Chapter 4: Drug and excipient profile
4. Drug and excipient profile

4.1 Drug profile

From the literature review meloxicam was selected for the formulation of pulsatile release systems for treatment of rheumatoid arthritis.

4.1.1 Generic name

Meloxicam

4.1.2 Category

Analgesic, Non steroidal anti inflammatory

4.1.3 Chemical name

4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

4.1.4 Chemical formula

C_{14}H_{13}N_{3}O_{4}S_{2} 351.4  (CAS- 71125-38-7)

4.1.5 Chemical structure

![Chemical structure of meloxicam]

4.1.6 Appearance

A pastel yellow coloured powder, with M. P. 242-250°C. It is practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol.

4.1.7 Partition coefficient

Meloxicam have (log P)_{app} value of 0.1 in n-octanol/buffer pH 7.4
4.1.8 Dissociation constant

The dissociation constant i.e., pKa values for meloxicam are 1.1 and 4.2

4.1.9 Mechanism of action

The mechanism of action of meloxicam, like that of other NSAIDs, may be related to prostaglandin synthetase (cyclo-oxygenase, selective COX II inhibitor) inhibition which is involved in the initial steps of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacyclin.

4.1.10 Contraindications

- Known hypersensitivity to meloxicam or any ingredient in the formulation.
- History of asthma, urticaria, or other sensitivity reaction precipitated by aspirin or other NSAIDs.

4.1.11 Warnings

**Cardiovascular effects**

Selective COX-2 inhibitors have been associated with an increased risk of serious adverse cardiovascular thrombotic events in certain situations. Several prototypical NSAIDs also have been associated with an increased risk of cardiovascular events. Current evidence suggests that use of meloxicam might be associated with increased cardiovascular risk.

NSAIDs should be used with caution and careful monitoring (e.g., It should be monitored for development of cardiovascular events), It is necessary to use NSAIDs at lowest effective dose for the shortest duration.

The short-term use to relieve acute pain, especially at low dosages, does not appear to be associated with increased risk of serious cardiovascular events.

Incidences of hypertension and worsening of pre-existing hypertension are reported. Either of events may contribute to the increased incidences of cardiovascular events. NSAIDs should be used with caution in patients with hypertension along with monitoring with BP. Impaired response to certain diuretics may occur.

Fluid retention and edema is reported. Caution in patients with fluid retention or heart failure is suggested.
GI effects

Serious GI toxicity (e.g., bleeding, ulceration, perforation) can occur with or without warning symptoms. Increased risk in those with a history of GI bleeding or ulceration, geriatric patients, smokers, those with alcohol dependence, and those in poor general health. Lower incidence of adverse GI effects compared with other prototypical NSAIDs (e.g., diclofenac, naproxen, piroxicam) may be because of selective inhibition of COX II enzyme than COX I. Other prototype NSAIDs inhibit both COX I as well as COX II enzyme. COX I enzyme is responsible for maintenance of the gastric mucosal lining. Inhibition of COX I lead to adverse GI effects like gastric irritation in some studies.

Renal effects

Direct renal injury, including renal papillary necrosis is reported in patients receiving long-term NSAID therapy.

4.1.12 Sensitivity reactions

Hypersensitivity reactions

Anaphylactic reactions are reported. In such cases immediate medical intervention and discontinuance for anaphylaxis is suggested.

4.1.13 General precautions

Hepatic effects

Severe reactions including jaundice, liver necrosis, and hepatic failure (sometimes fatal) are reported rarely with NSAIDs.

Monitor for symptoms and/or signs suggesting liver dysfunction; monitor abnormal liver function test results. Discontinue if signs or symptoms of liver disease or systemic manifestations (e.g., eosinophilia, rash) occur or if liver function test abnormalities persist or worsen.

Hematologic effects

Anemia is reported rarely. Determine hemoglobin concentration or hematocrit in patients receiving long-term therapy if signs or symptoms of anemia occur. Notable effects on platelets or bleeding times not observed.
4.1.14 Other precautions

Not a substitute for corticosteroid therapy; not effective in the management of adrenal insufficiency. It may mask certain signs of infection. During long term use it is suggested to obtain CBC and chemistry profile periodically.

Specific populations

Pregnancy

Category C. It’s use in third trimester should be avoided because of possible premature closure of the ductus arteriosus.

Lactation

Distributed into milk in rats; not known whether distributed into milk in humans. It is suggested to discontinue nursing or the drug.

Pediatric use

Its safety and efficacy not established in children <2 years of age. Safety and efficacy in pediatric patients 2–17 years of age with juvenile rheumatoid arthritis supported by evidence from controlled studies. Adverse effects like abdominal pain, vomiting, diarrhea, headache, and pyrexia reported more frequently in children than adults.

Geriatric use

Caution is advised. Fatal adverse GI effects are reported more frequently in geriatric patients than younger adults.

Hepatic impairment

Not studied in patients with severe hepatic impairment (Child-Pugh class III).

Renal impairment

It should be used with caution in renal disease. Not recommended in patients with advanced renal disease; close monitoring of renal function is advised if used.

4.1.15 Common adverse effects

Common adverse effects like abdominal pain, diarrhea, dizziness, dyspepsia, edema, flatulence, headache, nausea, rash, upper respiratory tract infection, influenza-like illness,
musculoskeletal and connective tissue signs and symptoms (back pain, muscle spasms, musculoskeletal pain) are reported.

4.1.16 Interactions for meloxicam

Table 4-1: Drugs specific interaction of meloxicam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Reduced BP response to ACE inhibitor. Possible deterioration of renal function in individuals with renal impairment.</td>
<td>BP should be monitored.</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>Reduced BP response to angiotensin II receptor antagonist. Possible deterioration of renal function in individuals with renal impairment.</td>
<td>BP should be monitored.</td>
</tr>
<tr>
<td>Antacids</td>
<td>Pharmacokinetic interaction unlikely.</td>
<td>Meloxicam can be administered without regard to antacids.</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Increased plasma meloxicam concentrations. Increased risk of GI ulceration and other complications. No consistent evidence that low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIDs.</td>
<td>Clinical importance of pharmacokinetic interaction is unknown Manufacturer states that concomitant use is not recommended</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Increased meloxicam clearance.</td>
<td>Clinical importance not established</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Pharmacokinetics of meloxicam not altered.</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No protein-binding interaction; pharmacokinetics of digoxin not altered.</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Diuretics (furosemide, thiazides)</td>
<td>Reduced natriuretic effects possible</td>
<td>Monitoring for diuretic efficacy and renal failure is suggested.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Increased plasma lithium concentrations.</td>
<td>Monitoring for lithium toxicity is suggested.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Possible toxicity associated with increased plasma methotrexate concentrations.</td>
<td>Caution is advised.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Possibility of bleeding complications.</td>
<td>Monitoring of anticoagulant activity; caution is advised.</td>
</tr>
</tbody>
</table>
4.1.17 Pharmacokinetics of meloxicam

Absorption

Bioavailability
Meloxicam is well absorbed following oral administration; bioavailability is about 89%. Peak plasma concentration usually attained within about 4–5 hours. Commercially available tablets and oral suspension are bioequivalent.

Food
No clinically important effect.

Special populations
In patients with mild or moderate hepatic impairment (Child-Pugh class I or II), no important differences in plasma concentrations compared with healthy individuals. In patients with mild or moderate renal impairment, some pharmacokinetic values altered (total plasma concentrations decreased, free concentrations unchanged).

Distribution
Total meloxicam concentration in synovial fluid is 40–50% of plasma concentration; free fraction in synovial fluid exceeds that in plasma.

Plasma protein binding
Plasma protein binding is 99.4% (principally albumin).

Metabolism
It is extensively metabolized to inactive metabolites by CYP isoenzymes, mainly by CYP2C9 and to a lesser extent by CYP3A4.

Elimination Route
Meloxicam undergoes biliary secretion and enterohepatic recirculation. It is excreted to an equal extent in urine and feces as metabolites.

Half-life
Adults: 15–20 hours.
Children 2–6 years of age: 15.2 hours.
Children 7–16 years of age: 13 hours.
4.2 Review of excipients

4.2.1 Spray Dried Lactose

Nonproprietary Names
None adopted.

Synonyms
FlowLac 90; FlowLac 100; Lactopress Spray-Dried; Lactopress Spray-Dried 250; NF Lactose–315; NF Lactose–316 Fast Flo; SuperTab 11SD; SuperTab 14SD.

Chemical name and CAS registry number
Spray-dried lactose is a mixture of amorphous lactose, which is a 1:1 mixture of α- and β-lactose, and O-b-D-galactopyranosyl- (1,4)-a-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5]. CAS numbers for lactose monohydrate are [5989-81-1] (lactose monohydrate); [10039-26-6] (lactose monohydrate, cyclic); [64044-51-5] (lactose monohydrate, open form).

Empirical formula and molecular weight
C₁₂H₂₂O₁₁ 342.30 (for amorphous)
C₁₂H₂₂O₁₁H₂O 360.31 (for monohydrate)

Functional category
Directly compressible tablet excipient; tablet and capsule diluent; tablet and capsule filler

Applications in pharmaceutical formulation or technology
Spray-dried lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting.

Structural formula

![Anhydrous α-lactose](image1)

![Anhydrous β-lactose](image2)
Description

Lactose occurs as white to off-white crystalline particles or powder. It is odorless and slightly sweet-tasting. Spray-dried direct compression grades of lactose are generally composed of 80–90% specially prepared pure a-lactose monohydrate along with 10–20% of amorphous lactose.

Stability and storage conditions

Spray-dried lactose should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Lactose is a reducing sugar. Amorphous lactose, which is the most reactive form of lactose present in spray-dried lactose, will interact more readily than conventional crystalline grades. Typical reactions include the Maillard reaction with either primary or secondary amines.

Regulatory status

GRAS listed. It is included in the FDA Inactive Ingredients Database (IM, IV: powder for injection solution; IV and sublingual preparations; oral: capsules and tablets; powder for inhalation; vaginal). It is included in nonparenteral and parenteral medicines licensed in UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

Related substances

Lactose, anhydrous; lactose, inhalation; lactose, monohydrate

4.2.2 Croscarmellose

Nonproprietary names

BP: Croscarmellose Sodium
JP: Croscarmellose Sodium
PhEur: Croscarmellose Sodium
USP-NF: Croscarmellose Sodium
Synonyms

Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical name and CAS registry number

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

Empirical formula and molecular weight

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium. Carboxymethylcellulose.

Functional category

Tablet and capsule disintegrant

Applications in pharmaceutical formulation or technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant,
although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Description

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Stability and storage conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Safety

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems. In UK, croscarmellose sodium is accepted for use in dietary supplements. WHO has not specified an acceptable daily intake for the related substance carboxymethylcellulose sodium, used as a food additive, since the levels necessary to achieve a desired effect were not considered sufficient to be a hazard to health.

Regulatory status

It is included in the FDA Inactive Ingredients Database (oral capsules, granules, sublingual tablets, and tablets). It is included in nonparenteral medicines licensed in the UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.
Related substances

Carboxymethylcellulose calcium; carboxymethylcellulose sodium

4.2.3 Talc

Nonproprietary names

BP: Purified Talc
JP: Talc
PhEur: Talc
USP: Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial;
Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star;
powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

Chemical name and CAS registry number

Talc [14807-96-6]

Empirical formula and molecular weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula
Mg₆(Si₂O₅)(OH)₄. It may contain small, variable amounts of aluminum silicate and iron.

Structural formula

Mg₃Si₄O₁₀(OH)₂

Functional category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in pharmaceutical formulation or technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents. However, it is widely used as a dissolution retardant in the development of controlled-release products.
Description
Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Stability and storage conditions
Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities
Incompatible with quaternary ammonium compounds.

Safety
Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants. Although, talc has been extensively investigated for its carcinogenic potential, and it has been suggested that there is an increased risk of ovarian cancer in women using talc, the evidence is inconclusive. However, talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products. Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.

Regulatory status
It is accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (buccal tablets; oral capsules and tablets; rectal and topical preparations). It is included in nonparenteral medicines licensed in the UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

Related substances
Bentonite; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate.
4.2.4 Magnesium stearate

Nonproprietary Names
BP: Magnesium Stearate
JP: Magnesium Stearate
PhEur: Magnesium Stearate
USP-NF: Magnesium Stearate

Synonyms
Dibasic magnesium stearate; magnesium distearate; magnesii stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

Chemical name and CAS registry number
Octadecanoic acid magnesium salt [557-04-0]

Empirical formula and molecular weight
\( \text{C}_{36}\text{H}_{70}\text{MgO}_{4} \quad 591.24 \)

The USP32–NF27 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (\( \text{C}_{32}\text{H}_{62}\text{MgO}_{4} \)).

Structural formula

\[ \text{[CH}_3\text{(CH}_2\text{)}_{16}\text{COO]}_2\text{Mg} \]

Functional category
Tablet and capsule lubricant.

Applications in pharmaceutical formulation or technology
Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.
Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to skin.

Stability and storage conditions

Magnesium stearate is stable and should be stored in a closed container in a cool, dry place.

Incompatibilities

It is incompatible with strong acids, alkalis, and iron salts. It's mixing with strong oxidizing materials should be avoided. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation. No toxicity information relating to normal routes of occupational exposure is available. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worstcase daily intake and heavy metal composition. Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled.

LD50 (rat, inhalation): >2 mg/L
LD50 (rat, oral): >10 g/kg

Regulatory acceptance

GRAS listed. It is accepted as a food additive in the USA and UK. Included in the FDA Inactive Ingredients Database (oral capsules, powders, and tablets; buccal and vaginal tablets; topical preparations intravitreal implants and injections). It is included in nonparenteral medicines licensed in the UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients. It is listed on the US TSCA inventory.

Related substances

Calcium stearate; magnesium aluminum silicate; stearic acid; zinc stearate.
4.2.5 Ethyl Cellulose

Nonproprietary Names

BP: Ethylcellulose
PhEur: Ethylcellulose
USP-NF: Ethylcellulose

Synonyms
Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcelluloseum; Surelease.

Chemical name and CAS registry number

Cellulose ethyl ether [9004-57-3]

Empirical formula and molecular weight

Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is \( C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5 \) where \( n \) can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of \( b \)-anhydroglucose units joined together by acetal linkages.

Structural formula

![Structural formula of Ethyl Cellulose]

Functional category

It is used as coating and flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

Applications in pharmaceutical formulation or technology

Ethylcellulose is widely used in oral and topical pharmaceutical Formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and
granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer. An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents. Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. High-viscosity grades of ethylcellulose are used in drug microencapsulation.

Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder, ethylcellulose being blended dry or wet granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethylcellulose has been studied as a stabilizer for emulsions. Ethylcellulose is additionally used in cosmetics and food products.

**Description**

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.

**Stability and storage conditions**

Ethylcellulose is a stable, slightly hygroscopic. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethylcellulose is subject to oxidative degradation in the presence of
sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range. Ethylcellulose should be stored at a temperature not exceeding 320C (900F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethylcellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys. Ethylcellulose is generally regarded as non toxic, non allergic, and non irritating material. As ethylcellulose is not considered to be a health hazard, WHO has not specified an acceptable daily intake. The highest reported level used in an oral product is 308.8 mg in an oral sustained release tablet.
LD50 (rabbit, skin): >5 g/kg
LD50 (rat, oral): >5 g/kg

Regulatory status

GRAS listed. It is accepted for use as a food additive in Europe. It is included in the FDA Inactive Ingredients Database (oral capsules, suspensions and tablets; topical emulsions and vaginal preparations). It is included in nonparenteral medicines licensed in Europe. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

Related substances

Hydroxyethyl cellulose; hydroxyethylmethyl cellulose; methylcellulose.

4.2.6 HPMC: Hypromellose

Nonproprietary names
BP: Hypromellose
JP: Hypromellose
PhEur: Hypromellose
USP: Hypromellose

**Synonyms**
Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

**Chemical name and CAS registry number**
Cellulose hydroxypropyl methyl ether [9004-65-3]

**Empirical formula and molecular weight**
The PhEur 6.3 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 32 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH₃). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH₂CH(OH)CH₃), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the various types of hypromellose.
Molecular weight is approximately 10 000–1 500 000.

**Structural Formula**

where R is H, CH₃, or CH₃CH(OH)CH₂
Functional category

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in pharmaceutical formulation or technology

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, Pharmacoat, and the Methocel E Premium LV series. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.
Stability and storage conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 50–90°C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. When hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety

Hypromellose is widely used as an excipient in oral, ophthalmic, nasal, and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have laxative effect. The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health. In fact, high dosages of hypromellose are being investigated for treating various metabolic syndromes.

LD50 (mouse, IP): 5 g/kg
LD50 (rat, IP): 5.2 g/kg
Regulatory status

GRAS listed. It is accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). It is included in nonparenteral medicines licensed in the UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

Related substances

Ethylcellulose; hydroxyethyl cellulose; hydroxyethylmethyl cellulose; hydroxypropyl cellulose; hypromellose acetate succinate; hypromellose phthalate; methylcellulose.

4.2.7 Hydroxypropyl cellulose, Low-substituted

Nonproprietary names

JP: Low substituted Hydroxypropylcellulose
USP-NF: Low-substituted Hydroxypropyl Cellulose

Synonyms

Cellulose, 2-hydroxypropyl ether; 2-hydroxypropyl ether (low substituted) cellulose; hyprolose, low-substituted; L-HPC; oxypropylated cellulose.

Chemical name and CAS registry number

Cellulose, 2-hydroxypropyl ether (low-substituted) [9004-64-2]

Empirical formula and molecular weight

The USP32–NF27 describes low-substituted hydroxypropyl cellulose as a low-substituted hydroxypropyl ether of cellulose. Compared to hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose has only a small proportion of the three free hydroxyl groups per glucose subunit converted to a hydroxypropyl ether. When dried at 105°C for 1 hour, it contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups (OCH₂CHOHCH₃). Low-substituted hydroxypropyl cellulose is commercially available in a number of different grades that have different particle sizes and substitution levels.
## Structural formula

![Structural formula](image)

*\( R \) is \( H \) or \([\text{CH}_2\text{CH}(\text{CH}_3)\text{O}]_n\text{H}\)

## Functional category

Tablet and capsule disintegrant; tablet binder.

## Applications in pharmaceutical formulation or technology

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used as a disintegrant, and as a binder for tablets and granules in wet or dry granulation. It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods. In addition, low substituted hydroxypropyl cellulose has been used as a binder/disintegrant included in the powder layering process on spherical cores and to prepare pellets by extrusion/spheronization. A low particle size and high hydroxypropyl content is recommended to produce round spheres and rapid dissolution. There are a number of grades that have different particle sizes and substitution levels. LH-11 has the longest fibrous particles, and is typically used as an anticaepping agent and disintegrant for direct compression. LH-21 is less fibrous and is used as a binder and disintegrant for tablets through the wet-granulation process. LH-31 is a small-particle grade used especially for extrusion to produce granules. LH-B1 is the nonfibrous, high-density grade designed for fluid-bed granulation, and can be used for direct compression and/or formulations with a high low-substituted hydroxypropyl cellulose loading. Lower substitution grades LH-22 and LH-32 can be used for better disintegration capability, depending on the characteristics of the active ingredients. The typical content of low-substituted hydroxypropyl cellulose in a formulation is approximately 5–50%.
Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odor, and it is tasteless.

Stability and storage conditions

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well closed container.

Incompatibilities

There may be interaction with alkaline substances.

Safety

Low-substituted hydroxypropyl cellulose is generally regarded as a nontoxic and nonirritant material. Animal toxicity studies showed no adverse effects in rats fed orally 6 g/kg/day over 6 months. No teratogenic effects were noted in rabbits and rats fed 5 g/kg/day.

LD50 (rat, oral): >15 g/kg

Regulatory status

It is included in the FDA Inactive Ingredients Database (oral capsules, tablets, pellets). It is approved for use in pharmaceuticals in Europe, Japan, USA, and other countries. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

Related substances

Hydroxyethylmethyl cellulose; hydroxypropyl cellulose; methylcellulose.

4.2.8 Polyethylene oxide

Nonproprietary names

USP-NF: Polyethylene Oxide

Synonyms

Polyox; polyoxinate; polyoxirane; polyoxyethylene.
Chemical name and CAS Registry number

Polyethylene oxide [25322-68-3]

Empirical formula and molecular weight

![Polymer Grades and Molecular Weights Table]

Structural formula

The USP32–NF27 Structure describes polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula \((\text{CH}_2\text{CH}_2\text{O})_n\), where \(n\) represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide or suitable antioxidant.

Functional category

Mucoadhesive; coating agent; tablet binder; thickening agent.

Applications in pharmaceutical formulation or technology

Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. Higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach. Polyethylene oxide has also been shown to facilitate coarse extrusion for tableting as well as being an aid in hot-melt extrusion. The relationship between swelling capacity and molecular weight is a good guide when selecting products for use in immediate- or sustained-release matrix formulations. Polyethylene oxide has been shown to be an excellent mucoadhesive polymer. Low levels of polyethylene oxide are effective thickeners, although alcohol is usually added to water based formulations to provide improved viscosity and stability. Polyethylene oxide films demonstrate good lubricant properties when wet. This property has
been utilized in the development of coatings for medical devices. Polyethylene oxide can be radiation crosslinked in solution to produce a hydrogel that can be used in wound care applications.

**Description**

White to off-white, free-flowing powder. Slight ammoniacal odor.

**Stability and storage conditions**

It should be stored in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.

**Incompatibilities**

Polyethylene oxide is incompatible with strong oxidizing agents.

**Regulatory status**

It is included in the FDA Inactive Ingredients Database (sustainedrelease tablets). It is included in the Canadian List of Acceptable Non medicinal Ingredients.

**Related substances**

Polyethylene glycol