Chapter-2

Drug Profile
2. DRUG PROFILE

2.1 Criteria for Selection of Drug:
A wide range of drugs have been incorporated within PLO for transdermal delivery. The skin is, however, a good barrier to drug permeation and drug flux is known to be low. In fact, drug absorption following application to the skin is so low that only a few drugs have been formulated for transdermal delivery.

An ideal drug for transdermal delivery is:
- A potent chemical with a daily dose of a few milligrams.
- A small molecule.
- One that has a high lipid solubility and reasonable water solubility.
- Non-irritating and non-sensitizing to the skin.
- Drug having short half-life.
- Drug should not be metabolized in the skin itself while permeating through it.

2.2 Drug profile
A. Lornoxicam

Lornoxicam (chlortenoxicam) is a strong analgesic and anti-inflammatory NSAID of the oxicam class with better tolerability profile when compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. Studies have shown that it is more effective than 10 mg morphine when used at doses \( \geq \) 8 mg to control pain. It has been shown to be effective in the treatment of postoperative pain and rheumatoid arthritis (RA).

**IUPAC Name**: 6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno-[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide

**Chemical formula**: \( \text{C}_{13}\text{H}_{10}\text{ClN}_{3}\text{O}_{4}\text{S}_{2} \)

**Chemical weight**: 371.82

**Molecular Structure**:

![Molecular Structure Image]
**Properties:** Orange to yellow crystals

**Melting point:** mp 225-230° (dec)

**pKa:** 4.7

**Log P** \((n\text{-octanol/pH 7.4 buffer})\): 1.8

**Absorption maximum:** 371 nm

**Bioavailability** (after i. m. administration): 97%

**Half life:** 3-4 hrs.

**Mode of action:**
Like other NSAIDs, lornoxicam inhibits prostaglandin biosynthesis by blocking the enzyme cyclooxygenase. Lornoxicam inhibits both isoforms in the same concentration range, that is, COX-1 inhibition: COX-2 inhibition = 1. It readily penetrates into the synovial fluid. Synovial fluid: plasma AUC ratio is 0.5 after administration of 4 mg twice daily.

**Pharmacokinetics:**
Absorption: Lornoxicam is absorbed rapidly and almost completely from the gastrointestinal tract. Maximum plasma concentrations are achieved after approximately 1 to 2 hours.

Distribution: The absolute bioavailability of Lornoxicam is 90-100%. No first-pass effect was observed.

Metabolism: Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The hydroxylated metabolite exhibits no pharmacological activity. CYP2C9 has been shown to be the primary enzyme responsible for the biotransformation of the lornoxicam to its major metabolite, 5’-hydroxylornoxicam.
Recently, it was reported that lornoxicam 5’-hydroxylation by the variant CYP2C9*3 and CYP2C9*13 was markedly reduced compared with wild type, both in vitro and in vivo.

Elimination: Approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance.

**Dosage:**
8 mg-16 mg per day in 2-3 doses. The total daily dose should not exceed 16 mg.

**Uses:**
Lornoxicam is a non-steroidal anti-inflammatory drug of the oxicam class, with analgesic, anti-inflammatory and antipyretic properties. It is available in oral and parenteral formulations.

**B. Flurbiprofen**
Flurbiprofen, which is a member of the phenylalkanoic acid derivative group of non-steroidal anti-inflammatory drugs used to treat the inflammation and pain of arthritis. Flurbiprofen is a racemic mixture of (+)s- and (-)r- enantiomers. Flurbiprofen is a white or slightly yellow crystalline powder. It is slightly soluble in water at pH 7.0 and readily soluble in most polar solvents.

**Chemical formula:** 2-(3-fluoro-4-phenylphenyl) propanoic acid

**Chemical formula:** C_{15}H_{13}FO_{2}

**Chemical weight:** 244.26

**Properties:** White or slightly yellow crystalline powder

**Melting point:** 110-112°C
Molecular Structure:

![Molecular Structure Image]

Absorption maximum: 248 nm

Bioavailability (oral): 94%

Half life: 3-4 hrs.

Pharmacokinetics:

Absorption:
The mean oral bioavailability of flurbiprofen from ansaid (flurbiprofen) tablets 100 mg is 96%. Flurbiprofen is rapidly and non-stereoselectively absorbed, with peak plasma concentrations occurring at about 2. Administration of flurbiprofen with either food or antacids may alter the rate but not the extent of flurbiprofen absorption. Readily absorbed from the gut (oral); peak plasma concentrations after 1-2 hours.

Distribution:
The apparent volume of distribution of both flurbiprofen enantiomers are more than 99% bound to plasma proteins, primarily albumin. Plasma protein binding is relatively constant for the typical average steady-state concentrations (≤ 10 g/ml) achieved with recommended doses. Flurbiprofen is poorly excreted into human milk.

Metabolism
Several flurbiprofen metabolites have been identified in human plasma and urine. These metabolites include 4'-hydroxy-flurbiprofen, 3’, 4'-dihydroxy-flurbiprofen, 3'-hydroxy-4'-methoxyflurbiprofen, their conjugates, and conjugated flurbiprofen. Unlike other arylopropionic acid derivatives (eg ibuprofen), metabolism of r-flurbiprofen to s-flurbiprofen is minimal. In vitro studies have demonstrated that
cytochrome p4502c9 (cyp2c9) plays an important role in the metabolism of flurbiprofen to its major metabolite 4’-hydroxy-flurbiprofen the total plasma clearance of unbound flurbiprofen is not stereoselective, and clearance of flurbiprofen is independent of dose when used within the therapeutic range.

**Excretion:**
Less than 3% of flurbiprofen is excreted unchanged in the urine, with about 70% of the dose eliminated in the urine as flurbiprofen, 4’-hydroxy-flurbiprofen, and their acyl-glucuronide conjugates. Renal elimination is a significant pathway of elimination of flurbiprofen metabolites. The mean terminal disposition half-lives (t½) of r- and s-flurbiprofen are about 4.5 and 5.5 hours.

**Uses:**
Flurbiprofen is used for musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and in peri-articular disorders such as bursitis and tendinitis. Also used in treatment of migraine headaches and prophylaxis. It is used for postoperative pain, painful and inflammatory conditions such as acute gout or soft tissue disorders and to reduce fever.

Flurbiprofen is known by the following **tradenames**: ansaid, marketed by pfizer, and froben, by abbott.

**C. Acelofenac**

**Chemical name:** 2-[[2-[(2,6dichlorophenyl) amino]phenyl acetyl ]oxy]acetic acid.

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

**Structural formula:**

![Structural formula of Acelofenac]

**Molecular Weight:** 354.2
Appearance: It is a white or almost white crystalline powder

Clinical Pharmacology:
Mode of Action:
Aceclofenac directly blocks PGE\textsubscript{2} secretion at the site of inflammation by inhibiting IL-Beta & TNF in the inflammatory cells (Intracellular Action) stimulates the synthesis of the extracellular matrix of the Human Articular Cartilages inhibits Neutrophil Adhesion & Accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of Neutrophils.

Pharmacokinetics
Aceclofenac after oral administration, Aceclofenac is rapidly absorbed and the bioavailability is almost 100%. Peak plasma concentrations are reached approximately 1.25 to 3 hours following ingestion. $t_{\text{max}}$ is delayed with concomitant food intake whereas the degree of absorption is not influenced. Aceclofenac is highly protein-bound (> 99.7%). Aceclofenac penetrates into the synovial fluid where the concentrations reach approximately 60% of those in plasma. The volume of distribution is approximately 30L.

The mean plasma elimination half-life is 4-4.3 hours. Approximately two-thirds of the administered dose is excreted via the urine, mainly as conjugated hydroxymetabolites. Only 1% of an oral single dose is excreted unchanged. Aceclofenac is probably metabolized via CYP2C9 to the main metabolite 4-hydroxyAceclofenac

Oral Bioavailability: Aceclofenac have almost 100% bioavailability.

Mean plasma Concentration ($C_{\text{max}}$):
Peak plasma concentrations are reached approximately 1.25 to 3 hours following ingestion $T_{\text{max}}$ is delayed with concomitant food intake whereas the degree of absorption is not influenced.

Elimination Half Life ($T_{1/2}$): Aceclofenac 4-4.3 Hours

Plasma Protein Binding: Aceclofenac is highly protein-bound (> 99.7%)
**Excretion:** Aceclofenac Approximately two-thirds of the administered dose is excreted via the urine, mainly as conjugated hydroxymetabolites. Only 1% of an oral single dose is excreted unchanged.

**Metabolites:** Aceclofenac is probably metabolized via CYP2C9 to the main metabolite 4-hydroxyAceclofenac

**Dosage and Administration:** The usual dose of Aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening. There is no evidence that the dosage of Aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDS caution should be exercised.

**Drug Interactions:**
Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anticoagulant, inhibits the activity of diuretics, enhance cyclosporin nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. Furthermore, hypo or hyperglycaemia may result from the concomitant administration of Aceclofenac and antidiabetic drugs, although this is rare. The co administration of Aceclofenac with other NSAIDS of corticosteroids may results in increased frequency of adverse event.

**Adverse Drug Reaction:** Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Most common events include dyspepsia (7.5%), abdominal pain (6.2%), nausea (1.5%), diarrhea (1.5%), flatulence (0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), ulcerative stomatitis (0.1%), pancreatitis (0.1%).

**D. Piroxicam**\(^{102-103}\)

- **Trade name:** Feldene
Structure

Molecular formula: $C_{15}H_{13}N_3O_4S$

IUPAC name: 4-Hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Mol. Wt: 331.35

Melting point: 198-200°C

Partition coefficient: 3

Physical Parameter:
- State: Solid
- Optical rotation: $+210°$ ~ $+217°$
- Loss on drying: 0.5% max
- Heavy metal: 20ppm max
- Density: 1.481 g/cm$^3$.

Stability: Stable at normal temperatures and pressures

Incompatibilities: Strong oxidizing agents.

 Decomposition: Carbon monoxide, CO$_2$, Nitrogen oxides, Sulfur oxides.

Solubility: Slightly soluble in ethanol (95%) and in aqueous alkaline solution; very slightly soluble in water (23 mg/liter), in dilute acid and most organic solvents.
Physical properties: Off white to light yellow powder; odourless.

Pharmacokinetic:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.5- 6.6</td>
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<tr>
<td>Bioavailability</td>
<td>45-75 %</td>
</tr>
<tr>
<td>pka</td>
<td>6.3</td>
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<tr>
<td>Urinary excretion unchanged</td>
<td>5 %</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>99 %</td>
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<tr>
<td>Total body Clearance</td>
<td>2.1 to 5.0(mean 3.4) ml/kg/hrs</td>
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<tr>
<td>Volume of distribution</td>
<td>0.12 to .25 (mean 0.16) lit/kg</td>
</tr>
<tr>
<td>Half-life</td>
<td>44 -50 hrs</td>
</tr>
<tr>
<td>Study state conc&lt;sup&gt;a&lt;/sup&gt;</td>
<td>about 7-12 days</td>
</tr>
<tr>
<td>Peak time (hrs)</td>
<td>3 to 5 hrs</td>
</tr>
<tr>
<td>Peak conc&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5 to 2 mcg /ml(single dose)</td>
</tr>
<tr>
<td></td>
<td>3to 8 mcg/ml (multiple doses)</td>
</tr>
</tbody>
</table>

Clinical pharmacology:

Pharmacodynamics:

Piroxicam is in a class of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). Piroxicam works by reducing hormones that cause inflammation and pain in the body. Piroxicam is used to reduce the pain, inflammation, and stiffness caused by rheumatoid arthritis and osteoarthritis.

Pharmacokinetics:

Absorption:

Well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses and generally peak within three to five hours after medication. The prolonged half-life (50 hours) results in the maintenance of
relatively stable plasma concentrations throughout the day on once daily doses and to significant accumulation upon multiple dosing. A single with food there is a slight delay in the rate but not the extent of absorption following oral administration. The concomitant administration of antacids (aluminum hydroxide or aluminum hydroxide with magnesium hydroxide) have been shown to have no effect on the plasma levels of orally administered piroxicam.

**Distribution:**
The apparent volume of distribution of piroxicam is approximately 0.14 L/kg. 99% of plasma piroxicam is bound to plasma proteins. Piroxicam is excreted into human milk. The presence in breast milk has been determined during initial and long-term conditions (52 days). Piroxicam appeared in breast milk at about 1% to 3% of the maternal concentration. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment.

**Metabolism:**
Metabolism of piroxicam occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. In vitro studies indicate cytochrome P4502C9 (CYP2C9) as the main enzyme involved in the formation to the 5′-hydroxy-piroxicam, the major metabolite. The biotransformation products of piroxicam metabolism are reported to not have any anti-inflammatory activity.

**Excretion:**
Piroxicam and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as in the feces. Approximately 5% of a piroxicam dose is excreted unchanged. However, a substantial portion of piroxicam elimination occurs by hepatic metabolism. Piroxicam is excreted into human milk.

**Mechanism of action:**
The anti-inflammatory effect of Piroxicam may result from the reversible inhibition of cyclooxygenase, causing the peripheral inhibition of prostaglandin synthesis. The
prostaglandins are produced by an enzyme called Cox-1. Piroxicam blocks the Cox-1 enzyme, resulting into the disruption of production of prostaglandins. Piroxicam also inhibits the migration of leukocytes into sites of inflammation and prevents the formation of thromboxane A2, an aggregating agent, by the platelets.\textit{(drugbank)}

**Indications and Usage:**
- Treatment of acute or long-term use of rheumatoid arthritis and osteoarthritis.
- Ankylosing spondylitis
- Acute gout
- Musculoskeletal injury
- Dysmenorrhoea
- Dentistry etc.

**Contraindications:**
Known allergy or hypersensitivity to aspirin, iodides, or any NSAID, including piroxicam.

**Dosage and Administration:**
Rheumatoid Arthritis, Osteoarthritis
Adults: Initiate and maintain at 10 to 20 mg/day in 1 to 2 divided doses.
**Category:** Analgesic; anti-inflammatory; antipyretic.

**Over dosage:**
Symptoms- Drowsiness, dizziness, mental confusion, disorientation, lethargy, paresthesia, numbness, vomiting, GI irritation, headache, tinnitus, seizure, etc.

**2.3 Excipient profile\textsuperscript{104-131}**

**A. Pluronic F-127**
Pluronic F-127 is a nonionic, surfactant polyol (molecular weight approximately 12,500 daltons) that has been found to facilitate the solubilization of water-insoluble dyes and other materials in physiological media. Pluronic F-127 has been used to help disperse acetoxyethyl (AM) esters of fluorescent ion indicators such as fura-2, indo-
1, fluo-3, and SBFI; it appears to be required with SBFI-AM or PBFI-AM, and optional with other indicators. Pluronic F-127 may also be useful for dispersing other lipophilic probes. Appropriate controls should be performed to make certain that Pluronic® F-127 is not altering the membrane properties of the cell. For the convenience of our customers, Invitrogen offers Pluronic F-127 in three forms.\textsuperscript{104}

**Characteristics and properties**

PF-127 is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers in a concentration ranging from 20-30%. In general, poloxamers are composed of white, waxy, free-flowing granules that are practically odorless and tasteless.

**Applications of Pluronic F-127**

The unique thermoreversible and promising drug release characteristics of PF-127 render it an attractive candidate as a pharmaceutical vehicle for drugs through different routes of administration.\textsuperscript{105}

**Topical and Dermal applications**

*Analgesic/Anti-inflammatory drugs*

Authors have suggested PF-127 gels as potential topical drug delivery systems having advantages over traditional bases in terms of ease of application, and drug release characteristics. It is interesting that many studies have focused in the development of topical/dermal formulations containing analgesic or anti-inflammatory drugs due to the fact that the possibility of delivering these drugs through the skin for local pain and inflammations at low doses is attractive. However, in many cases penetration enhancers may be present in the topical/dermal formulations because otherwise only small amounts of drug pass through the skin. Thermally reversible gels of PF-127 as vehicles for the percutaneous administration of indomethacin. *In vivo* percutaneous absorption studies using a rat model suggested that a 20% aqueous gel may be of practical use as a base for topical administration of the drug. The addition of isopropyl myristate or (+) - limonene to the gel formulation significantly improved percutaneous absorption, particularly when the gel was applied using an occlusive dressing technique.\textsuperscript{106}
B. Lecithin

Lecithin is a generic term to designate any group of yellow-brownish fatty substances occurring in animal and plant tissues composed of phosphoric acid, choline, fatty acids, glycerol, glycolipids, triglycerides, and phospholipids (e.g., phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol). Lecithin can easily be extracted chemically (using hexane) or mechanically from readily available sources such as soy beans. It has low solubility in water. In aqueous solution, its phospholipids can form either liposomes, bilayer sheets, micelles, or lamellar structures, depending on hydration and temperature. This results in a type of surfactant that is usually classified as amphipathic. Lecithin is sold as a food supplement and for medical uses. In cooking, it is sometimes used as an emulsifier and to prevent sticking, for example in nonstick cooking spray.

Molecular Structure:

![Molecular Structure Image]

Biology

Phosphatidylcholine occurs in all cellular organisms, being one of the major components of the phospholipid portion of the cell membrane.

Production

Commercial lecithin, as used by food manufacturers, is a mixture of phospholipids in oil. The lecithin can be obtained by degumming the extracted oil of seeds. It is a
mixture of various phospholipids, and the composition depends on the origin of the lecithin. A major source of lecithin is soybean oil. Because of the EU requirement to declare additions of allergens in foods, in addition to regulations regarding genetically modified crops, a gradual shift to other sources of lecithin (e.g., sunflower oil) is taking place. The main phospholipids in lecithin from soya and sunflower are phosphatidyl choline, phosphatidyl inositol, phosphatidyl ethanolamine, and phosphatidic acid. They are often abbreviated to PC, PI, PE, and PA, respectively. Purified phospholipids are produced by companies like Lipoid, VAV Life Sciences, Avanti Polar etc.\textsuperscript{108}

**Hydrolysed lecithin**

To modify the performance of lecithin to make it suitable for the product to which it is added, it may be hydrolysed enzymatically. In hydrolysed lecithins, a portion of the phospholipids have one fatty acid removed by phospholipase. Such phospholipids are called lysophospholipids. The most commonly used phospholipase is phospholipase A2, which removes the fatty acid at the C2 position of glycerol. Lecithins may also be modified by a process called fractionation. During this process, lecithin is mixed with an alcohol, usually ethanol. Some phospholipids, such as phosphatidylcholine, have good solubility in ethanol, whereas most other phospholipids do not dissolve well in ethanol. The ethanol is separated from the lecithin sludge, after which the ethanol is removed by evaporation to obtain a phosphatidylcholine-enriched lecithin fraction.\textsuperscript{109}

**Properties and applications**

Lecithin has emulsification and lubricant properties, and is a surfactant. It can be totally metabolized (see Inositol) by humans, so is well tolerated by humans and nontoxic when ingested; some emulsifiers can only be excreted via the kidneys.\textsuperscript{108} Lecithin is used for applications in human food, animal feed, pharmaceutical, paint, and other industrial applications.

Applications listed by one manufacturer, in addition to food applications, include:

- In the pharmaceutical industry, it acts as a wetting, stabilizing agent and a choline enrichment carrier, helps in emulsifications and encapsulation, and is a good dispersing agent. It can be used in manufacture of intravenous fat infusions and for therapeutic use.
• In animal feed, it enriches fat and protein and improves pelletization.
• In the paint industry, it forms protective coatings for surfaces with painting and printing ink, has antioxidant properties, helps as a rust inhibitor, is a colour-intensifying agent, catalyst, conditioning aid modifier, and dispersing aid; it is a good stabilizing and suspending agent, emulsifier, and wetting agent, helps in maintaining uniform mixture of several pigments, helps in grinding of metal oxide pigments, is a spreading and mixing aid, prevents hard settling of pigments, eliminates foam in water-based paints, and helps in fast dispersion of latex-based paints.
• Lecithin can also be used as a release agent for plastics, an antisludge additive in motor lubricants, an antigumming agent in gasoline, and an emulsifier, spreading agent, and antioxidant in textile, rubber and other industries.\textsuperscript{108}

C. Isopropyl myristate\textsuperscript{110}

**Molecular Structure:**

![Molecular Structure Image]

**Chemical formula:** Propan-2-yl tetradecanoate, Tetradecanoic acid, 1-methylethyl ester Myristic acid isopropyl ester

**Molecular formula:** $\text{C}_{17}\text{H}_{34}\text{O}_{2}$

**Molar mass:** 270.451 g/mol

**Density:** 0.85 g/cm$^3$, liquid

**Boiling point:** 167 °C (9 mmHg)

**Uses**

Isopropyl myristate is used in cosmetic and topical medicinal preparations where good absorption through the skin is desired. It is also used as a pesticide-free treatment against head lice which works by dissolving the wax that covers the exoskeleton of head lice, killing them by dehydration.
It is also the non-aqueous component of the two-phase mouthwash, Dentyl pH, where it removes bacteria from the oral cavity.

It is also used in the removal process of prosthetic makeup.

**D. Sodium sorbate**

Sodium sorbate is the Sodium salt of sorbic acid, chemical formula NaC₆H₇KO₂. Its primary use is as a food preservative (E number 202). Sodium sorbate is effective in a variety of applications including food, wine, and personal care products.

**Molecular Structure:**

![Molecular Structure of Sodium Sorbate]

**Chemical formula:** Sodium (2E,4E)-hexa-2,4-dienoate

**Chemical formula:** C₆H₇KO₂

**Chemical weight:** 134.108 g/mol

**Properties:** white crystals

**Melting point:** 270 °C (decomp.)

**Properties**

Sodium sorbate is produced by neutralizing Sodium hydroxide with sorbic acid, an unsaturated carboxylic acid that occurs naturally in some berries. The colourless salt is very soluble in water (58.2% at 20 °C).

**Production**

Sodium sorbate is produced by reacting sorbic acid with an equimolar portion of Sodium hydroxide. The resulting Sodium sorbate may be crystallized from aqueous ethanol.
Uses
Sodium sorbate is used to inhibit molds and yeasts in many foods, such as cheese, wine, yogurt, dried meats, apple cider, soft drinks and fruit drinks, and baked goods. It can also be found in the ingredients list of many dried fruit products. In addition, herbal dietary supplement products generally contain Sodium sorbate, which acts to prevent mold and microbes and to increase shelf life, and is used in quantities at which there are no known adverse health effects, over short periods of time. Labeling of this preservative on ingredient statements reads as "Sodium sorbate" and or "E202". Also, it is used in many personal care products to inhibit the development of microorganisms for shelf stability. Some manufacturers are using this preservative as a replacement for parabens.\textsuperscript{112}

Also known as "wine stabilizer", Sodium sorbate produces sorbic acid when added to wine. It serves two purposes. When active fermentation has ceased and the wine is racked for the final time after clearing, Sodium sorbate will render any surviving yeast incapable of multiplying. Yeast living at that moment can continue fermenting any residual sugar into CO\textsubscript{2} and alcohol, but when they die no new yeast will be present to cause future fermentation. When a wine is sweetened before bottling, Sodium sorbate is used to prevent refermentation when used in conjunction with Sodium metabisulfite. It is primarily used with sweet wines, sparkling wines, and some hard ciders but may be added to table wines which exhibit difficulty in maintaining clarity after fining.\textsuperscript{111}

Some molds (notably some \textit{Trichoderma} and \textit{Penicillium} strains) and yeasts are able to detoxify sorbates by decarboxylation, producing 1,3-pentadiene. The pentadiene manifests as a typical odor of kerosene or petroleum.\textsuperscript{112}

Toxicology
Sodium sorbate is a skin, eye and respiratory irritant, although some research implies it has a long term safety record and non-toxic profile.

E. Sodium benzoate\textsuperscript{113}
Sodium benzoate has the chemical formula NaC\textsubscript{6}H\textsubscript{5}CO\textsubscript{2}; it is a widely used food preservative, with E number \textbf{E211}. It is the sodium salt of benzoic acid and exists in this form when dissolved in water. It can be produced by reacting sodium hydroxide with benzoic acid.
Molecular Structure:

Molecular formula: \( \text{NaC}_6\text{H}_5\text{CO}_2 \)
Molar mass: 144.11 g/mol
Melting point: 300 °C
Boiling point: 228 °C (dec)
Acidity (pK\(_a\)): 4.202

Production

Sodium benzoate is created by adding benzoic acid to a hot concentrated solution of sodium carbonate until effervescence ceases. The solution is then evaporated, cooled and allowed to crystallize or evaporate to dryness, and then granulated.

Mechanism of food preservation

The mechanism starts with the absorption of benzoic acid into the cell. If the intracellular pH changes to 5 or lower, the anaerobic fermentation of glucose through phosphofructokinase is decreased by 95%, thereby inhibiting the growth and survival of micro-organisms that cause food spoilage.

Uses

Sodium benzoate is a preservative. It is bacteriostatic and fungistatic under acidic conditions. It is most widely used in acidic foods such as salad dressings (vinegar), carbonated drinks (carbonic acid), jams and fruit juices (citric acid), pickles (vinegar), and condiments. It is also used as a preservative in medicines and cosmetics. As a food additive, sodium benzoate has the E number E211.
It is also used in fireworks as a fuel in whistle mix, a powder that emits a whistling noise when compressed into a tube and ignited. The fuel is also one of the fastest burning rocket fuels and provides a lot of thrust and smoke. It does have its downsides: there is a high danger of explosion when the fuel is sharply compressed because of the fuel's sensitivity to impact.\textsuperscript{114}

Sodium benzoate is produced by the neutralization of benzoic acid with sodium hydroxide. Benzoic acid is detectable at low levels in cranberries, prunes, greengage plums, cinnamon, ripe cloves, and apples. Though benzoic acid is a more effective preservative, sodium benzoate is more commonly used as a food additive because benzoic acid does not dissolve well in water. Concentration as a preservative is limited by the FDA in the U.S. to 0.1\% by weight. The International Programme on Chemical Safety found no adverse effects in humans at doses of 647–825 mg/kg of body weight per day.\textsuperscript{114}

Cats have a significantly lower tolerance against benzoic acid and its salts than rats and mice. Sodium benzoate is, however, allowed as an animal food additive at up to 0.1\%, according to AFCO's official publication.\textsuperscript{114}

\textbf{F. Polyethylene glycol}\textsuperscript{115}

\textbf{Polyethylene glycol (PEG)} is a polyether compound with many applications from industrial manufacturing to medicine. The structure of PEG is (note the repeated element in parentheses): HO-CH$_2$-(CH$_2$-O-CH$_2$)$_n$-CH$_2$-OH

PEG is also known as \textbf{polyethylene oxide (PEO)} or \textbf{polyoxyethylene (POE)}, depending on its molecular weight, and under the tradename \textbf{Carbowax}.

\textbf{Molecular Structure:}
Chemical formula: poly(oxyethylene)(structure-based), poly(ethylene oxide) {source-base}

**Molecular formula**  \( C_{2n}H_{4n+2}O_{n+1} \)

**Molar mass**  variable

PEG, PEO, or POE refers to an oligomer or polymer of ethylene oxide. The three names are chemically synonymous, but historically PEG has tended to refer to oligomers and polymers with a molecular mass below 20,000 g/mol, PEO to polymers with a molecular mass above 20,000 g/mol, and POE to a polymer of any molecular mass. PEG and PEO are liquids or low-melting solids, depending on their molecular weights. PEGs are prepared by polymerization of ethylene oxide and are commercially available over a wide range of molecular weights from 300 g/mol to 10,000,000 g/mol. While PEG and PEO with different molecular weights find use in different applications, and have different physical properties (e.g. viscosity) due to chain length effects, their chemical properties are nearly identical. Different forms of PEG are also available, depending on the initiator used for the polymerization process - the most common initiator is a monofunctional methyl ether PEG, or methoxypoly(ethylene glycol), abbreviated mPEG. Lower-molecular-weight PEGs are also available as purer oligomers, referred to as monodisperse, uniform, or discrete. Very high purity PEG has recently been shown to be crystalline, allowing determination of a crystal structure by x-ray diffraction. Since purification and separation of pure oligomers is difficult, the price for this type of quality is often 10-1000 fold that of polydisperse PEG. \(^{116}\)

PEGs are also available with different geometries.

- **Branched** PEGs have three to ten PEG chains emanating from a central core group.
- **Star** PEGs have 10 to 100 PEG chains emanating from a central core group.
- **Comb** PEGs have multiple PEG chains normally grafted onto a polymer backbone.

**Production**

Polyethylene glycol is produced by the interaction of ethylene oxide with water, ethylene glycol, or ethylene glycol oligomers. The reaction is catalyzed by acidic or
basic catalysts. Ethylene glycol and its oligomers are preferable as a starting material instead of water, because they allow the creation of polymers with a low polydispersity (narrow molecular weight distribution). Polymer chain length depends on the ratio of reactants.

\[ \text{HOCH}_2\text{CH}_2\text{OH} + n(\text{CH}_2\text{CH}_2\text{O}) \rightarrow \text{HO(CH}_2\text{CH}_2\text{O)}_{n+1}\text{H} \]

**Medical uses**

PEG is the basis of a number of laxatives (e.g., macrogol-containing products, such as Movicol and **polyethylene glycol 3350**, or SoftLax, MiraLAX, or GlycoLax). Whole bowel irrigation with polyethylene glycol and added electrolytes is used for bowel preparation before surgery or colonoscopy. The preparation is sold under the brand names **GoLYTELY**, GaviLyte C, NuLytyel, GlycoLax, Fortrans, TriLyte, Colyte, Halflytely, Softlax, Lax-a-Day, ClearLax and MoviPrep. In the United States, MiraLAX and **Dulcolax Balance** are sold without prescription for short-term relief of chronic constipation, although there is now growing consensus in the medical community that these medications can be taken indefinitely to treat chronic constipation. A 2007 comparison showed that patients suffering from constipation had a better response to these two medications than to tegaserod. These medications work by softening the fecal mass and making the gut very slippery. Although very effective, fecal incontinence is a common side effect of this medication.\(^{116}\)

When attached to various protein medications, polyethylene glycol allows a slowed clearance of the carried protein from the blood. This makes for a longer-acting medicinal effect and reduces toxicity, and allows longer dosing intervals. Examples include PEG-interferon alpha, which is used to treat hepatitis C, and PEGfilgrastim (Neulasta), which is used to treat neutropenia. It has been shown that polyethylene glycol can improve healing of spinal injuries in dogs. One of the earlier findings, that polyethylene glycol can aid in nerve repair, came from the University of Texas (Krause and Bittner). Polyethylene glycol is also commonly used to fuse B-cells with myeloma cells in monoclonal antibody production.

PEG is used as an excipient in many pharmaceutical products. Lower-molecular-weight variants are used as solvents in oral liquids and soft capsules, whereas solid variants are used as ointment bases, tablet binders, film coatings, and lubricants.

PEG is also used in lubricating eye drops.\(^{118}\)
Chemical uses

- Polyethylene glycol has a low toxicity and is used in a variety of products. The polymer is used as a lubricating coating for various surfaces in aqueous and non-aqueous environments.
- Since PEG is a flexible, water-soluble polymer, it can be used to create very high osmotic pressures (on the order of tens of atmospheres). It also is unlikely to have specific interactions with biological chemicals. These properties make PEG one of the most useful molecules for applying osmotic pressure in biochemistry experiments, in particular when using the osmotic stress technique.
- Polyethylene glycol is also commonly used as a polar stationary phase for gas chromatography, as well as a heat transfer fluid in electronic testers.
- PEO (polyethylene oxide) can serve as the separator and electrolyte solvent in lithium polymer cells. Its low diffusivity often requires high temperatures of operation, but its high viscosity - even near its melting point - allows very thin electrolyte layers to be created. While crystallization of the polymer can degrade performance, many of the salts used to carry charge can also serve as a kinetic barrier to the formation of crystals. Such batteries carry greater energy for their weight than other lithium ion battery technologies.
- PEG has also been used to preserve objects that have been salvaged from underwater, as was the case with the warship Vasa in Stockholm, the Mary Rose in England and the Ma'agan Michael Ship in Israel. It replaces water in wooden objects, making the wood dimensionally stable and preventing warping or shrinking of the wood when it dries. In addition, PEG is used when working with green wood as a stabilizer, and to prevent shrinkage.
- PEG is often used (as an internal calibration compound) in mass spectrometry experiments, with its characteristic fragmentation pattern allowing accurate and reproducible tuning.
- PEG derivatives, such as narrow range ethoxylates, are used as surfactants.
- PEG has been used as the hydrophilic block of amphiphilic block copolymers used to create some polymersomes.
Biological uses

- PEG is commonly used as a precipitant for plasmid DNA isolation and protein crystallization. X-ray diffraction of protein crystals can reveal the atomic structure of the proteins.
- Polymer segments derived from PEG polyols impart flexibility to polyurethanes for applications such as elastomeric fibers (spandex) and foam cushions.
- In microbiology, PEG precipitation is used to concentrate viruses. PEG is also used to induce complete fusion (mixing of both inner and outer leaflets) in liposomes reconstituted in vitro.
- Gene therapy vectors (such as viruses) can be PEG-coated to shield them from inactivation by the immune system and to de-target them from organs where they may build up and have a toxic effect. The size of the PEG polymer has been shown to be important, with larger polymers achieving the best immune protection.
- PEG is a component of stable nucleic acid lipid particles (SNALPs) used to package siRNA for use in vivo.
- In blood banking, PEG is used as a potentiator to enhance detection of antigens and antibodies.
- When working with phenol in a laboratory situation, PEG 300 can be used on phenol skin burns to deactivate any residual phenol.

Commercial uses

- PEG is the basis of many skin creams (as cetomacrogol) and sexual lubricants (frequently combined with glycerin).
- PEG is used in a number of toothpastes as a dispersant. In this application, it binds water and helps keep xanthan gum uniformly distributed throughout the toothpaste.
- PEG is also under investigation for use in body armor, and in tattoos to monitor diabetes.
- In low-molecular-weight formulations (i.e PEG 400), it is used in Hewlett-Packard designjet printers as an ink solvent and lubricant for the print heads.
• PEG is also one of the main ingredients in paintball fills, due to its thickness and flexibility. However, as early as 2006, some Paintball manufacturers began substituting cheaper alternatives for PEG.

• PEG is a major ingredient in e-liquid, used in electronic cigarettes. It is generally used as a 30%-50% proportion of the liquid that is vaporized. Its use is designed to give a smoother effect to the vaporizing action.

• PEG is also used as an anti-foaming agent in food - its INS number is 1521 or E1521 in the EU.

Industrial uses

• Nitrate ester-plasticized polyethylene glycol is used in Trident II ballistic missile solid rocket fuel.

• Dimethyl ethers of PEG are the key ingredient of Selexol, a solvent used by coal-burning, integrated gasification combined cycle (IGCC) power plants to remove carbon dioxide and hydrogen sulfide from the gas waste stream.

• PEG has been used as the gate insulator in an electric double-layer transistor to induce superconductivity in an insulator.

• PEG is also used as a polymer host for solid polymer electrolytes. Although not yet in commercial production, many groups around the globe are engaged in research on solid polymer electrolytes involving PEG, with the aim of improving their properties, and in permitting their use in batteries, electrochromic display systems, and other products in the future.

G. Octanol

Octanol is a straight chain fatty alcohol with eight carbon atoms and the molecular formula \( \text{CH}_3(\text{CH}_2)\text{OH} \). Although the term octanol usually refers exclusively to the primary alcohol 1-octanol, there are other less common isomers of octanol such as the secondary alcohols 2-octanol, 3-octanol and 4-octanol.

Octanol occurs naturally in the form of esters in some essential oils. The primary use of octanol is in the manufacture of various esters (both synthetic and naturally occurring), such as octyl acetate, which are used in perfumery and flavors. Other uses include experimental medical applications utilizing octanol to control Essential Tremor and other types of involuntary neurological tremors.
Molecular Structure:

Chemical formula: Octan-1-ol-1-Octanol; Capryl alcohol; Octyl alcohol

Molecular formula: $\text{C}_8\text{H}_{18}\text{O}$

Molar mass: 130.23 g mol$^{-1}$

Density: 0.824 g/cm$^3$

Melting point: -16 °C, 257 K, 3 °F

Boiling point: 195 °C, 468 K, 383 °F

Solubility in water: Insoluble

Preparation

Octanol is produced industrially by the oligomerization of ethylene using triethylaluminium followed by oxidation of the alkylaluminium products. An idealized synthesis is shown:

$$\text{Al(C}_2\text{H}_5\text{)}_3 + 9 \text{C}_2\text{H}_4 \rightarrow \text{Al(C}_8\text{H}_{17}\text{)}_3$$

$$\text{Al(C}_8\text{H}_{17}\text{)}_3 + 3 \text{O} + 3 \text{H}_2\text{O} \rightarrow 3 \text{HOCH}_8\text{H}_{17} + \text{Al(OH)}_3$$

The process generates a range of alcohols that are separated by distillation.

H. Oleic acid$^{122}$

Oleic acid is a fatty acid that occurs naturally in various animal and vegetable fats and oils. It is odorless, colorless oil, although commercial samples may be yellowish. In chemical terms, oleic acid is classified as a monounsaturated omega-9 fatty acid. It has the formula $\text{CH}_3(\text{CH}_2)_7\text{CH=CH(CH}_2)_7\text{COOH}$. The term "oleic" means related to, or derived from, oil or olive, the oil of which is predominantly composed of oleic acid.

Molecular Structure:
Chemical Formula: 9Z)-Octadec-9-enoic acid

Molecular formula: \( \text{C}_{18}\text{H}_{34}\text{O}_2 \)

Molar mass: 282.4614 g/mol

Appearance: Pale yellow or brownish yellow oily liquid with lard-like odor

Density: 0.895 g/mL

Melting point: 13-14 °C (286 K)

Boiling point: 360 °C (633 K) (760mm Hg)

Solubility in water: Insoluble

Solubility in methanol: Soluble

Occurrence

Fatty acids (or as their salts) do not often occur as such in biological systems. Instead fatty acids like oleic acid occur as their esters, commonly the triglycerides, which are the greasy materials in many natural oils. Via the process of saponification, the fatty acids can be obtained.

Oleic acid (as triglyceride esters) compose the majority of olive oil, although there may be less than 2.0% as free acid in the virgin olive oil, with higher concentrations making the olive oil inedible. It also makes up 59-75% of pecan oil, 36-67% of peanut oil, 15-20% of grape seed oil, sea buckthorn oil, and sesame oil, and 14% of poppyseed oil. It is abundantly present in many animal fats, constituting 37 to 56% of chicken and turkey fat and 44 to 47% of lard.

Oleic acid is the most abundant fatty acid in human adipose tissue.

Production and chemical behavior

The biosynthesis of oleic acid involves the action of the enzyme stearoyl-CoA 9-desaturase acting on stearoyl-CoA. In effect, stearic acid is dehydrogenated to give the monounsaturated derivative oleic acid.\(^\text{123}\)

Oleic acid undergoes the reactions of carboxylic acids and alkenes. It is soluble in aqueous base to give soaps called oleates. Iodine adds across the double bond. Hydrogenation of the double bond yields the saturated derivative stearic acid. Oxidation at the double bond occurs slowly in air, and is known as rancidification in foodstuffs or drying in coatings. Reduction of the carboxylic acid group yields oleyl
alcohol. Ozonolysis of oleic acid is an important route to azelaic acid. The coproduct is nonanoic acid:

\[
H_{17}C_8CH=CHC_7H_{14}CO_2H + 4"O" \rightarrow H_{17}C_8CO_2H + HO_2CC_7H_{14}CO_2H
\]

Esters of azelaic acid find applications in lubrication and plasticizers.

The *trans* isomer of oleic acid is called elaidic acid (hence the name elaidinization for a reaction that converts oleic acid to elaidic acid).

**Uses**

The dominant use of oleic acid is as its sodium salt, which a major component of many kinds of soap. Small amounts of oleic acid are used as an excipient in pharmaceuticals, oleic acid is used as an emulsifying or solubilizing agent in aerosol products. Oleic acid is also used to induce lung damage in certain types of animals, for the purpose of testing new drugs and other means to treat lung diseases. Specifically in sheep, intravenous administration of oleic acid causes acute lung injury with corresponding pulmonary edema. This sort of research has been of particular benefit to premature newborns, for whom treatment for underdeveloped lungs (and associated complications) often is a matter of life and death.\(^{124}\)

**I. Triethanolamine**\(^{125}\)

Amine and a triol. A triol is a molecule with three alcohol groups. Like other amines, triethanolamine is a strong base. Triethanolamine can also be abbreviated as TEOA, which can help to distinguish it from triethylamine. Approximately 150000 metric tons were produced in 1999. It is a colourless compound although samples may appear yellow because of impurities.

**Molecular Structure:**

![Chemical structure of triethanolamine](image)

**Chemical formula:** 2, 2', 2"-Nitrilotriethanol
Molecular formula \( \text{C}_6\text{H}_{15}\text{NO}_3 \)

Molar mass 149.19 g mol\(^{-1}\)

Appearance Colourless liquid

Odour Ammoniacal

Density 1.124 g mL\(^{-1}\)

Melting point 22 °C, 294.75 K, 71 °F

Boiling point 335 °C, 608.55 K, 636 °F

Solubility in water 149 g L\(^{-1}\) (at 20 °C)

\( \log P \) −0.988

Vapour pressure 1 Pa (at 20 °C)

\( \lambda_{\text{max}} \) 280 nm

Refractive index \((n_D)\) 1.485

**Production**

Triethanolamine is produced from the reaction of ethylene oxide with aqueous ammonia, also produced are ethanolamine and diethanolamine. The ratio of the products can be controlled by changing the stoichiometry of the reactants.

**Applications**

Triethanolamine is used primarily as an emulsifier and surfactant. It is a common ingredient in formulations used for both industrial and consumer products. The triethanolamine neutralizes fatty acids, adjusts and buffers the pH, and solubilises oils and other ingredients that are not completely soluble in water. Some common products in which triethanolamine is found are liquid laundry detergents, dishwashing liquids, general cleaners, hand cleaners, polishes, metalworking fluids, paints and printing inks.\(^{126}\)
Cosmetics and medicine
Various ear diseases and infections are treated with eardrops containing triethanolamine polypeptide oleate-condensate, such as Cerumenex in the United States. In pharmaceutics, triethanolamine is the active ingredient of some ear drops used to treat impacted earwax. It also serves as a pH balancer in many different cosmetic products - ranging from cleansing creams and milks, skin lotions, eye gels, moisturizers, shampoos, shaving foams etc.\textsuperscript{127} TEA is a fairly strong base: a 1% solution has a pH of approximately 10, whereas the pH of skin is below pH 7. Cleansing milk/cream emulsions based on TEA are particularly good at removing makeup. Because of its high alkalinity and the possibility that it converts to nitrosamines (carcinogenic compounds), its use in cosmetics was once expected to diminish. It is still widely used as of 2009.\textsuperscript{128}

J. Carbopol 934 NF polymer\textsuperscript{129}
Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 to 6.0 micron average diameter. The flocculated agglomerates cannot be broken into the ultimate particles when produced. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking.

Molecular Structure:

![Molecular Structure Diagram]

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>White, fluffy powder</td>
</tr>
<tr>
<td>Odor</td>
<td>Slightly acetic</td>
</tr>
<tr>
<td>Test</td>
<td></td>
</tr>
<tr>
<td>Bulk Density</td>
<td>Approximately 208 kg/m$^3$</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.41</td>
</tr>
<tr>
<td>Moisture content</td>
<td>2.0% maximum</td>
</tr>
<tr>
<td>PKa</td>
<td>6.0 ± 0.5</td>
</tr>
</tbody>
</table>
Equivalent weight  76 ± 4

Carbopol 934 P is cross-linked with allyl sucrose and is polymerized in solvent benzene.

**Rheological properties:**

| Cabopol 934 NF Viscosity | 30500-39400 |

**Applications of Carbopol polymers:**

The readily water-swellable Carbopol polymers are used in a diverse range of pharmaceutical applications to provide:

- Controlled release in tablets.
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.
- Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals. Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

Several properties of Carbopol make it potentially valuable as a pharmaceutical excipient in numerous applications such as:

**Topical Applications**

Carbomers are very well suited to aqueous formulations of the topical dosage forms. Many commercial topical products available today have been formulated with these polymers, as they provide the following numerous benefits to topical formulations:

- **Safe & Effective** — Carbopol polymers have a long history of safe and effective use in topical gels, creams, lotions, and ointments. They are also supported by extensive toxicology studies.
- **Non-Sensitizing** — Carbopol polymers have been shown to have extremely low irritancy properties and are non-sensitizing with repeat usage.
- **No Effect on the Biological Activity of the Drug** — Carbopol polymers provide an excellent vehicle for drug delivery. Due to their extremely high molecular weight, they cannot penetrate the skin or affect the activity of the drug.
• Excellent Thickening, Suspending, & Emulsification Properties for Topical Formulations.\textsuperscript{131}