CHAPTER-4

Drug & Excipient profile

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4.0. DRUG PROFILE [27, 28, 29, 30, 31]

4.1. ISRADIPINE

Drug : ISRADIPINE

Solubility : Practically insoluble in water

Physical state : Solid

Melting point : 168-170 °C

CASNO : 75695-93-1

Structure:

![Chemical Structure of ISRADIPINE]

Molecular formula : C_{19}H_{21}N_{3}O_{5}

Molecular weight : Average: 371.3871, Monoisotopic: 371.148120797

Bioavailability : 15%-24%.

Half-life : 8 hours

Protein binding : 95%

Dose : 2.5mg-10mg

Category:

- Antihypertensive Agents
- Vasodilator Agents
- Calcium Channel Blockers
Pharmacokinetic Properties

Absorption and Bioavailability

Though Isradipine is absorbed up to 90%-95% it undergoes very extensive first-pass metabolism. This results in fall of bioavailability to 15%-24%.

Distribution

It is not known whether isradipine is distributed into milk.

Metabolism and Elimination

It undergoes hepatic metabolism completely before it gets excreted. Drug in its unchanged form cannot be seen in urine. Around 60% to 65% of given dose is excreted through urine and about 25% to 30% is lost in the feces.

Mechanism of Action

Isradipine is an example of calcium channel blockers (CCBs) and chemically it is a dihydropyridine (DHP). In *homosapiens*, calcium channels are of five types of namely L type, N type, P/Q type, R type and T-type. CCBs act on L-type channels present in muscle cells to mediate their contraction. Isradipine stabilizes the inactive state of calcium channels by directly binding on them. Depolarization in arterial smooth muscle is longer when compared to those in cardiac muscle; the number of inactive channels is more in smooth muscle cells. Isradipine is more selective to arteries due to alternative splicing in alpha-1 subunit of calcium channel. When used within sub toxic levels, Isradipine has very meager effect on myocardial cells and conduction cells.

Adverse Effects

Lightheadedness or fainting, shortness of breath, especially from minimal physical activity, swelling in the hands and feet, rapid and/or heavy heartbeat, Chest pain, dizziness, warmth, redness, or tingly feeling under your skin, headache weakness, tired feeling, nausea, vomiting, diarrhea, upset stomach, skin rash or itching.

Storage

Tight, light-resistant containers at 20–25°C.
4.2. NIMODIPINE

IUPAC name: 3-(2-methoxyethyl) 5-propan-2-yl 2, 6-dimethyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate

Synonyms: Nimotop, Periplus, Nimodipinum, Nimodipino, Nimodipine,

Solubility: Soluble in methanol (62.5 mg/ml), DMSO (25 mg/ml), dioxane, water (24.3 mg/L) at 25 °C, and ethanol (10 mM). Insoluble in 2-hydroxypropyl-b-cyclodextrin

Description:
Nimodipine is a 1,4-dihydropyridine. It belongs to class of calcium channel blockers. It stabilizes inactive state of L-type calcium channels (voltage sensitive) especially those present on cells of vascular smooth muscles. Nimodipine inhibits calcium influx and prevents contraction of smooth muscles as well as vasoconstriction. Nimodipine greatly affects cerebral circulation when compared to peripheral circulation. It can improve neurologic outcome in case of subarachnoid hemorrhage arisen as a result of ruptured intracranial aneurysm.

Melting point: 125 °C

CAS NO: 66085-59-4

Structure:

Molecular formulae: C_{21}H_{26}N_{2}O_{7}

Bioavailability: 13% (Oral)

Molecular weight: Average: 418.4403
Mono isotopic: 418.174001196 g/mol.

Half-life: 1.7-9 hours

Protein binding: 95%
Dosage forms: tablet, capsule (liquid filled).

Dose: 30mg, 60mg/ml.

Category:
- Antihypertensive agents,
- Vasodilator agents,
- Calcium channel blockers

Pharmacodynamics

Nimodipine is a calcium channel blocker. It can improve neurologic outcome in case of subarachnoid hemorrhage arisen as a result of ruptured intracranial aneurysm in patients who are in good neurological condition post-ictus (e.g., Hunt and Hess Grades I-III). It reduces both occurrence and severity of ischemic defects. Cells of smooth muscles require calcium ions for contraction. Nimodipine prevents calcium entry during depolarization to inhibit smooth muscle contraction. Nimodipine is more selective towards cerebral arteries than other arteries in the body. This is because of its high lipophilicity so that it easily crosses blood brain barrier.

Mechanism of Action

Nimodipine inhibits calcium influx across voltage sensitive calcium channels and also through receptors that control slow calcium ion channels located on the cell membranes of neuronal cells, cells of vascular smooth muscles and myocardial cells. Nimodipine selectively binds on voltage sensitive L-type calcium channels. Vascular smooth muscle contraction is prevented due to inhibition of calcium influx. In patients with subarachnoid hemorrhage, Nimodipine causes dilation of cerebral resistance vessels. As a result collateral circulation increases that deposit as clinical effect.

Pharmacokinetic Properties

Absorption: Nimodipine has rapid absorption rate on oral administration. Within one hour maximum concentrations are attained. On intravenous injection 100% bioavailability can be attained and bioavailability of 3-30% is seen in case of oral administration owing to its high first-pass metabolism.

Metabolism: Hepatic metabolism via CYP 3A4.
Elimination: Nimodipine is completely metabolized and is eliminated as metabolite. Less than 1% of drug in its unchanged form can be recovered from urine. Many inactive or less active metabolites are identified in urine.

Adverse effects: Itching, thrombocytopenia, congestive heart failure, gastrointestinal hemorrhage, diaphoresis, neurological deterioration, vomiting, decrease in platelet count, deep vein thrombosis, hyponatremia and disseminated intravascular coagulation.

Storage: Store at 4° C
4.3. AZILSARTAN MEDOXOMIL

IUPAC Name: (5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl 2-ethoxy-1-((4-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)phenyl]phenyl)methyl)-1H-1,3-benzodiazole-7-carboxylate

Synonyms: Azilsartan kamedoxomil, Azilsartan, Azilsartanum medoxomilum, Edarbi.

Solubility: Soluble to 100 mM in DMSO, insoluble in water

Description: Azilsartan medoxomil is an angiotensin II receptor antagonist used for treating mild-moderate hypertension. Azilsartan medoxomil is a prodrug of Azilsartan, the marketed name of “Edarbi” by Takeda. Azilsartan medoxomil is superior of olmesartan & valsartan for lowering blood pressure in humans.

Melting point: 212-214°C

CAS NO: 147403-03-0

Structure:

![Structure of Azilsartan Medoxomil](image)

Molecular formula: C_{30}H_{24}N_{4}O_{8}

Molecular weight: Average: 568.5336 Monoisotopic: 568.159413764 g/mol.

Bioavailability: 60%

Half-life: 11 hours, 5 days required to obtain steady state

Protein binding: Azilsartan medoxomil is 99% plasma protein bound.

Dosage forms: tablet

Dose: 40,80mg

Category: Angiotensin receptor antagonists
**Pharmacodynamics**

Azilsartan medoxomil decrease the pressor effect of angiotensin II and aldosterone, while angiotensin I, angiotensin II, and renin are increased.

**Mechanism of Action**

Azilsartan medoxomil blocks the angiotensin II type 1 receptor preventing angiotensin II from binding and causing vasoconstriction. Azilsartan's ability to remain tightly bound to AT1 receptors for very long periods after drug washout is among its most unusual features.

**Pharmacokinetic Properties**

Absorption: Azilsartan medoxomil is hydrolyzed to the active metabolite in GIT. The food presence will not alter oral absorption of drug, Bioavailability is 60% for drug. Optimum plasma concentration reaches in 1.5-3 hours.

Distribution: Vd of drug is 16L.

Metabolism: Drug is metabolized by CYP2C9, It decarboxylases of azilsartan to M-I and O-dealkylation of drug to M-II, M-I and M-II has no pharmacological activity.

Elimination: Renal clearance of drug is 2.3 L/minute.

**Adverse Effects**

Feeling like you might pass out, urinating less or not at all, confusion, loss of appetite, vomiting, pain in your side or lower back, swelling, rapid weight gain, diarrhea, nausea, cough, muscle spasm, mild dizziness, weakness, tired feeling.

**Storage**

Store at room temperature
4.4. EXCIPIENT PROFILE [32, 33]

- Hydroxy Propyl Methyl Cellulose (HPMC)

Nonproprietary names:
- BP : Hypromellose
- PhEur : Methylhydroxypropylcellulose
- USP : Hydroxy propyl methyl cellulose

Synonyms: HPMC, Methocel, Methyl cellulose propylene glycol ether, Methyl hydroxyl propyl Cellulose, Metolose, Pharmacoat, Cellulose, Hydroxy propyl methyl ether, Culminal MHPC; E464.

IUPAC name: \((2r,3r,4s,5r,6r)-2,3,4\text{-trimethoxy-6-}(\text{methoxymethyl})-5-((2s,3r,4s,5r,6r)-3,4,5\text{-trimethoxy-6-}(\text{methoxymethyl})\text{oxan2yl})\text{oxyxane; 1-}((2r,3r,4s,5r,6s)-3,4,5\text{-tris(2-hydroxypropoxy)-6-}((2r,3r,4s,5r,6r)-4,5,6\text{-tris(2-hydroxypropoxy)-2-(2-hydroxypropoxy methyl) oxan-3-yl})\text{methoxy propoxy methyl) oxan-3-yl})\text{methoxy) propan-2-ol.}

Molecular formula: \(C_{12}H_{23}O_6(C12H22O5)n\)

Structural formula:

\[
\text{Where } R \text{ is } H, \text{ CH}_3 \text{ or } \text{CH}_3 \cdot \text{C} \cdot \text{H(OH)} \cdot \text{CH}_2
\]

Molecular weight: 10,000 - 15,000

Description: Hydroxy propyl methyl cellulose is a tasteless, and white to slightly off white to slightly off white, fibrous or granular powder.

Melting Point: Browns at 190-200\(^\circ\)C, chars at 225-230\(^\circ\)C

Solubility: Soluble in cold water, practically insoluble in chloroform, ethanol (95%) & ether but soluble in mixture of ethanol & dichloromethane.
**Functional category:** Tile adhesives, cement renders, gypsum products, pharmaceutical, paints & coatings, food, cosmetics, detergents & cleaners, eye drops.

**Stability and storage:** It is stable although it is slightly hygroscopic. The bulk material is stored in a cool and dry place in an airtight container. Increased in temperature reduces the viscosity of the solution.

- **Eudragit S 100**

  **Structure:**

  ![Chemical structure of Eudragit S 100](image)

  For Eudragit S: \( R_1, R_3 = \text{CH}_3 \)
  \[ R_2 = \text{H} \]
  \[ R_4 = \text{CH}_3 \]

  **Chemical name:** Poly (methacrylic acid, methyl methacrylate) 1:2

  **Types:** Eudragit S 12.5, Eudragit S 12.5 P

  **Description:** Fine white powder or creamy-white granules

  **Solubility:** Soluble in acetone and alcohols. Soluble in intestinal fluid from pH 7

  **Density:** 0.831–0.852 g/cm³

  **Viscosity:** 50–200 mPa

  **Stability:** Dry powder polymer films are stable at temperatures less than 30°C. Above this temperature, powder tends to form lumps. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

  **Uses:**

  1. Film forming agent
  2. In the preparation of sustained release dosage forms.
Eudragit L 100

Chemical name: Poly (methacrylic acid, methyl methacrylate) 1:1

Structure:

\[
\begin{align*}
R_1, R_3 &= \text{CH}_3 \\
R_2 &= \text{H} \\
R_4 &= \text{CH}_3
\end{align*}
\]

Types: Eudragit L 12.5, Eudragit L 12.5 P

Description: Creamy-white granules

Solubility: Acetone, alcohols, Soluble in intestinal fluid from pH 6

Density: 0.831–0.852 g/cm³

Viscosity: 50–200 mPa

Stability: Dry powder polymer films are stable at temperatures less than 30°C. Above this temperature, powder tends to form lumps.

Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Uses:

1. Film forming agent
2. In the preparation of sustained release dosage forms
MAGNESIUM STEARATE

Non proprietary names

- **BP**: Magnesium stearate
- **JP**: Magnesium stearate
- **PhEur**: Magnesiistearas
- **USPNF**: magnesium stearate

**Synonyms**:
Magnesium salt of octadecanoic acid (octadecanoate), Magnesium salt of stearic acid

**IUPAC name**: Magnesium octadecanoate

**Structure**:

![Chemical Structure](image)

**Chemical formula**: Mg(C\(_{18}H_{35}O_2\))

**Molecular weight**: 591.27 g/mol

**Functional category**: Tablet and capsule lubricant

**Description**:
- Color: Light white
- Odour: Faint stearic acid like odour
- Taste: Characteristic
- Appearance: It is a very fine powder with low bulk density. The powder readily sticks to skin and is greasy to touch.

**Solubility**: Insoluble in ethanol, water and ether. It is slightly soluble in warm ethanol (95%) and warm benzene.
Applications: It finds profound use in foods, pharmaceutical formulations and cosmetics like barrier creams. It is mainly used as a lubricant in tablet and capsule formulation usually within the concentration range of 0.25% and 5.0% W/W.

Storage: Store in a dry place away from direct sunlight.

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**MICRO CRYSTALLINE CELLULOSE**

Non Proprietary names: Avicel, emcocel and tabulose.

Description: White coloured, odourless, taste less, crystalline powder, composed of porous particles

Iupacname: 4-o-((1s)-hexopyranosyl)-D-glycero-hexopyranose.

Structure:

![Chemical structure of MICRO CRYSTALLINE CELLULOSE](image)

Chemical formula: \((\text{C}_6\text{H}_{10}\text{O}_5)_n\)

Molecular weight: 2.01588 g/mol

Solubility: It is insoluble in water, slightly soluble in 5% w/v sodium hydroxide solution.

Melting point: 260 – 270°C

Functional category: Adsorbent, suspending agent diluent, disintegrant.

Storage conditions: Should be stored in well closed container in cool and dry place.
TALC

Chemically it is magnesium silicate, hydrated and purified. Molecular formula is Mg₆(Si₂O₅)₆(OH)

Proprietary names: Also called Hydrous magnesium calcium silicate, purified french chalk hydrous magnesium calcium silicate soapstone, hydrous magnesium calcium silicate; steatite, powdered talc; purified french chalk.

Description:
- Colour: White to greyish white
- Odour: Odour less
- Taste: Tasteless
- Appearance: Fine, crystalline powder. free from gritty particles. readily sticks to skin and unctuous and soft to the touch.

Chemical formula: Mg₃Si₄O₁₀(OH)₂

Molecular structure:

![Molecular structure of Talc](image)

IUPAC name: Trimagnesiumdioxido(oxo)silanehydroxy-oxido-oxosilane

Functional category: Anti caking agent, glidant, tablet and capsule diluent.

Melting point: 800 °C

Molecular weight: 379.27 g/mol

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

Storage conditions: It is stored in a container which is tightly closed and kept in a dry place.

Incompatible: Incompatible with quaternary ammonium compounds.
Table 4.1: List of Materials Used

<table>
<thead>
<tr>
<th>Name of the material</th>
<th>Source</th>
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<tbody>
<tr>
<td>Azilartan medoximil</td>
<td>Natco LABS</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Natco LABS</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Natco LABS</td>
</tr>
<tr>
<td>Methocel K100LV CR</td>
<td>Signet Chemical Corporation, Mumbai, India.</td>
</tr>
<tr>
<td>Ethocel 7F P</td>
<td>Merck Specialities Pvt Ltd, Mumbai, India.</td>
</tr>
<tr>
<td>CMEC</td>
<td>Merck Specialities Pvt Ltd, Mumbai, India.</td>
</tr>
<tr>
<td>Eudragit</td>
<td>Merck Specialities Pvt Ltd, Mumbai, India.</td>
</tr>
<tr>
<td>Carbopol</td>
<td>Merck Specialities Pvt Ltd, Mumbai, India.</td>
</tr>
<tr>
<td>HPMC</td>
<td>Merck Specialities Pvt Ltd, Mumbai, India.</td>
</tr>
<tr>
<td>Talc</td>
<td>Merck Specialities Pvt Ltd, Mumbai, India.</td>
</tr>
<tr>
<td>Mg. stearate</td>
<td>Signet Chemical Corporation, Mumbai, India.</td>
</tr>
<tr>
<td>Aerosil</td>
<td>Signet Chemical Corporation, Mumbai, India.</td>
</tr>
<tr>
<td>MCC</td>
<td>Signet Chemical Corporation, Mumbai, India.</td>
</tr>
<tr>
<td>Di calcium phosphate</td>
<td>Signet Chemical Corporation, Mumbai, India.</td>
</tr>
</tbody>
</table>

Table 4.2. List of Equipment’s used

<table>
<thead>
<tr>
<th>Name of the Equipment</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighing Balance</td>
<td>Wensar</td>
</tr>
<tr>
<td>Tablet Compression Machine</td>
<td>Karnavathi</td>
</tr>
<tr>
<td>Hardness tester</td>
<td>Sisco, Mumbai, India.</td>
</tr>
<tr>
<td>Vernier calipers</td>
<td>Mitutoyo, Japan</td>
</tr>
<tr>
<td>Roche Friabilator</td>
<td>Labindia, Mumbai, India</td>
</tr>
<tr>
<td>Dissolution Apparatus</td>
<td>Labindia, Mumbai, India</td>
</tr>
<tr>
<td>UV-Visible Spectrophotometer</td>
<td>Labindia, Mumbai, India</td>
</tr>
<tr>
<td>pH meter</td>
<td>Labindia, Mumbai, India</td>
</tr>
<tr>
<td>FT-IR Spectrophotometer</td>
<td>Per kin Elmer, UnitedStates of America</td>
</tr>
</tbody>
</table>