DRUG PROFILES

Structural formula of Losartan potassium

Physicochemical properties of Losartan potassium

1. Description  White crystalline powder
2. Molecular Formula  C_{22}H_{23}ClN_{6}O
3. Molecular Weight  461.00
4. Chemical Name  Butyl–4Chloro–1–[2–(1Htetrazol–5–yl)[11–biphenyl]– 4-yl] methyl–1H–imidazole–5–methanol potassium
5. Melting point  184 °C
6. Solubility  Freely soluble in water, methanol and insoluble in Chloroform
7. BCS Classification  Losartan Potassium is class III drug (High Solubility & low Permeability).
8. Metabolite  Oxidation of the 5-hydroxymethyl group on the Imidazole ring results in the active metabolite of Losartan.

Pharmacodynamics

Losartan potassium is a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol mono potassium salt, angiotensin II receptor (type AT1) antagonist (Mechael et al., 2011). Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland).
Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>33 %</td>
</tr>
<tr>
<td>Cmax</td>
<td>41.8 ± 7.7 ng/ml</td>
</tr>
<tr>
<td>Tmax</td>
<td>1 Hr</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>2 Hr</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>99.0 %</td>
</tr>
<tr>
<td></td>
<td>99.8 % (Anand et al., 2003)</td>
</tr>
</tbody>
</table>

Absorption:
Following oral administration, Losartan is well absorbed (based on absorption of radiolabeled Losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of Losartan is approximately 33%. About 14% of an orally administered dose of Losartan is converted to the active metabolite (Sardo et al., 2004).

Distribution:
The volume of distribution of Losartan and the active metabolite is about 34 liters and 12 liters, respectively.

Metabolism:
Losartan Potassium undergoes substantial first-pass metabolism by cytochrome P450 enzymes. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of 14<sup>C</sup>-labeled Losartan potassium, circulating plasma radioactivity is primarily attributed to Losartan and its active metabolite. In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of Losartan to its metabolites. Minimal conversion of Losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

Excretion:
When Losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of Losartan and its metabolites. Following oral 14C-labeled Losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of 14C-labeled Losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.
Protein Binding:
Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that Losartan crosses the blood-brain barrier.

Bioavailability
The terminal half-life of Losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of Losartan and its active metabolite are linear with oral Losartan doses up to 200 mg and do not change over time by (Dickstein et al., 1993). Neither Losartan nor its metabolite accumulates in plasma upon repeated once-daily dosing. The systemic bioavailability of Losartan is approximately 33%.

Clopidogrel Bi-sulfate

![Structural formula of Clopidogrel Bi-sulfate]

Physicochemical properties of Clopidogrel Bi-sulfate:

1. Description white to off-white powder
2. Molecular Formula \( C_{16}H_{16}ClNO_2S\cdotH_2SO_4 \)
3. Molecular Weight 419.9 g/mol
4. Chemical Name methyl(+)-(S)-\( \alpha \)-(2-chlorophenyl)-6,7 dihydrothieno [3, 2-c] pyridine-5(4H)-acetate sulfate
5. Melting point 184°C
6. Solubility Freely soluble at pH 1, Methanol
7. BCS Classification Clopidogrel bisulphate is class II
Pharmacological profile:
Mechanism of action: Clopidogrel inhibits adenosine diphosphate (ADP) binding to its platelet receptor and subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thus inhibiting platelet aggregation. Because clopidogrel irreversibly modifies the ADP receptor, platelets are affected for the remainder of their lifespan. An active metabolite, not yet isolated, is responsible for the medication's activity. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphor diesterase activity (Chan et al., 2005).

Pharmacokinetic profile:
Bioavailability: Absorption is rapid. Bioavailability is greater than 50% and has not been found to be affected by food. Protein binding: Very high, for clopidogrel and its main circulating metabolite (98% and 94%, respectively). Binding is nonsaturable in vitro up to a concentration of 100 micrograms per ml.
Metabolism: Hepatic
Half-life: 2hrs, 7-8hrs (inactive metabolite)
Onset of action: Dose-dependent inhibition of platelet aggregation. After single dose - 2hours, after repeated doses of 75mg - On the first day
Peak plasma concentration: Approximately 3mg per liter (carboxylic acid derivative) after repeated doses of 75 mg.
Time to peak plasma concentration: Steady-state inhibition of platelet aggregation with repeated doses of 75 mg per day usually occurs between day 3 and day 7.
Duration of action: Platelet aggregation and bleeding time gradually return to baseline levels within about 5 days after treatment is withdrawn.
Elimination: 50% Renal, 46% Biliary excretion

POLYMER PROFILES
Polyethylene oxide (PEO)

Structural formula
**Functional Category:** Polyethylene oxide (PEO) is used as a matrix binder for tablets and capsules.

**Applications:** Extended release.

**Description:** It is a white, tasteless, free flowing powder.

**Melting point:** 68°C

**Solubility:** Polyethylene oxide (PEO) is soluble in water.

**Molecular Weight:** 100000-700000.

**Stability and Storage Conditions:** Polyethylene oxide (PEO) is stored in a well-closed air tight light resistance container in a cool, dry place (Raymond et al., 2009).

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**Hydroxypropyl methyl cellulose**

![Structural formula](image)

R is H, CH₃, or CH₃CH(OH)CH₂

**Structural formula**

**Functional Category:** Coating agent; extended release agent.

**Applications:** Tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations.

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

**Glass transition temperature:** 170–180°C.

**Melting point:** 190–200°C.

**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. Few grades of HPMC are soluble in acetone, mixtures of dichloromethane and propanol, and other solvents (Yamashita et al., 2003).

**Viscosity:** Wide range viscosity grades are available in the market.
**Stability and Storage Conditions:** Hypromellose powder is a stable material, although it is hygroscopic after drying.

**Hydroxypropyl methyl cellulose Phthalate**

![Structural formula]

**Functional Category:** Coating agent; extended release agent.

**Applications:** Tablet enteric coating agent, film-coating, and as a matrix for use in extended-release tablet formulations.

**Description:** Hypromellose phthalate occurs as white to slightly off-white, free-flowing flakes or as a granular powder. It is tasteless and odorless or slightly acidic odor. Glass transition temperature: 133–137°C.

**Melting point (MP):** 150°C.

**Solubility:** Readily soluble in a mixture of acetone and methyl or ethyl alcohol (1: 1), in a mixture of methyl alcohol and dichloromethane (1: 1), and in aqueous alkali. It is insoluble in water and dehydrated alcohol and slightly soluble in acetone (Sertsou et al., 2002).

**Viscosity:** Wide range viscosity grades are available in the market.

**Stability and Storage Conditions:** Hypromellose phthalate is chemically and physically stable at ambient temperature for at least 3–4 years and for 2–3 months at 40°C and 75% relative humidity. It is stable on exposure to UV light for up to 3 months at 25°C and 70% relative humidity.

**Carbopol 971P**

![Structural Formula]
**Functional Category:** Controlled release in tablets, bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications, topical lotions, creams and gels, oral suspensions and transdermal gel reservoirs.

**Description:** Fluffy, white, mildly acidic polymer.

**Glass transition temperature:** 100–105°C

**Moisture:** 2%

**Specific gravity:** 1.41

**pH in 1 % Water:** 2.5-3.0

**Solubility:** Carbomers readily absorb water, get hydrated and swell. Its hydrophilic nature and cross-linked structure makes Carbopol a potential candidate for use in controlled release drug delivery systems (Amsellem et al., 1998).

**Viscosity:** Wide range viscosity grades are available in the market.

**Stability and Storage Conditions:** Store in a dry area and close container when not in use.

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**Xanthan Gum**

![Xanthan Gum Structure](image)

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

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

**Melting point:** Charts at 270°C.

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

**Viscosity (dynamic):** 1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

**Applications:** 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. Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets (Billa et al., 2000).

**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.

**Sodium Alginate**

**Functional Category:** Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

**Applications:** Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant; it has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions. In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions (Raymond et al., 2009).

**Description:** Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored Powder.

**Solubility:** Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other
organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water and to form a viscous colloidal solution

**Pectin**

![Pectin structure](image)

**Functional Category:** Adsorbent; emulsifying agent; gelling agent; thickening agent; stabilizing agent.

**Applications in Pharmaceutical Formulation or Technology:**
Pectin has been used as an adsorbent and bulk-forming agent, and is present in multi ingredient preparations for the management of diarrhea, constipation, and obesity; it has also been used in a colon biodegradable pectin matrix with a pH-sensitive polymeric coating, which retards the onset of drug release, overcoming the problems of pectin solubility in the upper GI tract.

**Description:** Pectin occurs as a coarse or fine, yellowish-white, odorless powder that has a mucilaginous taste.

**Solubility:** soluble in water; insoluble in ethanol (95%) and other organic solvents.

**Stability and Storage Conditions:** Pectin is a non reactive and stable material; it should be stored in a cool, dry place.

**Chitosan**

![Chitosan structure](image)

**Functional Category** Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity-increasing agent.
Applications in Pharmaceutical Formulation or Technology:
Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications, use as a component of mucoadhesive dosage forms, rapid release dosage forms, colonic drug delivery systems and use for gene delivery.

**Description**  Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look 'cottonlike'

**Solubility:** Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids.