CHAPTER 3

DRUG AND POLYMER PROFILE

3.1 Nisoldipine drug profile

Description: Nisoldipine is a 1,4 –dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, Nisoldipine prevents calcium dependent smooth muscle contraction and subsequent vasoconstriction. Nisoldipine may be used alone or in combination with other agents in the management of hypertension.[39]

Categories: Antihypertensive agent, Vasodilator, Calcium channel blocker

Chemical Structure:

![Chemical Structure](image)

**IUPAC Name:** Isobutyl methyl, 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

**Chemical formula:** C_{20}H_{24}N_{2}O_{6}

**Molecular weight:** 388.42

Brand names: Baymycard, NisocorSular (First Horizon) Syscor, Zadipina

**t ½:** 7-12 hours
\[\lambda_{\text{max}} \text{ VALUE : } 237\text{nm}\]

**Assay (HPLC):** 98.0 - 102.0%

**Melting Point:** 150-155°C

**Absolute bioavailability:** 5%

**Mechanism of action:** Nisoldipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.[40]

**Storage:** The drug is photosensitive so it should be protected from light and stored below 30°C.

**Pharmacokinetics**

**Absorption:** Relatively well absorbed from GI tract. High fat foods significantly affect release of drug from the coat core formulation.

**Distribution:** About 99% plasma protein bound.

**Metabolism:** Extensively metabolized with five major metabolites identified.

**Excretion:** Excreted in urine: half-life ranges from 7 to 12 hours.

**Interactions**

**Drug-drug**

**Cimetidine:** Increased bioavailability of Nisoldipine as well as increasing peak level. Use together cautiously.

**Quinidine:** Decreased bioavailability, but not peak level of nisoldipine. Advice clinician to monitor blood pressure.

**Drug food:** Grape fruit juice, high fat meals: May decrease absorption. Advice patient not to take drug with these foods.
Adverse reactions:

CNS : Headache, dizziness.

CV : Vasodilation, palpitations, chest pain, Peripheral edema.

EENT: Pharyngitis, sinusitis.

GI : Nausea.

Skin : Rash.

3.2 Amlodipine Besylate drug profile

- **Chemical Structure**

![Chemical Structure Diagram]

- **Chemical Name** 2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6- methyl-3,5- pyridinedicarboxylic acid 3-ethyl 5-methyl ester
- **Molecular weight** 567.05
- **Nature** white or light yellow crystalline powder, no foul bitter pungent.
- **Melting point** 199-201°C
- **Storage** To be stored under 25°C
- **Solubility** Poorly soluble in water and slightly soluble in Ethanol.
- **Stability:** Stored for 48 months at 25°C/60% RH for 6 months showed no significant changes.

- **Mechanism of action:**
  - Amlodipine inhibits the transmembrane influx of calcium ions, thereby it shows the vasodilator activity.
  - In cardiac tissue it have negative inotropic chronotropic and dromotropic activity.
  - It decrease peripheral vascular resistance and decrease in blood pressure.
  - It is used for the stable angina and Prinzmetal’s angina (by blocking the spasm of coronary arteries.)

- **Pharmacokinetics:**
  - Plasma Concentration: Peak level obtained in 2-4 hrs
  - Metabolism: 90% metabolised into inactive by the cytochrome P450.
  - Elimination half-life: 35-45 hrs
  - Bound in Plasma: highly protein bound primarily to albumin (90-99 %)
  - Volume of Distribution: 21.0 L/kg

- **Adverse Effects:**
  - Headache, fatigue, somnolence, dizziness, allergic reaction, flushing and dyspepsia.

- **Contraindications:**
  - I. **Absolute:**
    - Allergy to Amlodipine or any dihydropyridines
  - II. **Relative:**
    - Cardiogenic shock
• **Drug interactions:**
  ► Amlodipine with sildenafil can lead to an increase in hypotension.

• **Adult dose:**
  ► For adults 5-10mg given orally once a day.
  ► For elders 2.5mg given orally once a day.
3.3 Polymers Profile

The choice of the carrier can be influenced by the dissolution characteristics of dispersed drug significantly, because in a multi-component carrier, drug release rate of the drug from the surface is influenced by the second component. Therefore an hydrophilic carrier results in enhanced drug release from the matrix and hydrophobic carrier results in slower drug release from the matrix [41].

The carrier should possess the following characteristics

1. Rapid solubility in water and gastrointestinal fluid.
2. Physiological inertness
3. Non-toxic
4. Pharmacologically inert.
5. Chemically compatible with drug

3.4 Poloxamer 188

![Chemical structure of Poloxamer 188](image)

Non proprietary names:
- **BP:** Poloxamers
- **USP:** Poloxamer
- **PhEur:** Poloxamers

**Synonyms:** Lutrol; Monolan; Pluronic; Poloxalcol; Poloxamera.

**Chemical name:** α-Hydro-ω-hydroxypropylene (oxyethylene) poly (oxypropylene) poly-(oxyethylene) block copolymer

**Empirical formula:**
Series of closely related block copolymers of ethylene oxide and propylene oxide confirming to the general formula HO(C₂H₄O)a(C₃H₆O)b(C₂H₄O)aH
Description:
They are white in colour and tasteless in nature

Functional category:
Solubilizing agent, dispersing agent, wetting agent.

Table 3.1 Typical properties

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melting point</strong></td>
<td>52-57°C</td>
</tr>
<tr>
<td><strong>Density</strong></td>
<td>1.06g /cm³ at 25° C</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>1000 mpas(1000cp) as a melt at 77°C</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>P 188 Aqueous solutions are stable in acidic and alkaline medium.</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td>Poloxamer 188 freely soluble in 95% ethanol and poorly soluble in water</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>To be stored in air tight container.</td>
</tr>
</tbody>
</table>

Applications

- Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes and in the preparation of solid dispersion systems
- More recently, poloxamers have found use in drug delivery systems
3.5 Poloxamer 407

Non proprietary names:

- **BP:** Poloxamers
- **USP:** Poloxamer
- **PhEur:** Poloxamers

**Synonyms:**
Supronic, Synperonic, Poloxalcol, Poloxamera.

**Chemical name**
α-Hydro-ω-hydroxy poly (oxyethylene) poly (oxypropylene) poly-(oxyethylene) block copolymer

**Empirical formula**
Series of closely related block copolymers of ethylene oxide and propylene oxide confirming to the general formula \( HO(C_2H_4O)^a(C_3H_6O)^b(C_2H_4O)^a \)

**Description:**
Poloxamers generally occurs as white, waxy, free flowing and tasteless.

**Functional category:**
Solubilizing agent, dispersing agent, wetting agent.
Table 3.2 Typical properties of Poloxamer 407

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidity / alkalinity</td>
<td>pH 5.0 to 7.4 for a 2.5% w/v aqueous solution</td>
</tr>
<tr>
<td>Density</td>
<td>1.06g/cm³ at 25°C</td>
</tr>
<tr>
<td>Viscosity</td>
<td>1000 mpas (1000cp) as a melt at 77°C for P 407</td>
</tr>
<tr>
<td>Stability</td>
<td>P 407 Aqueous solutions are stable in acidic medium</td>
</tr>
<tr>
<td>Solubility</td>
<td>Poloxamer 407 is freely soluble in 95% ethanol, water and propan-2-ol.</td>
</tr>
<tr>
<td>Storage</td>
<td>Bulk materials should be stored in air tight container</td>
</tr>
</tbody>
</table>

Applications
Poloxamer 407 is used as an emulsifying agent and wetting agent in many of the pharmaceutical preparations.

- Poloxamer 407 is used as solution for contact lenses.