4.1 DRUG PROFILE

4.1.1 Levofloxacin hemihydrate

Generic and additional names Levofloxacin hemihydrate

Synonyms BAY 12-8039

Molecular formula C\textsubscript{18}H\textsubscript{20}FN\textsubscript{3}O\textsubscript{4}, \(\frac{1}{2}\) H\textsubscript{2}O

Molecular weight 370.4

Description LFX is a yellowish white to yellow powder

Solubility Freely soluble in glacial acetic acid, chloroform; sparingly soluble in water

Melting point 214- 216ºC

Category Anti-Bacterial Agents, Anti-Infective Agents, Quinolones

Pharmacokinetics

- Absorption LFX is rapidly and entirely absorbed after oral dose.
- bioavailability 99%
- Protein Binding 24 – 38 %
- Excretion Urinary
- Plasma Half Life 6 to 8 hr

Mechanism of action

LFX is L form of the racemate, OFX, a quinolone antimicrobial agent. The antibacterial activity of OFX resides primarily in L-isomer. The MOA of LFX involves destroying of bacterial topoisomerase and di-nucleotide adenosine gyrase enzymes required for di-nucleotide adenosine replication, transcription, repair and recombination. LFX exhibits in vitro MIC of two mcg/mL or less against most (\(\bullet\)90%) strains [137,138].
4.1.2 Ofloxacin

**Empirical formula** $\text{C}_{18}\text{H}_{20}\text{FN}_{3}\text{O}_{4}$

**Molecular weight** 361.4

**Description** A pale yellow or bright yellow crystalline powder.

**Solubility** Slightly soluble in water and methyl alcohol; slightly soluble to soluble in dichloromethane; soluble in glacial acetic acid.

**Melting point** 250-257°C

**Category** Antimicrobial agent

**Indications** Used topically for the treatment of conjunctivitis and corneal ulcers.

**Storage** Stored in airtight, light resistant plastic containers.

**Mechanism of action** OFX is a bactericidal and acts by inhibiting the subunit of the enzyme DNA gyrase/topoisomerase; which needed in the reproduction of bacterial DNA. Fluorine is added at 6th position in quinoline ring. 4-methyl piperazinyl at 7th position is considered to be for its antibacterial activity. It has a wide spectrum of activity and is more potent than the other FQ such as CFX.

**Pharmacokinetics**

**Absorption** OFX is absorbed through the cornea into aqueous humor after application topically to the eye; shows enhanced absorption in ocular inflammation and/or epithelial inflammation/defects. Some systemic absorption of OFX also occurs after topical application.

**Distribution** OFX distribution is likely to be greater in the presence of inflammation or infection because of disruption of the blood-ocular barrier. Following oral or IV administration of OFX in patients undergoing cataract extraction, peak drug concentrations in aqueous humor generally have averaged 20–44% of concurrent serum concentrations. Limited data suggest that drug concentrations in vitreous
humor following systemic administration of other fluoroquinolones (e.g., ciprofloxacin) are similar to those in aqueous humor. About 25% of OFX is bound to plasma proteins. It is widely distributed in body fluids, including cerebrospinal fluid (CSF), and its tissue penetration is good. It readily crosses the placenta and appears in breast milk and bile.

**Metabolism** The half-life of OFX in tear film following topical application to the eye was approximately 210 minutes. Systemically absorbed OFX metabolized to desmethyl OFX and \( N \)-oxide metabolites. These possess moderate antibacterial activity.

**Elimination** OFX is eliminated primarily by the kidneys. Excretion is by tubular secretion and glomerular filtration in the kidneys. About 65 to 80% is excreted unchanged in the urine over one or two days, resulting in high urine concentrations. While very less ie less than 5% is excreted in the urine as metabolites. About four to 8% of a dose may be excreted in the faecal matter.

**Adverse effects** OFX shows adverse effects such as nausea, vomiting, flatulence, anorexia, dry mouth, headache, dizziness, insomnia etc.

**Dosage forms** Oral administration - Uncoated tablets 200mg, 400mg.
Parenteral administration- i.v infusion 0.2% w/v
Topical preparation - Eye drops 0.3% w/v as aqueous solution.

**Dosage regimen**

**Oral**-200 mg to 400 mg b.i.d

**Parenteral** - 0.2%w/v 100ml solution is infused over 30 minutes.

**Ophthalmic**- 0.3% w/v eye drops to be instilled 5 times a day [139,140].
4.1.3 Norfloxacin

**Generic and additional names** Norfloxacin

**Synonyms** BAY 12-8039, Noroxin

**Molecular formula** $\text{C}_{16}\text{H}_{18}\text{FN}_{3}\text{O}_{3}$

**Molecular weight** 319.3

**Description** NFX is a slightly yellow to yellow crystalline odour less powder

**Solubility** water, ethanol, 2-propanol and acetone

**Melting point** 220- 221°C

**Drug category** Anti-Bacterial Agents, Anti-Infective Agents, Quinolones

**Indication**

For treatment of sinus and lung infections such as, sinusitis, pneumonia and secondary infections in chronic bronchitis. Also in the treatment of bacterial eye infection.

**Pharmacokinetics**

**Absorption** NFX is rapidly absorbed; 30% to 40% absorbed in fasting patients. Food and dairy products decrease absorption. Steady state is 2 days, $C_{\text{max}}$ is 0.8 to 2.4 mcg/ml and $T_{\text{max}}$ is approximately 1 hr after dosing.

**Distribution** Protein binding is 10% to 15% and crosses the placenta.

**Half-life** 3-4 hr

**Metabolism** Suggested as first-pass metabolism; however, further study is needed.

**Elimination** NFX is eliminated in urine (26% to 32% as norfloxacin, 5% to 8% as active metabolites) and feces (30%).
**Mechanism of action**

NFX is a having broad spectrum of activity. It functions by inhibiting Di-Nucleotide Adenosine gyrase. It is a type II and IV, enzymes necessary to separate bacterial DNA, thereby hampering cell replication.

**Pharmacology**

NFX is bactericidal and its mechanism of action based on stopping/blocking of bacterial replication. It bind itself to an enzyme called Di-Nucleotide Adenosine gyrase, which allows the untwisting required to replicate one DNA duplex helix into two. Notably the drug has hundreds times higher affinity for bacterial gyrase than for humans/mammalian.

**Interactions**

All FQ agents interact with multivalent cations and the product containing calcium, iron or zinc.

**Antimicrobial spectrum**

NFX in general is more active, with a broader spectrum of inhibition, than older quinolones. The antimicrobial activity *in vitro* is diminished by low pH and high concentrations of Mg$^{2+}$ ions in the medium [131].
4.2 EXCIPIENT PROFILE

4.2.1 Poloxamers

Nonproprietary names    BP PXMs, PhEur PXMa, USPNF PXM.

Synonyms

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

Structure

![Structure](image)

Description

PXMs generally occur as white, waxy, free-flowing prilled granules, or as cast solids. They are practically odorless and tasteless.

Functional category

Dispersing agent, emulsifying and co-emulsifying agent, solubilizing agent, tablet lubricant, wetting agent.

Applications in pharmaceutical formulation or technology

PXMs are used as emulsifying agents in intravenous fat emulsions and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. PXM may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings. PXM may also be used therapeutically as wetting agents in eye-drop formulations.
Stability and storage conditions

PXMs are stable materials. Aq. solutions are stable in the presence of acids, bases and metals. However, aq. solutions support mold growth. The raw material should be stored in a tight container in a cool, moisture free place.

Regulatory status

Available in FDA Inactive Ingredients Guide (IV injections; inhalations, ophthalmic preparations; oral powders, solutions, suspensions, and syrups; topical preparations).
4.2.2  CP 974P

Nonproprietary names  B.P- Carbomer, USPNF- Carbomer.

Synonyms  Acritamer, Acrylic acid polymer, CP, carboxyvinyl polymer.

Structure

\[
\begin{array}{c}
\text{Acrylic acid monomer unit in carbomer resins.}
\end{array}
\]

Description  White colored, fluffy, acidic, hygroscopic powder with a slight characteristics odour.

Functional category  Bioadhesive, emulsifying agent, release modifying agent, suspending agent, tablet binder and gelling agent.

Storage  Carbomer powder should be stored in as airtight; corrosive resistant container in a cool, dry place. CP is hydrophilic and produced sparkling clear gels, when neutralized. It can tolerate large amount of alcohol. Gel viscosity is strongly dependent on pH. Carbomer gels possess good stability at varying temperature such that viscosity and yield value are remain unchanged by variable temperature. As a topical product, carbomer gels possess optimum rheological properties. The inherent pseudoplastic flow permits reversible change of viscosity. When shear action is stopped; intense yield value and instant break make it suitable for dispersing.

Regulatory status  Available in FDA IIG (ophthalmic, rectal, topical preparations; oral suspensions and tablets, and syrups; topical preparations).
4.2.3 Gellan gum

**Synonym** Gelrite

**Chemical name** Gellan gum

**Description** Gellan gum occurs as an off-white powder. It is a high molecular weight poly-saccharide gum produced by *Pseudo E*. It is principally composed of a tetra-saccharide repeating unit constituted by one moiety of rhamnose, one moiety of glucuronic acid and two moieties of glucose.

**Solubility** Soluble in hot water, not soluble in ethanol.

**Category** Thickening agent, gelling agent, stabilizer.

**Pharmaceutical applications** As gelling agent, thickening agent.

**Mechanism of gelation of gellan gum** It is an ion sensitive polymer which forms clear gel on contact with Ca$^{+2}$, Na$, K^+$ ie divalent and monovalent. It forms double helices which are very weak at room temperature ie. Vander Waals attraction. In the presence of cations, the helix arranges into aggregates and causes cross-linking.
4.2.4  Chitosan

**Nonproprietary names**  BP Chitosan hydrochloride. PhEur Chitosan hydrochloridum

**Synonyms**  2-Amino-2-deoxy-(1,4)-β-D-glucopyranan; Deacetylated chitin; deacetylchitin; β -1,4-poly-Dglucosamine; Poly-D-glucosamine; Poly-(1,4- β -D-glucopyranosamine).

**Description**  Chitosan occurs as odorless, white or creamy-white powder or flakes.

**Functional category**  Coating agent, disintegrating agent, film-forming agent, mucoadhesive, tablet binder, viscosity increasing agent.

**Applications in pharmaceutical formulation or technology**  Chitosan has been used in different pharmaceutical gels, films, beads, microspheres, tablets and coatings. Furthermore, chitosan may be used as drug carrier systems using several techniques as spray drying, coacervation, direct compression, and granulation processes.
Stability and storage

Chitosan powder is a stable material at ambient temperature, it is hygroscopic after drying. Chitosan must be preserved in a tightly closed container in a cool, dry place. The PhEur 2002 specifies that chitosan should be stored at a cool temperature conditions.

Regulatory status

Chitosan is registered as a supplement of food in some parts.
4.2.5 Sodium alginate

**Nonproprietary names** BP Sodium alginate, PhEur Natrii alginas, USPNF

Sodium alginate

**Synonym** Algin, Alginic Acid, Keltone, Sodium Polymannuronate.

**Structural formula** \((C6H8O6)\ n\)

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

**Functional category** Stabilizing agent, suspending agent, sustained release adjuvant, tablet binder, table disintegrant, and viscosity modifier.

**Applications in pharmaceutical formulation or technology**

In topical formulations, used as a thickening, suspending agent in pastes, creams and gels, as a stabilizing agent for emulsions. Recently, sodium alginate has been used for the aq. microencapsulation of drugs to replace use organic solvent systems. It has also been used in the formation of nanoparticles.

**Stability and storage conditions**

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature. Solutions should not be stored in metal containers. Sodium alginate solutions are prone on storage to microbial attack, which may affect formulation viscosity.

**Regulatory status**

GRAS listed. Accepted in Europe for use as a food additive. Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.
4.2.6 Hydroxypropyl methylcellulose

**Synonyms**  Hydroxypropyl methylcellulose; Hypromellose; methyl hydroxypropyl cellulose; propylene glycol ether of methyl cellulose; methyl cellulose propylene glycol ether

**Chemical names**  Cellulose, 2- hydroxypropylmethylether; Cellulose hydroxypropylmethyl ether

**Empirical formula**  \( C_8H_{15}O_6 - (C_{10}H_{18}O_6) - C_8H_{15}O_5 \)

**Molecular weight**  Approx. 86,000

**Description**  An odorless, tasteless, white or creamy white fibrous or granular powder.

**Solubility**  Soluble in cold water; insoluble in alcohol, ether and chloroform, but soluble in mixture of methyl alcohol and methylene chloride. Undergoes a reversible sol to gel transition upon heating and cooling respectively.

**Functional categories**  Suspending and/or viscosity increasing agent; tablet binder; coating agent; adhesive anhydrous ointment ingredient; film former; emulsion stabilizer.
4.2.7 Hydroxyethyl cellulose

Nonproprietary names BP Hydroxyethylcellulose, PhEur Hydroxyethylcellulosum, USP NF Hydroxyethyl cellulose

Synonyms Cellosize; cellulose hydroxyethyl ether; cellulose hydroxyethylate; ethylhydroxy cellulose; ethylose; HEC; HE cellulose; 2-hydroxyethyl cellulose ether; hydroxyethyl ether cellulose; hydroxyethyl starch; hyetellose; Natrosol; oxycellulose; Tylose PHA.

Structure

Where R is H or \([—CH2CH2O—]mH\)

Description

Hydroxyethyl cellulose occurs as a light tan or cream to white-colored, odorless and tasteless, hygroscopic powder.

Functional category

Coating agent; suspending agent; tablet binder; thickening agent; viscosity modifier

Applications in pharmaceutical formulation or technology

Hydroxyethyl cellulose is a nonionic, water-soluble polymer widely used in pharmaceutical formulations. It is primarily used as a thickening agent in ophthalmic and topical formulations. It is used as lubricant in preparations for dry eye and in preparations for care of contact lens.
Stability and storage conditions

Aq. solutions of hydroxyethyl cellulose are relatively stable at wide pH range with the viscosity of solutions being largely unaffected. However, solutions are less stable below pH 5 owing to hydrolysis. Hydroxyethyl cellulose powder should be stored in a well-closed container, in a cool, dry place.

Regulatory status

Included in the FDA IIG (ophthalmic preparations; oral syrups and tablets; otic and topical preparations). Hydroxyethyl cellulose is not currently approved for use in food products in Europe or the USA, although it is permitted for use in indirect applications such as packaging. This restriction is due to the high levels of ethylene glycol residues that are formed during the manufacturing process.
4.2.8 Benzalkonium chloride

Nonproprietary names

BP Benzalkonium chloride, PhEur Benzalkonium chloride, USPNF Benzalkonium chloride

Synonyms

Alkylbenzyldimethylammonium chloride; alkyl dimethyl benzyl ammonium chloride; BKC; Hyamine 3500; Pentonium; Zephiran.

Structure

![Structure of Benzalkonium Chloride](image)

Description

It appears as a white or yellowish white amorphous powder or a thick gel like or gelatinous flakes.

Functional category

Antimicrobial preservative; antiseptic; disinfectant; solubilizing agent; wetting agent.

Applications in pharmaceutical formulation

Benzalkonium chloride is one of the most widely used preservative, at concentration of 0.01-0.02% w/v.

Stability and storage conditions

It is hygroscopic and may be affected by light, air and metals. Solutions are stable over a wide pH and temperature range and may be sterilized by autoclaving without
loss of effectiveness. Solutions may be stored for prolonged periods at room temperature.

4.2.9 Mannitol

Nonproprietary names BP Mannitol, JP D-Mannitol, PhEur Mannitolum, USP

Mannitol

Synonyms Cordycepic acid; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.

Structure

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomer of sorbitol. Mannitol occurs as a white, odorless, crystalline powder or free-flowing granules. It has a sweet as sweet as glucose and 50% as sweet as sucrose. It imparts cooling sensation in the mouth.

Functional category

Diluent; diluent for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.
Applications in pharmaceutical formulation or technology

Mannitol used in direct-compression tablet applications, of chewable tablet formulations, to prevent thickening in aq. antacid suspensions, as a plasticizer in SGC, as a component of sustained-release tablet formulations and as a carrier in dry powder inhalers.

Stability and storage conditions

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

Regulatory status

GRAS listed and accepted for use as a food additive in Europe. Included in the FDA IIG (IP, IM, IV, and SC injections; ophthalmic preparations; topical solutions). Included in nonparenteral and parenteral medicines, licensed in UK [141].