablet lubricant</td>
<td>1.0 – 3.0</td>
</tr>
</tbody>
</table>
7) Hydrogenated vegetable oil\(^{[29]}\)

1. Nonproprietary Names
   
   BP: Hydrogenated vegetable oil  
   JP: Hydrogenated oil

2. Synonyms:
   
   *Hydrogenated cottonseed oil:* Akofine; Lubritab; Sterotex.  
   *Hydrogenated palm oil:* Softisan 154.  
   *Hydrogenated soybean oil:* Lipovol HS-K; Sterotex HM.

3. Chemical Name:
   
   Hydrogenated vegetable oil  
   Hydrogenated soybean oil

4. Empirical Formula:
   
   The USPNF 23 defines two types of hydrogenated vegetable oil, type I and type II, which differ in their physical properties and applications.

5. Structural Formula
   
   \[ R_1\text{COOCH}_2\text{—CH(OOCR}_2\text{)—CH}_2\text{OOCR}_3 \]
   
   where \( R_1 \), \( R_2 \), and \( R_3 \) are mainly \( C_{15} \) and \( C_{17} \).

6. Functional Category
   
   Tablet and capsule lubricant; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology
   
   Hydrogenated vegetable oil type I is used as a lubricant in tablet and capsule formulations. It is used at concentrations of 1–6% w/w, usually in combination with talc. It may also be used as an auxiliary binder in tablet formulations. Hydrogenated vegetable oil type I is additionally used as the matrix-forming material in lipophilic-based controlled-release formulations; it may also be used as a coating aid in controlled-release formulations. Other uses of hydrogenated vegetable oil type I include use as a viscosity modifier in the preparation of oil-based liquid and semisolid formulations; in the preparation of suppositories, to reduce the sedimentation of suspended components and to improve the solidification process; and in the formulation of liquid and semisolid fills for hard gelatin
8. Melting range: 61–69° C

9. Description
Hydrogenated vegetable oil is a mixture of triglycerides of fatty acids. The two types that are defined in the USPNF 23 are characterized by their physical properties; Hydrogenated vegetable oil type I occurs in various forms, e.g. fine powder, flakes, or pellets.

10. Stability and Storage Conditions:
Hydrogenated vegetable oil type I is a stable material; typically it is assigned a 2-year shelf-life. The bulk material should be stored in a well-closed container in a cool, dry place.

8) Ethylcellulose\textsuperscript{[30]}

1. Nonproprietary Names
   - BP: Ethylcellulose
   - USPNF: Ethylcellulose

2. Synonyms
*Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.*

3. Chemical Name
Cellulose ethyl ether

4. Empirical Formula and Molecular Weight
Ethylcellulose with complete ethoxyl substitution (DS=3) is $\text{C}_{12}\text{H}_{23}\text{O}_6(\text{C}_{12}\text{H}_{22}\text{O}_5)_n\text{C}_{12}\text{H}_{23}\text{O}_5$

5. Structural Formula

\[
\text{CH}_2\text{OOC}_2\text{H}_5
\]

\[
\text{O}_5\text{C}_2\text{H}_5
\]

\[
\text{O}_5\text{C}_2\text{H}_5
\]

6. Functional Category
Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.
7. Applications in pharmaceutical formulation or technology

It is used in sustained release dosage formulations.

8. Description

Ethylcellulose is a tasteless, free-flowing, and white to light tan-colored powder

Table 3.5: Uses of ethyl cellulose

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microencapsulation</td>
<td>10.0 – 20.0</td>
</tr>
<tr>
<td>Sustained-release tablet coating</td>
<td>3.0 – 20.0</td>
</tr>
<tr>
<td>Tablet coating</td>
<td>1.0 – 3.0</td>
</tr>
<tr>
<td>Tablet granulation</td>
<td>1.0 – 3.0</td>
</tr>
</tbody>
</table>

9. Typical Properties

**Density**: 0.4 g/cm³

**Solubility**: Ethylcellulose is practically insoluble in glycerine, propylene glycol and water.

**Viscosity**: The viscosity of ethylcellulose is measured typically at 25°C using 5% w/v ethyl cellulose dissolved in a solvent blend of 80% toluene: 20% ethanol (w/w).

10. Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, but more sensitive to acidic materials than are cellulose esters.

11. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

9) Dibasic calcium phosphate[^31]

1. Nonproprietary Names

- BP: Anhydrous calcium hydrogen phosphate

2. Synonyms

A-TAB; calcium monohydrogen phosphate; calcium orthophosphate; *Di-Cafos AN*; dicalcium orthophosphate; E341; Emcompress Anhydrous; Fujicalin; phosphoric acid calcium salt (1:1); secondary calcium phosphate.
3. Chemical Name:
Dibasic calcium phosphate

4. Empirical Formula: CaHPO₄

5. Molecular Weight: 136.06

6. Structural Formula: CaHPO₄

7. Functional Category
Tablet and capsule diluent.

8. Applications in Pharmaceutical Formulation or Technology
Anhydrous dibasic calcium phosphate is used both as an excipient and as a source of calcium in nutritional supplements. It is used particularly in the nutritional/health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material. The predominant deformation mechanism of anhydrous dibasic calcium phosphate coarse-grade is brittle fracture and this reduces the strain-rate sensitivity of the material, thus allowing easier transition from the laboratory to production scale. However, unlike the dihydrate, anhydrous dibasic calcium phosphate when compacted at higher pressures can exhibit lamination and capping. Anhydrous dibasic calcium phosphate is abrasive and a lubricant is required for tableting.

9. Description
Anhydrous dibasic calcium phosphate is a white, odorless, tasteless powder or crystalline solid. It occurs as triclinic crystals.

10. Melting point:
It does not melt; decomposes at ≈ 425°C to form calcium pyrophosphate.

10) Microcrystalline cellulose (Avicel)-[32]

1. Nonproprietary Names
   - BP: Microcrystalline cellulose

2. Synonyms
   Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.
3. Chemical Name:
Cellulose

4. Empirical Formula and Molecular Weight
\((C_6H_{10}O_5)_n \approx 36000\)

5. Structural Formula

![Structural Formula](image)

6. Functional Category
Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology
Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 3.6: Uses of microcrystalline cellulose

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorbent</td>
<td>20-90</td>
</tr>
<tr>
<td>Antiadherent</td>
<td>5-20</td>
</tr>
<tr>
<td>Capsule binder/diluents</td>
<td>20-90</td>
</tr>
<tr>
<td>Tablet disintegrant</td>
<td>5-15</td>
</tr>
<tr>
<td>Tablet binder/diluents</td>
<td>20-90</td>
</tr>
</tbody>
</table>

8. Description
Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.
9. Solubility:
It is slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

10. Stability and Storage Conditions
Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

11) Spray Dried Lactose-[33]

1. Synonyms
FlowLac 100; Lactopress Spray-Dried; NF Lactose–316 Fast Flo; NF Lactose–315; Pharmatose DCL 11; Pharmatose DCL 14; Super-Tab Spray-Dried.

2. Chemical Name
Spray-dried lactose is a mixture of amorphous lactose, which is a 1:1 mixture of α-and-β-lactose, and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate.

3. Empirical Formula
C₁₂H₂₂O₁₁·H₂O (for monohydrate)

4. Molecular Weight
360.31 (for monohydrate)

5. Functional Category
Binding agent; directly compressible tablet excipient; tablet and capsule diluent; tablet and capsule filler.

6. Applications in Pharmaceutical Formulation or Technology
Spray-dried lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting.

8. Description
Lactose occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting.
9. Stability and Storage Conditions
Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

10. 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.

11. Applications in Pharmaceutical Formulation or Technology
Lactose is widely used in pharmaceutical formulations as a filler and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Lactose is excreted unchanged when administered intravenously.

12) Magnesium stearate[34]

Synonyms: Stearic acid magnesium salt, Magnesium octadecanoate.
Chemical Name: Octadecanoic acid magnesium salt
Nonproprietary Names:
BP: Magnesium stearate.
PhEur: Magnesii stearate.
USPNF: Magnesium stearate.
Description:
Magnesium stearate is a fine, white, precipitated, milled, impalpable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to touch and readily adheres to skin.

Applications:
Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.25 –5.0% (w/w).
**13) Mannitol**[^35]

**Nonproprietary Names:** B.P. Mannitol USP - Mannitol

**Empirical Formula and Molecular Weight:** C$_6$H$_{14}$O$_6$

**Molecular weight:** 182.17

**Structural Formula:**

![Structural formula of Mannitol]

**Description:**

Mannitol is D-mannitol. It is hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules. It has sweet taste, approximately as sweet as glucose and half sweet as sucrose, imparts cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

**Typical Properties**

- **Density (bulk):** 0.430 g/cm$^3$ for powder
- **Density (tapped):** 0.734 g/cm$^3$ for powder
- **Density (true):** 1.514 g/cm$^3$
- **Flowability:** Powder is cohesive, granules are free flowing
- **Heat of Combustion:** 16.17kJ/g
- **Melting point:** 166-168$^\circ$C
- **Solubility:** 1 in 5.5 parts

**Stability and Storage Conditions:**

Stable in the dry state and in aqueous solution. Solution may be sterilized by filtration or by autoclaving. It is not attacked by cold, dilute acids or alkali. Mannitol does not undergo Maillard reactions. The bulk material should be stored in well closed container in a cool, dry place.
Applications:
In pharmaceutical preparations it is primarily used as diluents in tablet formulation (Concentration 10-90 % W/W). Mannitol may be used in direct compression tablet. It is available in granular form and spray dried form.

14) Poloxamer-[36]

Nonproprietary Names
- BP: Poloxamers
- PhEur: Poloxamer

Synonyms
Lutrol; Monolan; poloxalkol;polyethylene–propylene glycol copolymer;polyoxyethylene–polyoxypropylene copolymer; Supronic; Synperonic.

Chemical Name
α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymer [9003-11-6]

Description
Poloxamers generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid.

Empirical Formula and Molecular Weight
The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula \( HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH \). The grades included in the PhEur 2005 and USPNF 23 is shown in 3.6. The PhEur 2005 states that a suitable antioxidant may be added.

Melting point: 55-60°C

Structural Formula

![Structural Formula](image)
CHAPTER 3

Functional Category
Dispersing agent; emulsifying and coemulsifying agent; solubilizing agent; tablet lubricant; wetting agent.

Applications in Pharmaceutical Formulation or Technology
Poloxamers are nonionic polyoxyethylene–polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available; Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings.

Table 3.7: Uses of poloxamer

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat emulsifier</td>
<td>0.3</td>
</tr>
<tr>
<td>Flavor solubilizer</td>
<td>0.3</td>
</tr>
<tr>
<td>Fluorocarbon emulsifier</td>
<td>2.5</td>
</tr>
<tr>
<td>Gelling agent</td>
<td>15-50</td>
</tr>
<tr>
<td>Spreading agent</td>
<td>1</td>
</tr>
<tr>
<td>Stabilizing agent</td>
<td>1-5</td>
</tr>
<tr>
<td>Suppository base</td>
<td>4-6 or 90</td>
</tr>
<tr>
<td>Tablet coating</td>
<td>10</td>
</tr>
<tr>
<td>Tablet excipients</td>
<td>5-10</td>
</tr>
<tr>
<td>Wetting agent</td>
<td>0.01-5</td>
</tr>
</tbody>
</table>

Stability and Storage Conditions
Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis, and metal ions. However, aqueous solutions support mold growth. The bulk material should be stored in a well-closed container in a cool, dry place.
15) Croscarmellose Sodium[^37]

Synonyms:
Ac-Di-Sol, Cross-linked Carboxy methyl cellulose (CMC) Sodium, Explocel, Modified Cellulose Gum, Nymcel ZSX, Primellose, Vivosol.

**Structural Formula:**

![Structural formula of Croscarmellose Sodium](image)

**Chemical Name:**
Cellulose, carboxymethyl ether, sodium salt, cross linked. (7481165-77)

**Empirical formula and Molecular Weight:**
Cross linked polymer of CMC sodium, The USP 28 describes carboxymethylcellulose sodium as the sodium salt of polycarboxymethyl ether of cellulose. Typical’ molecular weight is 90 000 -700 000.

**Functional Category:** Tablet and capsule disintegrant.

**Description:**
Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

**Solubility:**
Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

**Stability & Storage Conditions:**
Croscarmellose sodium is a stable though hygroscopic material. It should be stored in a well-closed container in a cool, dry place.
Incompatibilities:
Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminium, mercury, and zinc.

Applications in Pharmaceutical Formulation or Technology:
As a disintegrant for tablets (wet granulation and direct compression), capsules and granules at a concentration of 2-5%.
3.3 REFERENCES

TRAMADOL HYDROCHLORIDE

6. www.drugbank.ca/tramadol/DB00193

METOPROLOL SUCCINATE

12. www.drugbank.ca/metoprolol succinate/DB00264

CYCLOBENZAPRINE HYDROCHLORIDE


16. www.drugbank.ca/cyclobenzaprine/DB00924

ACECLOFENAC


POLYMERS AND EXCIPIENTS


