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Second Edition

Edited by
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Acacia

1. Nonproprietary Names

BP: Acacia
PhEur: Acaciae gummi
USPNF: Acacia

2. Synonyms

E414; gum acacia; gum arabic; talha gum.

3. Chemical Name and CAS Registry Number

Acacia [9000-01-5]

4. Empirical Formula Molecular Weight

Acacia is a complex, loose aggregate of sugars and hemicelluloses with a molecular weight of approximately 240 000-580 000. The aggregate consists essentially of an arabic acid nucleus to which are connected calcium, magnesium and potassium along with the sugars arabinose, galactose and rhamnose.

5. Structural Formula

See Section 4.

6. Functional Category

Emulsifying agent; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges, and as a tablet binder, although used incautiously it can produce tablets with a prolonged disintegration time.
Acacia is also used in cosmetics, confectionery and food products.
See also Section 19.

Use	Concentration (%)
Emulsifying agent	5-10
Pastille base	10-30
Suspending agent	5-10
Tablet binder	1-5

8. Description

Acacia occurs as white or yellowish-white colored thin flakes, spheroidal tears, granules or powder. It is odorless and has a bland taste.

9. Pharmacopeial Specifications

The BP 1993 includes monographs on acacia, powdered acacia and spray-dried acacia which differ only in their physical characteristics. The PhEur 1992 similarly has monographs on acacia and spray-dried acacia, while the USPNF XVII describes acacia in a single monograph which encompasses tears, flakes, granules and spray-dried powder.

Test	PhEur 1992	USPNF XVII
Identification	+	+
Botanic characteristics	+	+
Microbial limit	+	+
Water	≤ 15% ≤ 10%[a]	≤ 15% —
Total ash	≤ 4.0%	≤ 4.0%
Acid-insoluble ash	—	≤ 0.5%
Insoluble residue	≤ 0.5%	≤ 1.0%
Arsenic	—	≤ 3 ppm
Lead	—	≤ 0.001%
Heavy metals	—	≤ 0.004%
Starch or dextrin	+	+
Tannin-bearing gums	+	+
Agar & tragacanth	+	—
Agar & sterculia gum	+	—
Sucrose & fructose	+	—

Note: a. Spray-dried acacia.

10. Typical Properties

Acidity/alkalinity:
pH = 4.5-5.0 (5% w/v aqueous solution)
Acid value: 2.5
Hygroscopicity: at relative humidities between 25-65%, the equilibrium moisture content of powdered acacia at 25°C is between 8-13% w/w, but at relative humidities above about 70% it absorbs substantial amounts of water.
Moisture content: *see* HPE Data.
Solubility: soluble 1 in 20 of glycerin, 1 in 20 of propylene glycol, 1 in 2.7 of water; practically insoluble in ethanol (95%).
Specific gravity: 1.35-1.49
Viscosity (dynamic): 100 mPa s (100 cP) for a 30% w/v aqueous solution at 20°C.
The viscosity of aqueous acacia solutions varies depending upon the source of the material, processing, storage conditions, pH and the presence of salts. Viscosity increases slowly up to about 25% w/v concentration and exhibits Newtonian behavior. Above this concentration, viscosity rapidly increases. Increasing temperature or prolonged heating of solutions results in a decrease of viscosity due to depolymerization or particle agglomeration. *See also* Section 12.

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content	MC-1	5	10.75%[a]
	MC-1	5	12.54%[b]
	MC-1	5	3.92%[c]

Supplier: a. Penick; b. EM Industries Inc; c. Fisher Scientific.

11. Stability and Storage Conditions

Aqueous solutions are subject to bacterial or enzymatic degradation but may be preserved by initially boiling the solution for a short time to inactivate any enzymes present; microwave irradiation can also be used.[1] Aqueous solutions may also be preserved by the addition of an antimicrobial preservative such as 0.1% w/v benzoic acid, 0.1% w/v sodium benzoate or a mixture of 0.17% w/v methylparaben and 0.03% propylparaben.
Powdered acacia should be stored in an airtight container in a cool, dry, place.

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12. Incompatibilities

Acacia is incompatible with a number of substances including amidopyrine, cresol, ethanol (95%), ferric salts, morphine, phenol, physostigmine, tannins, thymol, and vanillin.

An oxidizing enzyme is present in acacia which may affect preparations containing easily oxidizable substances. The enzyme may however be inactivated by heating at 100°C for a short time, *see* Section 11.

Many salts reduce the viscosity of aqueous acacia solutions, while trivalent salts may initiate coagulation. Aqueous solutions carry a negative charge and will form coacervates with gelatin and other substances. In the preparation of emulsions, solutions of acacia are incompatible with soaps.

13. Method of Manufacture

Acacia is the dried gummy exudate obtained from the stems and branches of *Acacia senegal* (Linné) Willdenow or other related species of *Acacia* (Fam. Leguminosae) which grow mainly in the Sudan and Senegal regions of Africa.

The bark of the tree is incised and the exudate allowed to dry on the bark. The dried exudate is then collected, processed to remove bark, sand and other particulate matter, and graded. Various acacia grades differing in particle size and other physical properties are thus obtained. A spray-dried powder is also commercially available.

14. Safety

Acacia is used in cosmetics, foods, and oral and topical pharmaceutical formulations. Although generally regarded as an essentially nontoxic material, there have been a limited number of reports of hypersensitivity to acacia after inhalation or ingestion.[2,3] Severe anaphylactic reactions have occurred following the parenteral administration of acacia and it is now no longer used for this purpose.[2]

The WHO has not set an acceptable daily intake for acacia as a food additive since the levels necessary to achieve a desired effect were not considered to represent a hazard to health.[4]

LD_{50} (rabbit, oral): 8.0 g/kg[5]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acacia can be irritant to the eyes, skin, and upon inhalation. Gloves, eye protection and a dust respirator are recommended.

16. Regulatory Status

GRAS listed. Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Guide (oral preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Cz, Egypt, Eur, Fr, Ger, Ind, It, Jpn, Neth, Nord, Port, Rom, Swiss, USPNF and Yug.

See also Section 9.

18. Related Substances

Tragacanth.

19. Comments

Concentrated aqueous solutions are used to prepare pastilles since on drying they form solid rubbery, or glass-like masses depending upon the concentration used.

20. Specific References

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22. Authors

USA: E Shefter.

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Benzalkonium Chloride

1. Nonproprietary Names

BP: Benzalkonium chloride
PhEur: Benzalkonii chloridum
USPNF: Benzalkonium chloride

2. Synonyms

Alkylbenzyldimethylammonium chloride; alkyl dimethyl benzyl ammonium chloride; BKC; *Catigene DC 100*; *Exameen 3580*; *Hyamine 3500*; *Pentonium*; *Roccal*; *Zephiran*.

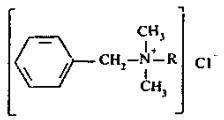
3. Chemical Name and CAS Registry Number

Alkyldimethyl(phenylmethyl)ammonium chloride
[8001-54-5]

4. Empirical Formula Molecular Weight

The USPNF XVII describes benzalkonium chloride as a mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5CH_2N(CH_3)_2R]Cl$, where R represents a mixture of alkyls, including all or some of the group beginning with n-C_8H_{17} and extending through higher homologs, with n-$C_{12}H_{25}$, n-$C_{14}H_{29}$, and n-$C_{16}H_{33}$ comprising the major portion. The average molecular weight of benzalkonium chloride is 360.

5. Structural Formula



R = mixture of alkyls: n-C_8H_{17} to n-$C_{18}H_{37}$; mainly n-$C_{12}H_{25}$ (dodecyl), n-$C_{14}H_{29}$ (tetradecyl) and n-$C_{16}H_{33}$ (hexadecyl).

6. Functional Category

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

7. Applications in Pharmaceutical Formulation or Technology

Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative in applications similar to other cationic surfactants, such as cetrimide.

In ophthalmic preparations, benzalkonium chloride is one of the most widely used preservatives, at a concentration of 0.01-0.02% w/v. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*.

In nasal and otic formulations a concentration of 0.002-0.02% is used, sometimes in combination with 0.002-0.005% w/v thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small volume parenteral products.

Benzalkonium chloride is additionally used as a preservative in cosmetics.

8. Description

Benzalkonium chloride occurs as a white or yellowish white amorphous powder, a thick gel, or gelatinous flakes. It is hygroscopic, soapy to the touch and has a mild aromatic odor and very bitter taste.

9. Pharmacopeial Specifications

Test	PhEur 1985	USPNF XVII
Identification	+	+
Acidity or alkalinity	+	—
Appearance of solution	+	—
Water	⩽ 10.0%	⩽ 15.0%
Residue on ignition	—	⩽ 2.0%
Sulfated ash	⩽ 0.1%	—
Water-insoluble matter	—	+
Foreign amines	+	+
Ratio of alkyl components	—	+
Assay (dried basis)		
of n-$C_{12}H_{25}$	—	⩾ 40.0%
of n-$C_{14}H_{29}$	—	⩾ 20.0%
of n-$C_{12}H_{25}$ & n-$C_{14}H_{29}$	—	⩾ 70.0%
for total alkyl content	95.0-104.0%	97.0-103.0%

10. Typical Properties

Acidity/alkalinity:
pH = 5-8 for a 10% w/v aqueous solution.

Antimicrobial activity: benzalkonium chloride solutions are active against a wide range of bacteria, yeasts and fungi. Activity is more marked against Gram-positive than Gram-negative bacteria and minimal against bacterial endospores and acid fast bacteria. The antimicrobial activity of benzalkonium chloride is significantly dependent upon the alkyl composition of the homolog mixture.[1] Benzalkonium chloride is ineffective against some *Pseudomonas aeruginosa* strains, *Mycobacterium tuberculosis*, *Trichophyton interdigitale* and *T. rubrum*. However, combined with disodium edetate (0.01-0.1% w/v), benzyl alcohol, phenylethanol or phenylpropanol, the activity against *Pseudomonas aeruginosa* is increased.[2] Antimicrobial activity may also be enhanced by the addition of phenylmercuric acetate, phenylmercuric borate, chlorhexidine, cetrimide or *m*-cresol.[3,4] In the presence of citrate and phosphate buffers (but not borate), activity against *Pseudomonas* can be reduced. *See also* Sections 11 and 12.

Benzalkonium chloride is relatively inactive against spores and molds, but is active against some viruses, including HIV.[5] Inhibitory activity increases with pH although antimicrobial activity occurs between pH 4-10. Typical minimum inhibitory concentrations (MICs) are shown in Table I.

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Table I: Minimum inhibitory concentrations (MICs) of benzalkonium chloride.

Microorganism	MIC (μg/mL)
Aerobacter aerogenes	64
Clostridium histolyticum	5
Clostridium oedematiens	5
Clostridium tetani	5
Clostridium welchii	5
Escherichia coli	16
Pneumococcus II	5
Proteus vulgaris	64
Pseudomonas aeruginosa	30
Salmonella enteritidis	30
Salmonella paratyphi	16
Salmonella typhosa	4
Shigella dysenteriae	2
Staphylococcus aureus	1.25
Streptococcus pyrogenes	1.25
Vibrio cholerae	2

Density: ≈ 0.98 g/cm^3 at 20°C
Melting point: ≈ 40°C
Partition coefficients: the octanol: water partition coefficient varies with the alkyl chain length of the homolog; 9.98 for C_{12}, 32.9 for C_{14} and 82.5 for C_{16}.
Solubility: practically insoluble in ether; very soluble in acetone, ethanol (95%), methanol, propanol and water. Aqueous solutions of benzalkonium chloride foam when shaken, have a low surface tension and possess detergent and emulsifying properties.

11. Stability and Storage Conditions

Benzalkonium chloride 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. Dilute solutions stored in polyvinyl chloride or polyurethane foam containers may lose antimicrobial activity. The bulk material should be stored in an airtight container, protected from light and contact with metals, in a cool, dry, place.

12. Incompatibilities

Incompatible with aluminum, anionic surfactants, citrates, cotton, fluorescein, hydrogen peroxide, hydroxypropyl methylcellulose,[6] iodides, kaolin, lanolin, nitrates, nonionic surfactants in high concentration, permanganates, protein, salicylates, silver salts, soaps, sulfonamides, tartrates, zinc oxide, zinc sulfate, some rubber mixes and some plastic mixes.

13. Method of Manufacture

Benzalkonium chloride is formed by the reaction of a solution of *N*-alkyl-*N*-methyl-benzamine with methyl chloride in an organic solvent suitable for precipitating the quaternary compound as it is formed.

14. Safety

Benzalkonium chloride is usually nonirritating, nonsensitizing and well tolerated in the dilutions normally employed on the skin and mucous membranes. However, benzalkonium chloride has been associated with adverse effects when used in some pharmaceutical formulations.[7]
Ototoxicity can occur when benzalkonium chloride is applied to the ear[8] and prolonged contact with the skin can occasionally cause irritation and hypersensitivity. Benzalkonium chloride is also known to cause bronchoconstriction in some asthmatics when used in nebulizer solutions.[9-13]
Toxicity experiments with rabbits have shown benzalkonium chloride, in concentrations higher than that normally used as a preservative, to be harmful to the eye. However, the human eye appears to be less affected than the rabbit eye and many ophthalmic products have been formulated with benzalkonium chloride 0.01% w/v as the preservative. Benzalkonium chloride is not suitable for use as a preservative in solutions used for storing and washing hydrophilic soft contact lenses, as the benzalkonium chloride can bind to the lenses and may later produce ocular toxicity when the lenses are worn.[14] Solutions stronger than 0.03% w/v concentration entering the eye require prompt medical attention.
Local irritation of the throat, esophagus, stomach and intestine can occur following contact with strong solutions (> 0.1% w/v). The fatal oral dose of benzalkonium chloride in humans is estimated to be 1-3 g. Adverse effects following oral ingestion include vomiting, collapse and coma. Toxic doses lead to paralysis of the respiratory muscles, dyspnea and cyanosis.

LD_{50} (guinea pig, oral): 200 mg/kg[15]
LD_{50} (mouse, IP): 10 mg/kg
LD_{50} (mouse, IV): 10 mg/kg
LD_{50} (mouse, oral): 175 mg/kg
LD_{50} (mouse, SC): 64 mg/kg
LD_{50} (rat, IP): 14.5 mg/kg
LD_{50} (rat, IV): 13.9 mg/kg
LD_{50} (rat, oral): 240 mg/kg
LD_{50} (rat, SC): 400 mg/kg
LD_{50} (rat, skin): 1.56 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzalkonium chloride is irritant to the skin and eyes and repeated exposure to the skin may cause hypersensitivity. Concentrated benzalkonium chloride solutions accidentally spilled on the skin may produce corrosive skin lesions with deep necrosis and scarring, and should be washed immediately with water, followed by soap solutions applied freely. Gloves, eye protection and suitable protective clothing should be worn.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (inhalations, IM injections, nasal, ophthalmic, otic and topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Braz, Egypt, Eur, Fr, Gr, Hung, It, Jpn, Mex, Neth, Port, Swiss, Turk, Yug and USPNF. Also in BP Vet.

18. Related Substances

Benzethonium Chloride; Cetrimide.

19. Comments

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22. Authors

USA: NM Vemuri.

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Benzethonium Chloride

1. Nonproprietary Names

USP: Benzethonium chloride

2. Synonyms

Benzyldimethyl[2-[2-(*p*-1,1,3,3-tetramethylbutylphenoxy)ethoxy]ethyl]ammonium chloride; BZT; diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride; *Hyamine 1622*.

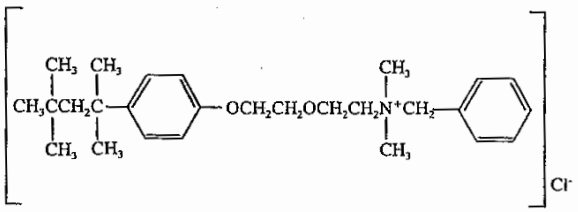
3. Chemical Name and CAS Registry Number

N,*N*-Dimethyl-*N*-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]benzene-methanaminium chloride [121-54-0]

4. Empirical Formula and Molecular Weight

$C_{27}H_{42}ClNO_2$ 448.10

5. Structural Formula



6. Functional Category

Antimicrobial preservative; antiseptic; disinfectant.

7. Applications in Pharmaceutical Formulation or Technology

Benzethonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative. Typically, it is used for this purpose in injections, ophthalmic and otic preparations at concentrations between 0.01-0.02% w/v. Benzethonium chloride may also be used as a wetting and solubilizing agent, and as a topical disinfectant.

In cosmetics such as deodorants, benzethonium chloride may be used as an antimicrobial preservative in concentrations up to 0.5% w/v.

The physical properties and applications of benzethonium chloride are similar to other cationic surfactants such as cetrimide.

8. Description

Benzethonium chloride occurs as a white crystalline material with a mild odor and very bitter taste.

9. Pharmacopeial Specifications

Test	USP XXII
Identification	+
Melting range	158-163°C
Loss on drying	⩽ 5.0%
Residue on ignition	⩽ 0.1%
Ammonium compounds	+
Assay (dried basis)	97.0-103.0%

10. Typical Properties

Acidity/alkalinity:
pH = 4.8-5.5 for a 1% w/v aqueous solution.

Antimicrobial activity: optimum antimicrobial activity occurs between pH 4-10. Preservative efficacy is enhanced by ethanol and reduced by soaps and other anionic surfactants. Typical minimum inhibitory concentrations (MICs) are shown below:[1]

Microorganism	MIC (μg/mL)
Aspergillus niger	128
Candida albicans	64
Escherichia coli	32
Penicillium notatum	64
Proteus vulgaris	64
Pseudomonas aeruginosa	250
Pseudomonas cepacia	250
Pseudomonas fluorescens	250
Staphylococcus aureus	0.5
Streptococcus pyogenes	0.5

Solubility: soluble 1 in less than 1 of acetone, chloroform, ethanol (95%) and water; soluble 1 in 6000 of ether. Dissolves in water to produce a foamy, soapy solution.

11. Stability and Storage Conditions

Benzethonium chloride is stable. Aqueous solutions may be sterilized by autoclaving.

The bulk material should be stored in an airtight container protected from light, in a cool, dry, place.

12. Incompatibilities

Benzethonium chloride is incompatible with soaps and other anionic surfactants and may be precipitated from solutions greater than 2% w/v concentration by the addition of mineral acids and some salt solutions.

13. Method of Manufacture

p-Diisobutylphenol is condensed in the presence of a basic catalyst with β,β′-dichlorodiethyl ether to yield 2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl chloride. Alkaline dimethylamination then produces the corresponding tertiary amine which, after purification by distillation, is dissolved in a suitable organic solvent and treated with benzyl chloride to precipitate benzethonium chloride.[2]

14. Safety

Benzethonium chloride is readily absorbed and is generally regarded as a toxic substance when administered orally. Ingestion may cause vomiting, collapse, convulsions and coma. The probable lethal human oral dose is estimated to be 50-500 mg/kg body-weight.

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The topical use of solutions containing greater than 5% w/v benzethonium chloride can cause irritation although benzethonium chloride is not regarded as a sensitizer. The use of 0.5% w/v benzethonium chloride in cosmetics is associated with few adverse effects. A maximum concentration of 0.02% w/v benzethonium chloride is recommended for use in cosmetics used in the eye area and this is also the maximum concentration generally used in pharmaceutical formulations such as injections and ophthalmic preparations.[3]
See also Benzalkonium Chloride.

LD_{50} (mouse, IP): 8 mg/kg[4]
LD_{50} (mouse, IV): 30 mg/kg
LD_{50} (mouse, oral): 340 mg/kg
LD_{50} (rat, IP): 17 mg/kg
LD_{50} (rat, IV): 19 mg/kg
LD_{50} (rat, oral): 370 mg/kg
LD_{50} (rat, SC): 120 mg/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM and IV injections, ophthalmic and otic preparations).

17. Pharmacopeias

Egypt, Jpn, Nord and US.

18. Related Substances

Benzalkonium Chloride; Cetrimide.

19. Comments

Benzethonium chloride has been used therapeutically in the past as a disinfectant and topical anti-infective agent. However, its use in these applications has largely been superseded by other more effective antimicrobials and it is now largely used solely as a preservative in a limited number of pharmaceutical and cosmetic formulations.

20. Specific References

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4. Sweet DV, editor. Registry of toxic effects of chemical substances. Cincinnati: US Department of Health, 1987.

21. General References

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22. Authors

UK: PJ Weller.

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Calcium Stearate

1. Nonproprietary Names
USPNF: Calcium stearate

2. Synonyms
Calcium distearate; *HyQual*; stearic acid, calcium salt.

3. Chemical Name and CAS Registry Number
Octadecanoic acid calcium salt [1592-23-0]

4. Empirical Formula and Molecular Weight
$C_{36}H_{70}CaO_4$ 607.03 (for pure material)

The USPNF XVII describes calcium stearate as a compound of calcium with a mixture of solid organic acids obtained from fats and consists chiefly of variable proportions of calcium stearate and calcium palmitate ($C_{32}H_{62}CaO_4$). It contains the equivalent of 9.0-10.5% of calcium oxide.

5. Structural Formula
$[CH_3(CH_2)_{16}COO]_2Ca$

6. Functional Category
Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology
Calcium stearate is primarily used in pharmaceutical formulations as a lubricant in tablet and capsule manufacture at concentrations up to 1.0% w/w. Although it has good antiadherent and lubricant properties, calcium stearate has poor glidant properties.

Calcium stearate is also employed as an emulsifier, stabilizing agent and suspending agent. It is also used in cosmetics and food products.

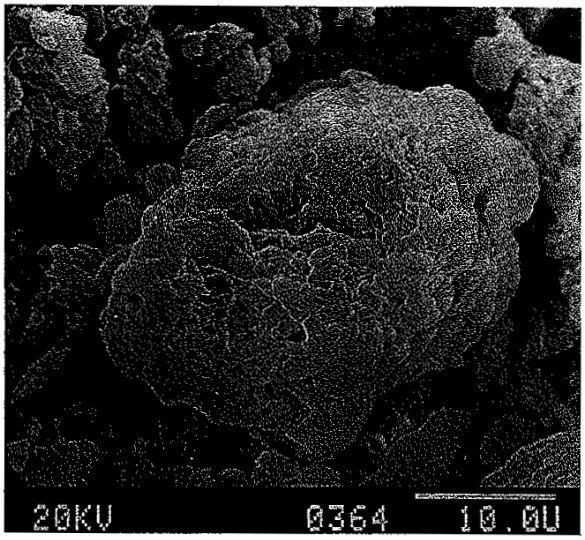
8. Description
Calcium stearate occurs as a fine, white to yellowish white-colored, bulky powder having a slight, characteristic odor. It is unctuous and free from grittiness.

9. Pharmacopeial Specifications

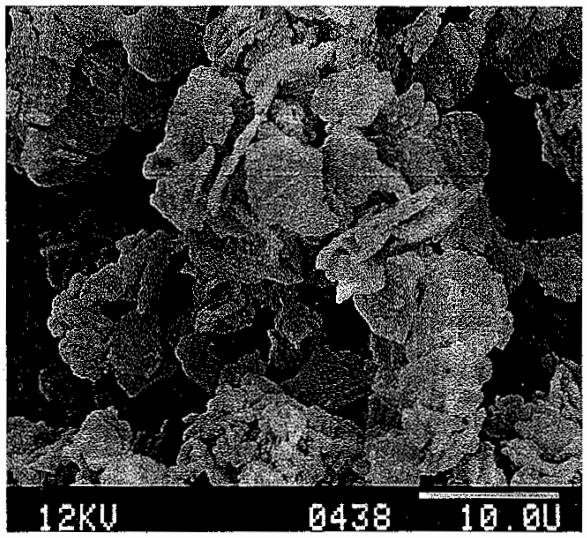
Test	USPNF XVII (Suppl 5)
Identification	+
Loss on drying	⩽ 4.0%
Arsenic	⩽ 3 ppm
Heavy metals	⩽ 0.001%
Assay (as CaO)	9.0-10.5%

10. Typical Properties
Acid value: 191-203
Ash: 9.9-10.3%
Chloride: < 200 ppm
Density: 1.04 g/cm^3

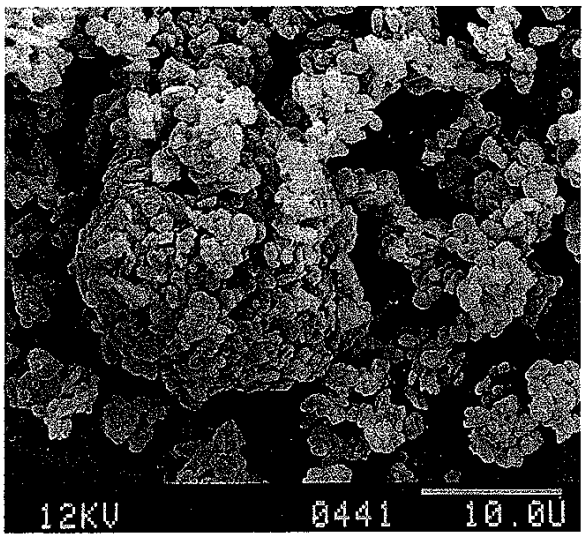
SEM: 1
Excipient: Calcium stearate (Standard)
Manufacturer: Durham Chemicals
Lot No.: 0364
Voltage: 20 kV



SEM: 2
Excipient: Calcium stearate (Precipitated)
Manufacturer: Witco Corporation
Lot No.: 0438
Voltage: 12 kV

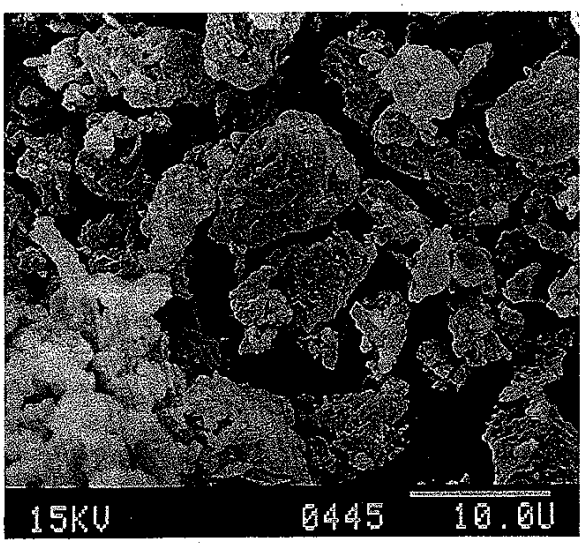


SEM: 3
Excipient: Calcium stearate (EA)
Manufacturer: Witco Corporation
Voltage: 12 kV

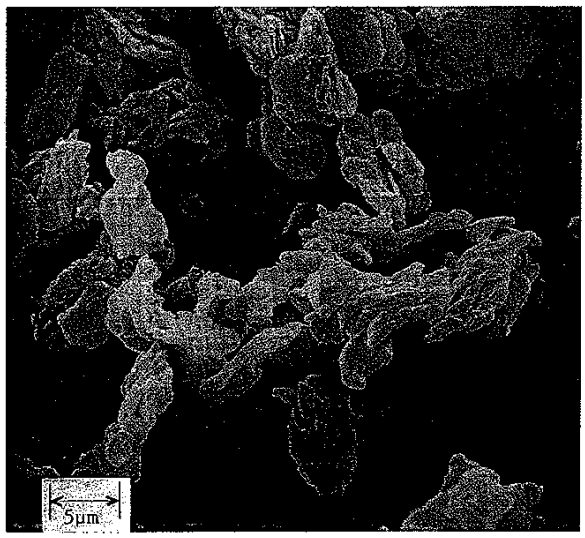


SEM: 5
Excipient: Calcium stearate
Manufacturer: Mallinckrodt Speciality Chemicals Co
Lot No.: JMP
Magnification: 600x
Voltage: 5 kV

SEM: 4
Excipient: Calcium stearate (Fused)
Manufacturer: Witco Corporation
Voltage: 15 kV



SEM: 6
Excipient: Calcium stearate
Manufacturer: Mallinckrodt Speciality Chemicals Co
Lot No.: JMP
Magnification: 2400x
Voltage: 5 kV



Density (bulk & tapped):

	Bulk Density g/cm^3	Tapped Density g/cm^3
Durham Chemicals		
(Standard)	—	0.26
(A)	—	0.45
(AM)	—	0.33
Witco Corporation		
(EA)	0.21	0.27
(Fused)	0.38	0.48
(Precipitated)	0.16	0.20

Flowability: 21.2-22.6% (Carr compressibility index)
Free fatty acid: 0.3-0.5%
Melting point: 149-160°C
Moisture content: *see* HPE Data.
Particle size distribution: 1.7-60 μm.
100% through a 73.7 μm (#200 mesh); 99.5% through a 44.5 μm (#325 mesh).
Shear strength: 14.71 MPa
Softening point: 160°C
Solubility: practically insoluble in ethanol (95%), ether and water.
Specific surface area: 5.76-7.44 m^2/g
Sulfate: < 0.25%

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content	MC-23	21	2.96% [a]
Moisture content	MC-12	18	2.97% [b]

Supplier: a. Witco Corporation; b. Mallinckrodt Speciality Chemicals Co.

11. Stability and Storage Conditions

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

12. Incompatibilities

–

13. Method of Manufacture

Calcium stearate is prepared by the reaction of calcium chloride with a mixture of the sodium salts of stearic and palmitic acids. The calcium stearate formed is collected and washed with water to remove any sodium chloride.

14. Safety

Calcium stearate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Calcium stearate should be used in a well-ventilated environment; eye protection, gloves and a respirator are recommended.

16. Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Jpn and USPNF.

18. Related Substances

Magnesium Stearate; Stearic Acid; Zinc Stearate.

19. Comments

See Magnesium Stearate for further information and references.

20. Specific References

–

21. General References

Büsch G, Neuwald F. Metallic soaps as water-in-oil emulsifiers [in German]. J Soc Cosmet Chem 1973; 24: 763-769.

22. Authors

USA: LV Allen.

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Microcrystalline Cellulose

1. Nonproprietary Names

BP: Microcrystalline cellulose
PhEur: Cellulosum microcristallinum
USPNF: Microcrystalline cellulose

2. Synonyms

Avicel; cellulose gel; crystalline cellulose; E460; *Emcocel*; *Fibrocel*; *Tabulose*; *Vivacel.*

3. Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

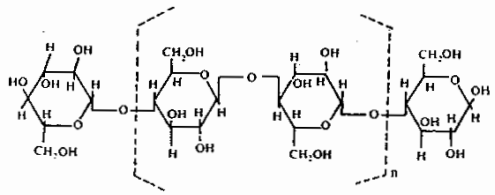
4. Empirical Formula

$(C_6H_{10}O_5)_n$
Where n ≈ 220.

Molecular Weight

≈ 36 000

5. Structural Formula



6. Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals primarily as a diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes.[1-7] In addition to its use as a diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.
Microcrystalline cellulose is also used in cosmetics and food products.

Use	Concentration (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule diluent	20-90
Tablet disintegrant	5-15
Tablet diluent	20-90

8. Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white-colored, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size grades which have different properties and applications.

SEM: 1
Excipient: Microcrystalline cellulose (*Avicel PH 101*)
Manufacturer: FMC Corporation
Lot No.: 08345J
Magnification: 360x

9. Pharmacopeial Specifications

Test	PhEur 1984	USPNF XVII (Suppl 9)
Identification	+	+
pH	5.0-7.5	5.0-7.0 [a] 5.5-7.0 [b]
Solubility	+	—
Loss on drying	⩽ 6.0%	⩽ 5.0%
Residue on ignition	—	⩽ 0.05%
Sulfated ash	⩽ 0.1%	—
Ether-soluble substances	⩽ 0.05%	—
Water-soluble substances	⩽ 0.2%	⩽ 0.24% [a] ⩽ 0.16% [b]
Heavy metals	⩽ 10 ppm	⩽ 0.001%
Starch	+	+
Organic impurities	+	+
Assay (dried basis)	—	97.0-102.0%

Note:
a. Grades with less than 5% retained on a 37 µm screen.
b. Grades with more than 5% retained on a 37 µm screen.

10. Typical Properties

Angle of repose: 34.4° for *Emcocel 90M*.[9]
Density (bulk):
0.32 g/cm^3 for *Avicel PH 101*;[10]
0.29 g/cm^3 for *Emcocel 90M*.[9]
Density (tapped):
0.45 g/cm^3 for *Avicel PH 101*;[10]
0.35 g/cm^3 for *Emcocel 90M*.[9]
Flowability: 1.41 g/s for *Emcocel 90M*.[9]
Melting point: chars at 260-270°C.
Moisture content: typically, less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.[11] *See* HPE Data and Table I.

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Table I: Properties of some commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH 101 [a]	50	60	⩽ 1.0	⩽ 5.0
		200	⩽ 30.0	
Avicel PH 102 [a]	100	60	⩽ 8.0	⩽ 5.0
		200	⩾ 45.0	
Avicel PH 103 [a]	50	60	⩽ 1.0	⩽ 3.0
		200	⩽ 30.0	
Avicel PH 105 [a]	20	400	⩽ 1.0	⩽ 5.0
Avicel PH 112 [a]	100	60	⩽ 8.0	⩽ 1.5
		200	⩾ 45.0	
Avicel PH 200 [a]	180	60	⩾ 10.0	⩽ 5.0
		100	⩾ 50.0	
Emcocel 50M [b]	51	60	⩽ 0.25	⩽ 5.0
		200	⩽ 30.0	
Emcocel 90M [b]	91	60	⩽ 8.0	⩽ 5.0
		200	⩾ 45.0	
Vivacel 101 [c]	50	50	⩾ 35.0	⩽ 5.0
		150	⩽ 10.0	
Vivacel 102 [c]	100	50	⩾ 50.0	⩽ 5.0
		150	⩽ 30.0	
Vivacel 12 [c]	180	50	⩾ 70.0	⩽ 5.0
		500	⩽ 1.0	
Vivacel 20 [c]	20	50	⩽ 2.0	⩽ 5.0
		150	⩽ 0.1	

Suppliers: a. FMC Corporation; b. Edward Mendell Co Inc; c. J. Rettenmaier & Söhne GmbH.

HPE Laboratory Project Data			
Method	**Grade***	**Lab #**	**Results**
Bulk/tap density			
BTD-8	PH 101	36	B: 0.320 g/cm^3
			T: 0.386 g/cm^3
BTD-8	PH 102	36	B: 0.307 g/cm^3
			T: 0.370 g/cm^3
BTD-8	PH 103	36	B: 0.301 g/cm^3
			T: 0.370 g/cm^3
BTD-8	PH 105	36	B: 0.260 g/cm^3
			T: 0.333 g/cm^3
Density			
DE-1	PH 101	31	1.618 g/cm^3
DE-1	PH 102	31	1.554 g/cm^3
DE-1	PH 103	31	1.571 g/cm^3
DE-1	PH 105	31	1.573 g/cm^3
Moisture content			
MC-3	PH 101	31	3.745%
MC-3	PH 105	31	4.655%
MC-3	PH 103	31	3.065%
MC-3	PH 102	31	3.315%
EMC-1	PH 101	5	*See* Fig. 1.
SI-1	PH 102	13	*See* Fig. 2.
SI-1	PH 103	13	*See* Fig. 2.
SI-1	PH 105	13	*See* Fig. 2.
Solubility in water at 25°C			
SOL-8	PH 101	30	1 mg/mL
SOL-8	PH 102	30	0.2 mg/mL

* Supplier: FMC Corporation (*Avicel*).

Particle size distribution: typical mean particle size is 20-200 μm. Different grades may have a different nominal mean particle size, *see* Table I.
Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids and most organic solvents.
Specific surface area: 1.18 m^2/g for *Avicel PH 101*.[10]

11. Stability and Storage Conditions

Microcrystalline cellulose is a stable, though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

Incompatible with strong oxidizing agents.

13. Method of Manufacture

Microcrystalline cellulose is manufactured by the controlled hydrolysis, with dilute mineral acid solutions, of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14. Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a nontoxic and nonirritant material.
Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential.

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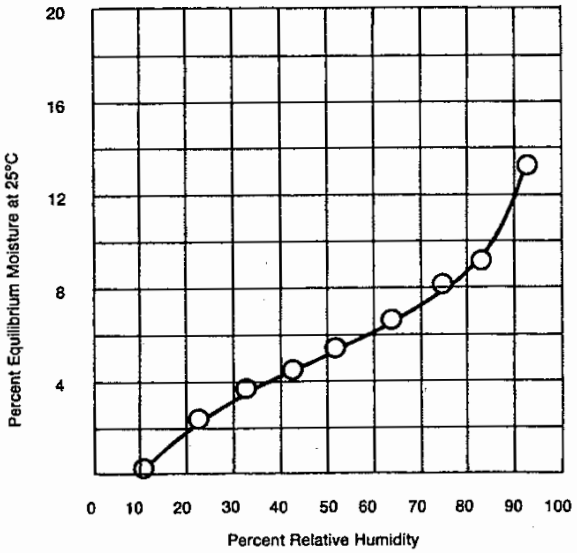

Fig. 1: Equilibrium moisture content of microcrystalline cellulose (*Avicel PH 101*, Lot #1929).

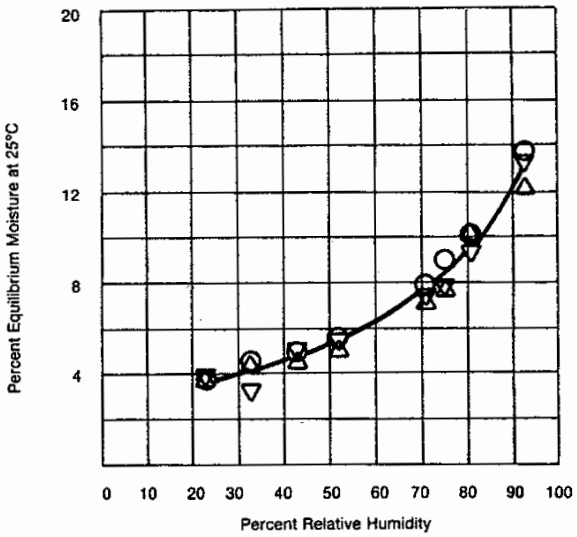

Fig. 2: Equilibrium moisture content of microcrystalline cellulose.
○ *Avicel PH 102*, Lot #2911-2904.
△ *Avicel PH 105*, Lot #5926.
▽ *Avicel PH 103*, Lot #3445.

Consumption of large quantities of cellulose may however have a laxative effect although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.
Deliberate abuse of formulations containing cellulose, either by inhalation or injection, has resulted in the formation of cellulose granulomas.[12]

15. Handling Precautions

Observe normal precautions appropriate to the circumstance and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection and a dust mask are recommended. In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 5 mg/m^3 for respirable dust; short-term the limit for total inhalable dust has been set at 20 mg/m^3.[13]

16. Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (inhalations, oral capsules, powders, suspensions, syrups and tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Eur, Fr, Gr, Hung, Ind, It, Jpn, Mex, Neth, Port, Swiss and USPNF.

18. Related Substances

Microcrystalline cellulose and carboxymethylcellulose sodium
Powdered Cellulose.

Microcrystalline cellulose and carboxymethylcellulose sodium
Synonyms: *Avicel RC-581*; *Avicel RC-591*; *Avicel CL-611*; colloidal cellulose; dispersible cellulose.
Appearance: white colored, odorless and tasteless hygroscopic powder.
Pharmacopeias: Br, Jpn and USPNF.
Acidity/alkalinity:
pH = 6-8 for a 1.2% w/v aqueous dispersion.
Moisture content: not more than 6.0% w/w.
Particle size distribution: ⩽ 0.1% retained on a #60 mesh and ⩽ 50% retained on a #325 mesh for *Avicel CL-611*; ⩽ 0.1% retained on a #60 mesh and ⩽ 35% retained on a #200 mesh for *Avicel RC-581*; ⩽ 0.1% retained on a #60 mesh and ⩽ 45% retained on a #325 mesh for *Avicel RC-591*.
Solubility: practically insoluble in dilute acids and organic solvents. Partially soluble in dilute alkali and water (carboxymethylcellulose sodium fraction).
Viscosity (dynamic): 5-20 mPa s (5-20 cP) for a 1.2% w/v aqueous dispersion of *Avicel CL-611*; 72-168 mPa s (72-168 cP) for *Avicel RC-581* and 39-91 mPa s (39-91 cP) for *Avicel RC-591* at the same concentration.
Comments: mixtures of microcrystalline cellulose and carboxymethylcellulose sodium that are dispersible in water and produce thixotropic gels are suitable as suspending vehicles in pharmaceutical formulations. The amount of carboxymethylcellulose present can vary between 8.3-18.8% w/w depending upon the grade of material.

19. Comments

Several different grades of microcrystalline cellulose are commercially available which differ in their method of manufacture,[14,15] particle size, moisture, flow, and other physical properties.[16-23] The larger particle size grades generally provide better flow properties in pharmaceutical machinery. Low moisture grades are used with moisture-sensitive materials.

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21. General References

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22. Authors

USA: L Mathur.

Docusate Sodium

1. Nonproprietary Names

BP: Docusate sodium
USP: Docusate sodium

2. Synonyms

Bis(2-ethylhexyl) sodium sulfosuccinate; *Cropol 35*; *Cropol 60*; *Cropol 70*; dioctyl sodium sulfosuccinate; dioctyl sodium sulphosuccinate; DSS; sodium dioctyl sulfosuccinate; sulfobutanedioic acid 1,4-bis(2-ethylhexyl) ester, sodium salt.

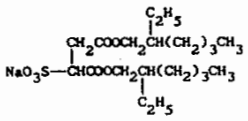
3. Chemical Name and CAS Registry Number

Sodium 1,4-bis(2-ethylhexyl) sulfosuccinate
[577-11-7]

4. Empirical Formula and Molecular Weight

$C_{20}H_{37}NaO_7S$ 444.56

5. Structural Formula



6. Functional Category

Anionic surfactant; therapeutic agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Docusate sodium and docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Docusate sodium is mainly used in capsule and direct compression tablet formulations to assist in wetting and dissolution. Docusate salts are also widely used in oral formulations as laxatives and fecal softeners.

Use	Concentration (%)
IM injections	0.015
Surfactant (wetting/dispersing/emulsifying agent)	0.01-1.0
Tablet coating agent	20*
Tablet disintegrant	≈ 0.5

* Formulation of a tablet coating solution: 20% docusate sodium; 2-15% sodium benzoate; 0.5% propylene glycol; solution made in ethanol (70%).

8. Description

Docusate sodium is a white or almost white, wax-like, bitter tasting, plastic solid with a characteristic octanol-like odor. It is hygroscopic and usually available in the form of pellets, flakes or rolls of tissue-thin material. A 50-75% solution in various solvents is also available.

9. Pharmacopeial Specifications

Test	BP 1993 (Ad 1994)	USP XXII
Identification	+	+
Clarity of solution	—	+
Alkalinity	+	—
Water	—	⩽ 2.0%
Loss on drying	⩽ 3.0%	—
Residue on ignition	—	15.5-16.5%
Arsenic	—	⩽ 3 ppm
Heavy metals	⩽ 10 ppm	⩽ 0.001%
Bis(2-ethylhexyl) maleate	—	⩽ 0.4%
Chloride	+	—
Related nonionic substances	+	—
Sodium sulfate	⩽ 2.0%	—
Assay	98.5-100.5%	99.0-100.5%

10. Typical Properties

Acidity/alkalinity:
pH = 5.8-6.9 (1% w/v aqueous solution).
Acid value: ⩽ 2.5
Critical micelle concentration:
0.11% w/v aqueous solution at 25°C.
Density: 1.1 g/cm^3
Hydroxyl value: 6-8
Interfacial tension: in water versus mineral oil at 25°C, *see* table below.

Concentration (% w/v)	Interfacial tension (mN/m)
0.01	20.7
0.1	5.9
1.0	1.84

Iodine number: ⩽ 0.25
Melting point: 153-157°C
Saponification value: 240-253
Solubility: *see* table below and also HPE Data.

Solvent	Solubility at 20°C Unless otherwise stated
Acetone	soluble
Chloroform	1 in 1
Ethanol (95%)	1 in 3
Ether	1 in 1
Glycerin	freely soluble
Vegetable oils	soluble
Water	1 in 70 at 25°C*
	1 in 56 at 30°C
	1 in 44 at 40°C
	1 in 33 at 50°C
	1 in 25 at 60°C
	1 in 18 at 70°C

* In water, higher concentrations form a thick gel.
Surface tension:

Concentration in water at 25°C (% w/v)	Surface tension (mN/m)
0.001	62.8
0.1	28.7
1.0	26.0

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	HPE Laboratory Project Data		
	Method	Lab #	Results
Density	DE-1	7	1.16 ± 0.03 g/cm^3
Moisture content	MC-29	23	1.51%
Solubility			
Ethanol (95%) at 25°C	SOL-6	23	> 1.0 g/mL
Ethanol (95%) at 37°C	SOL-6	23	> 1.0 g/mL
Hexane at 25°C	SOL-6	23	> 2.5 g/mL
Hexane at 37°C	SOL-6	23	> 2.5 g/mL
Propylene glycol at 25°C	SOL-6	23	0.80-1.25 g/mL
Propylene glycol at 37°C	SOL-6	23	0.80-1.25 g/mL
Water at 25°C	SOL-6	23	0.028 g/mL
Water at 37°C	SOL-6	23	0.107-0.111 g/mL

Supplier: American Cyanamid Co.

11. Stability and Storage Conditions

Docusate sodium is stable in the solid state when stored at room temperature. Dilute aqueous solutions of docusate sodium between pH 1 and pH 10 are stable at room temperature. However, at very low pH (pH < 1) and very high pH (pH > 10) docusate sodium solutions are subject to hydrolysis.

The solid material is hygroscopic and should be stored in an airtight container in a cool, dry, place.

12. Incompatibilities

Electrolytes, e.g. 3% sodium chloride, added to aqueous solutions of docusate sodium can cause turbidity.[1,2] However, docusate sodium possesses greater tolerance to calcium, magnesium and other polyvalent ions as compared to other surfactants. Docusate sodium is incompatible with acids at pH < 1 and alkalis at pH > 10.

13. Method of Manufacture

Maleic anhydride is treated with 2-ethylhexanol to produce dioctyl maleate, which is then reacted with sodium bisulfite.

14. Safety

Docusate salts are widely used in oral formulations as therapeutic agents for their fecal softening and laxative properties. As a laxative in adults, up to 500 mg of docusate sodium is administered daily in divided doses; in children over 6 months old up to 75 mg, in divided doses, is used. The quantity of docusate sodium used as an excipient in oral formulations should therefore be controlled to avoid unintended laxative effects. Adverse effects associated with docusate sodium include: diarrhea; nausea; vomiting; abdominal cramps and skin rashes.

Docusate salts are absorbed from the gastrointestinal tract and excreted in bile; they may cause alteration of the gastrointestinal epithelium.[3,4] The gastrointestinal or hepatic absorption of other drugs may also be affected by docusate salts, enhancing activity and possibly toxicity. Docusate sodium should not be administered with mineral oil as it may increase the absorption of the oil.

LD_{50} (mouse, IV): 0.06 g/kg[5]
LD_{50} (mouse, oral): 2.64 g/kg
LD_{50} (rat, IP): 0.59 g/kg
LD_{50} (rat, oral): 1.9 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Docusate sodium may be irritant to the eyes, skin and on inhalation. Eye protection, gloves and a dust mask or respirator are recommended. When heated to decomposition docusate sodium emits toxic fumes.

16. Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (IM injections, oral capsules, suspensions and tablets, also topical formulations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br and US.

18. Related Substances

Docusate calcium; docusate potassium.

Docusate calcium: $C_{40}H_{74}CaO_{14}S_2$
Molecular weight: 883.23
CAS number: [128-49-4]
Synonyms: 1,4-bis(2-ethylhexyl) sulfosuccinate, calcium salt; dioctyl calcium sulfosuccinate.
Appearance: white amorphous solid with a characteristic octanol-like odor.
Pharmacopeias: US.
Solubility: soluble 1 in 1 of ethanol (95%) and 1 in 3300 of water; very soluble in corn oil and polyethylene glycol 400.

Docusate potassium: $C_{20}H_{37}KO_7S$
Molecular weight: 460.67
CAS number: [7491-09-0]
Synonyms: dioctyl potassium sulfosuccinate; potassium 1,4-bis(2-ethylhexyl) sulfosuccinate.
Appearance: white amorphous solid with a characteristic octanol-like odor.
Pharmacopeias: US.
Solubility: soluble in ethanol (95%) and glycerin; sparingly soluble in water.

19. Comments

A convenient way of making a 1% w/v aqueous solution of docusate sodium is to add 1 g of solid to about 50 mL of water and to apply gentle heat. The docusate sodium dissolves in a short time and the resulting solution can be made up to 100 mL with water. Alternatively, 1 g may be soaked overnight in 50 mL of water and the additional water may then be added with gentle heating and stirring.

Docusate sodium may alter the dissolution characteristics of certain dosage forms and the bioavailability of some drugs.

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Shah DN, Feldkamp JR, White JL, Hem SL. Effect of the pH-zero point of charge relationship on the interaction of ionic compounds and polyols with aluminum hydroxide gel. J Pharm Sci 1982; 71: 266-268.

22. Authors

USA: AW Malick.

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Gelatin

1. Nonproprietary Names

BP: Gelatin
PhEur: Gelatina
USPNF: Gelatin

2. Synonyms

Crodyne BY19; gelatine; *Pharmagel A*; *Pharmagel B*; *Vee Gee*.

3. Chemical Name and CAS Registry Number

Gelatin [9000-70-8]

4. Empirical Formula Molecular Weight

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Gelatin may be a mixture of both types.
The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15 000-250 000.

5. Structural Formula

See Section 4.

6. Functional Category

Coating agent; film-former; gelling agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Gelatin is widely used in a variety of pharmaceutical formulations (*see* Section 16) although it is most frequently used to form either hard or soft gelatin capsules.[1,2]
Gelatin capsules are unit dosage forms, which are filled with an active drug and generally designed for oral administration. Whilst gelatin is poorly soluble in cold water, a gelatin capsule will swell in gastric fluid to rapidly release its contents.
Hard capsules are manufactured in two pieces by dipping stainless steel pins into a gelatin solution which is distributed evenly around the pin. The gelatin is then set with a blast of chilled air and dried to remove any moisture. The capsule halves are then removed, trimmed and filled before they are joined and closed with a tamper-evident seal. The USPNF XVII permits gelatin, used to produce hard capsules, to contain various coloring agents, antimicrobial preservatives and sodium lauryl sulfate. Manufacturers may also add a hardening agent, such as sucrose, to hard gelatin capsules. Capsules varying in size from 0.13-1.37 mL volume are commercially available.
Soft gelatin capsules are formed from an aqueous gelatin solution which contains a plasticizer such as glycerin or sorbitol. Two soft gelatin strips are formed which run between suitable dies. As the dies meet, capsules are formed by injecting the filling material, followed by the capsule halves being sealed together.
Gelatin is also used for the microencapsulation of drugs, where the active drug is sealed inside a microsized capsule that may then be handled as a powder. Gelatin forms simple coacervates at temperatures above 40°C with dehydrating agents such as ethanol or 7% sodium sulfate solution. A gelatin solution is first adjusted to its isoelectric point and then a dehydrating agent added slowly over a period of one hour. Complex coacervation between gelatin and acacia requires dilute solutions of equal concentration. The temperature should be controlled at 40°C and the pH adjusted to between 3.8-4.6, depending on the system being encapsulated. The concentration of the two colloid solutions should not be greater than 2%.
Low molecular weight gelatin has been investigated for its ability to enhance the dissolution of orally ingested drugs.[3]
Other uses of gelatin include the preparation of pastes, pastilles, pessaries and suppositories. In addition, it is used as a vehicle for parenteral formulations, as a tablet binder and coating agent, and as a viscosity-increasing agent for solutions and semi-solids.
Therapeutically, gelatin has been used as a plasma substitute and in the preparation of wound dressings.[4]
Gelatin is also widely used in food products and photographic emulsions.

8. Description

Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odorless and tasteless and is available as translucent sheets and granules, or as a powder.

9. Pharmacopeial Specifications

Test	PhEur 1986	USPNF XVII (Suppl 8)
Identification	+	+
Microbial limits	+	+
Residue on ignition	⩽ 2.0%	⩽ 2.0%
Loss on drying	⩽ 15.0%	—
Odor & water-insoluble substances	—	+
Acidity or alkalinity	+	—
Clarity and color of solution	+	—
Sulfur dioxide	⩽ 200 ppm	⩽ 0.15%
Arsenic	⩽ 1 ppm	⩽ 0.8 ppm
Heavy metals	⩽ 50 ppm	⩽ 0.005%
Peroxides	⩽ 100 ppm	—
Phenolic preservatives	+	—
Jelly strength	+	—

10. Typical Properties

Acidity/alkalinity:
for a 1% w/v aqueous solution at 25°C.
pH = 3.8-6.0 (type A);
pH = 5.0-7.4 (type B).
Density:
1.325 g/cm^3 for type A;
1.283 g/cm^3 for type B.
Iso-electric point:
7-9 for type A;
4.7-5.3 for type B.
Moisture content: *see* HPE Data.[5]
Solubility: practically insoluble in acetone, chloroform, ethanol (95%), ether, and methanol.
Soluble in glycerin, acids and alkalis, although strong acids or alkalis cause precipitation. In water, gelatin swells and softens, gradually absorbing between 5-10 times its own weight of water. Gelatin is soluble in hot water, forming a jelly, or gel,

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on cooling to 35-40°C. At temperatures > 40°C, the system exists as a sol. This gel-sol system is heat reversible, the melting temperature being slightly higher than the setting point; the melting point can be varied by the addition of glycerin.
Viscosity (dynamic): 4.3-4.7 mPa s (4.3-4.7 cP) for a 6.67% w/v aqueous solution at 60°C; 18.5-20.5 mPa s (18.5-20.5 cP) for a 12.5% w/v aqueous solution at 60°C.

	HPE Laboratory Project Data		
	Method	**Lab #**	**Results**
Moisture content	MC-11	14	10.6% [a]
	MC-26	18	10.6% [b]
	MC-10	28	8.82% [b]
	MC-10	28	11.02% [b]
	MC-10	28	11.75% [a]
	EMC-1	18	*See* Fig. 1.[b]
	SDI-1	14	*See* Fig. 2.[a]

Supplier:
a. Leiner (Lot No.: 627);
b. Kind & Knox (*Pharmagel A*).

11. Stability and Storage Conditions

Dry gelatin is stable in air.
Aqueous gelatin solutions are also stable for long periods if stored under cool, sterile conditions. At temperatures above about 50°C aqueous gelatin solutions may undergo slow depolymerization and a reduction in gel strength on resetting may occur. Depolymerization becomes more rapid at temperatures above 65°C, and gel strength may be reduced by half when a solution is heated at 80°C for 1 hour. The rate and extent of depolymerization depends on the molecular weight of the gelatin, with a lower molecular weight material decomposing more rapidly.[6]
Gelatin may be sterilized by dry heat.
The bulk material should be stored in an airtight container in a cool, dry, place.

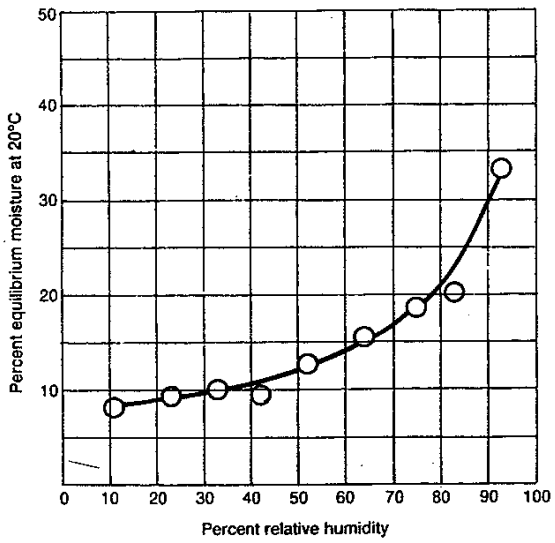

Fig. 1: Equilibrium moisture content of gelatin (*Pharmagel A*).

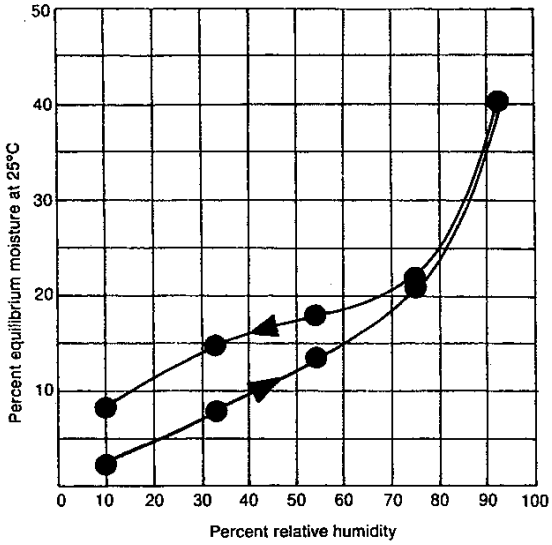

Fig. 2: Sorption-desorption isotherm of gelatin.

12. Incompatibilities

Gelatin is an amphoteric material and will thus react with both acids and bases. It is also a protein and thus exhibits chemical properties characteristic of such materials, e.g. gelatin may be hydrolyzed by most proteolytic systems to yield its amino acid components.
Gelatin will also react with aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives and surfactants. It is precipitated by alcohols, chloroform, ether, mercury salts and tannic acid. Gels can be liquefied by bacteria unless preserved.
Some of these interactions are exploited to favorably alter the physical properties of gelatin, e.g. gelatin is mixed with a plasticizer, such as glycerin, to produce soft gelatin capsules and suppositories, *see* Section 7.

13. Method of Manufacture

Gelatin is extracted from animal tissues rich in collagen such as skin, sinews and bone. Although it is possible to extract gelatin from these materials using boiling water it is more practical to first pretreat the animal tissues with either acid or alkali. Gelatin obtained from the acid process is called type A, whilst that obtained from the alkali process is called type B.
In the US, most type A gelatin is obtained from pig skins. This material is washed in cold water for a few hours to remove extraneous matter and is then digested in dilute mineral acid (either HCl, H_2SO_4, H_2SO_3 or H_3PO_4) at pH 1-3 and 15-20°C until maximum swelling has occurred. This process takes approximately 24 hours. The swollen stock is then washed with water to remove excess acid and the pH adjusted to pH 3.5-4.0 for the conversion to gelatin by hot water extraction.
The hydrolytic extraction is carried out in a batch-type operation, with successive portions of hot water, at progressively higher temperatures until the maximum yield of gelatin is obtained. The gelatin solution is then chilled to form jelled sheets which are dried in temperature-controlled ovens. The dried gelatin is then ground to the desired particle size.
In the alkali process, demineralized bones (ossein) or cattle skins are usually used. The animal tissue is held in a calcium

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hydroxide (lime) slurry for a period of one to three months at 15-20°C. At the end of the liming, the stock is washed with cold water to remove as much of the lime as possible. The stock solution is then neutralized with acid (HCl, H_2SO_4, H_3PO_4) and the gelatin extracted with water in an identical manner to the acid process.

14. Safety

Gelatin is widely used in a variety of pharmaceutical formulations including oral and parenteral products.

In general, when used in oral formulations gelatin may be regarded as a nontoxic and nonirritant material. However, there have been rare reports of gelatin capsules adhering to the esophageal lining which may cause local irritation.[7] Hypersensitivity reactions, including serious anaphylactoid reactions, have been reported following the use of gelatin in parenteral products.[8]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Gelatin should be handled in a well-ventilated environment.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations, inhalations, injections, oral capsules, solutions, syrups and tablets, topical and vaginal preparations). Included in medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Braz, Chin, Cz, Egypt, Eur, Fr, Ger, Gr, Hung, Ind, It, Jpn, Mex, Neth, Nord, Port, Rom, Rus, Swiss, Turk, USPNF and Yug.

18. Related Substances

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19. Comments

Various grades of gelatin are commercially available with different particle sizes, molecular weights, etc. Grading is usually by jelly strength, expressed as 'Bloom strength', which is the weight in grams which, when applied under controlled conditions to a plunger 12.7 mm in diameter, will produce a depression exactly 4 mm deep in a matured jelly containing 6.66% w/w of gelatin in water.

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22. Authors

USA: JC Price.

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Guar Gum

1. Nonproprietary Names
USPNF: Guar gum

2. Synonyms
E412; guar flour; jaguar gum.

3. Chemical Name and CAS Registry Number
Galactomannan polysaccharide [9000-30-0]

4. Empirical Formula / Molecular Weight
$(C_6H_{12}O_6)_n$ ≈ 220 000
See Section 5.

5. Structural Formula
Guar gum consists of linear chains of (1→4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D-galactose to D-mannose is 1:2. *See also* Section 8.

6. Functional Category
Suspending agent; tablet binder; tablet disintegrant; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology
Guar gum is used in cosmetics, food products and pharmaceutical formulations.
In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant[1-3] and in liquid oral and topical products as a suspending, thickening and stabilizing agent.
Therapeutically, guar gum has been used as part of the diet of patients with diabetes mellitus.[4,5] Guar gum has also been used as an appetite suppressant although its use for this purpose, in tablet form, is now banned in the UK,[6,7] *see* Section 14.

Use	Concentration (%)
Emulsion stabilizer	1
Tablet binder	up to 10
Thickener for lotions & creams	up to 2.5

8. Description
The USPNF XVII describes guar gum as a gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (Linné) Taub. (Fam. Leguminosae). It consists chiefly of a high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan.
Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a bland taste.

9. Pharmacopeial Specifications

Test	USPNF XVII
Identification	+
Loss on drying	≤ 15%
Ash	≤ 1.5%
Acid-insoluble matter	≤ 7%
Arsenic	≤ 3 ppm
Lead	≤ 0.001%
Heavy metals	≤ 0.002%
Protein	≤ 10%
Starch	+
Galactomannans	≥ 66.0%

10. Typical Properties
Acidity/alkalinity:
pH = 5.0-7.0 (1% w/v aqueous dispersion)
Solubility: practically insoluble in organic solvents. In cold or hot water guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs between pH 7.5-9.0. Finely-milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.
Viscosity (dynamic): 2-3.5 Pa s (2000-3500 cP) for a 1% w/v dispersion. Viscosity is dependent upon temperature, time, concentration, pH, rate of agitation and particle size of the guar gum powder. Synergistic rheological effects may occur with other suspending agents such as xanthan gum, *see* Xanthan Gum.

11. Stability and Storage Conditions
Aqueous guar gum dispersions have a buffering action and are stable between pH 4-10.5. However, prolonged heating reduces the viscosity of dispersions.
Bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15% methylparaben and 0.02% propylparaben as a preservative. In food applications benzoic acid, citric acid, sodium benzoate or sorbic acid may be used.
Guar gum powder should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities
Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, alcohol, tannins, strong acids and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum. However, the addition of borate ions to hydrated guar gum produces cohesive structural gels and further hydration is then prevented. The gel formed can be liquefied by reducing the pH to below pH 7 or by heating.
Guar gum may reduce the absorption of penicillin V from some formulations by a quarter.[8]

13. Method of Manufacture
Guar gum is obtained from the ground endosperm of the guar plant, *Cyamopsis tetragonolobus* (Linné) Taub. (Fam. Leguminosae), which is grown in India, Pakistan and the semi-arid southwestern region of the USA.
The seed hull can be removed by grinding, after soaking in sulfuric acid or water, or by charring. The embryo (germ) is removed by differential grinding, since each component possesses a different hardness. The separated endosperm,

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containing 80% galactomannan is then ground to different particle sizes depending upon final application.

14. Safety

Guar gum is widely used in foods and oral and topical pharmaceutical formulations. Excessive consumption may cause gastrointestinal disturbance such as flatulence, diarrhea or nausea. Therapeutically, daily oral doses of up to 25 g of guar gum have been administered to patients with diabetes mellitus.[4]

Although generally regarded as a nontoxic and nonirritant material the safety of guar gum when used as an appetite suppressant has been questioned. When consumed the gum swells in the stomach to promote a feeling of fullness. However, it is claimed that premature swelling of guar gum tablets may occur and cause obstruction or damage to the oesophagus. Consequently, appetite suppressants containing guar gum in tablet form have been banned in the UK.[7] Appetite suppressants containing microgranules of guar gum are however claimed to be safe.[6] The use of guar gum for pharmaceutical purposes is unaffected by the ban.

In food applications an acceptable daily intake of guar gum has not been specified by the WHO.[9]

LD_{50} (hamster, oral): 6 g/kg[10]
LD_{50} (mouse, oral): 8.1 g/kg
LD_{50} (rabbit, oral): 7 g/kg
LD_{50} (rat, oral): 7.06 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Guar gum may be irritating to the eyes. Eye protection, gloves and a dust mask or respirator are recommended.

16. Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral suspensions, syrups and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Fr, Ind and USPNF.

18. Related Substances

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19. Comments

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Vemuri S. Flow and consistency index dependence of pseudoplastic guar gum solutions. Drug Dev Ind Pharm 1988; 14: 905-914.

22. Authors

USA: T-SH Chen.

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Hydroxyethyl Cellulose

1. Nonproprietary Names

BP: Hydroxyethylcellulose
PhEur: Hydroxyethylcellulosum
USPNF: Hydroxyethyl cellulose

2. Synonyms

Alcoramnosan; *Cellosize*; cellulose, hydroxyethyl ether; HEC; *Idroramnosan*; *Liporamnosan*; *Natrosol*.

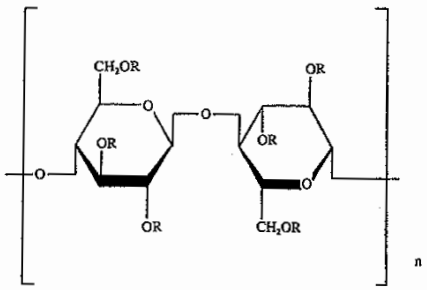
3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxyethyl ether [9004-62-0]

4. Empirical Formula Molecular Weight

The USPNF XVII describes hydroxyethyl cellulose as a partially substituted poly(hydroxyethyl) ether of cellulose. It is available in several grades, varying in viscosity and degree of substitution, and some grades are modified to improve their dispersion in water. The grades are distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/v solution measured at 20°C. Hydroxyethyl cellulose may also contain a suitable anticaking agent.
See Section 5.

5. Structural Formula



Where R is H or $[-CH_2CH_2O-]_mH$

6. Functional Category

Coating agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

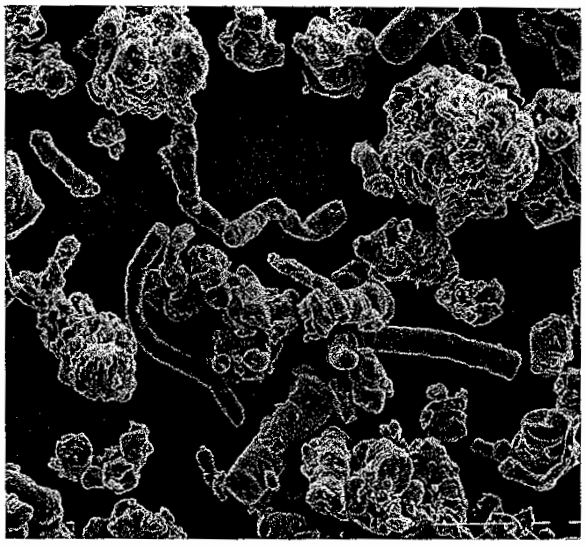
7. Applications in Pharmaceutical Formulation or Technology

Hydroxyethyl cellulose is a nonionic, water soluble polymer widely used in pharmaceutical formulations. It is primarily used as a thickening agent in ophthalmic[1] and topical formulations[2] although it is also used as a binder[3] and film-coating agent for tablets.[4]
The concentration of hydroxyethyl cellulose used in a formulation is dependent upon the solvent and the molecular weight of the grade.
Hydroxyethyl cellulose is also widely used in cosmetics.

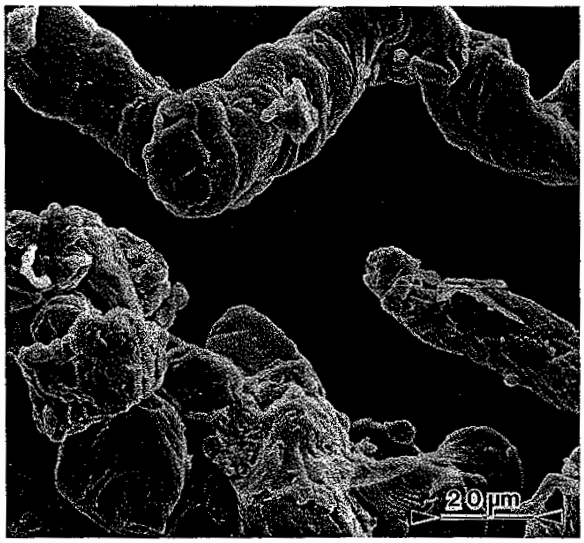
8. Description

Hydroxyethyl cellulose occurs as a light tan or cream to white-colored, odorless and tasteless, hygroscopic powder.
See Sections 4 and 5.

SEM: 1
Excipient: Hydroxyethyl cellulose (*Natrosol*)
Manufacturer: Aqualon
Magnification: 120x



SEM: 2
Excipient: Hydroxyethyl cellulose (*Natrosol*)
Manufacturer: Aqualon
Magnification: 600x



9. Pharmacopeial Specifications

Test	PhEur 1984	USPNF XVII (Suppl 6)
Identification	+	+
Appearance of solution	+	—
Viscosity	+	+
pH (1 in 100)	5.5-8.5	6-8.5
Loss on drying	⩽ 10.0%	⩽ 10.0%
Lead	—	⩽ 0.001%
Residue on ignition	—	⩽ 5.0%
Sulfated ash	⩽ 4.0%	—
Arsenic	—	⩽ 3ppm
Chlorides	⩽ 1.0%	—
Heavy metals	⩽ 20 ppm	⩽ 0.004%
Organic volatile impurities	—	+
Nitrates	+	—

10. Typical Properties

Acidity/alkalinity: pH = 5.5-8.5 for a 1% w/v aqueous solution.

Ash:
2.5% w/w for *Cellosize*;
3.5% w/w for *Natrosol*.

Autoignition temperature: 420°C

Density (bulk):
0.35-0.61 g/cm^3 for *Cellosize*;
0.60 g/cm^3 for *Natrosol*.

Melting point: softens at 135-140°C, decomposes at about 205°C.

Moisture content: commercially available grades of hydroxyethyl cellulose contain less than 5% w/w of water. However, hydroxyethyl cellulose is hygroscopic, the amount of water absorbed depending upon the initial moisture content and the relative humidity of the surrounding air. Typical equilibrium moisture values for *Natrosol 250* at 25°C are: 6% w/w at 50% relative humidity and 29% w/w at 84% relative humidity.

Particle size distribution: for *Cellosize*, 100% through a US #80 mesh (177 μm); for *Natrosol* (regular grind), 10% retained on a US #40 mesh (420 μm); for *Natrosol* (X-grind) 0.5% retained on a US #60 mesh (250 μm).

Refractive index:
n_D^{20} = 1.336 for a 2% w/v aqueous solution.

Solubility: hydroxyethyl cellulose is soluble in either hot or cold water, forming clear, smooth, uniform solutions. Practically insoluble in acetone, ethanol, ether, toluene and most other organic solvents. In some polar organic solvents, such as the glycols, hydroxyethyl cellulose either swells or is partially soluble.

Specific gravity: 1.38-1.40 for *Cellosize*; 1.0033 for a 2% w/v aqueous hydroxyethyl cellulose solution.

Surface tension: *see* Table I.

Table I: Surface tension (mN/m) of different *Cellosize* (Amerchol Corp) grades at 25°C.

Concentration of aqueous solution (% w/v)	WP-02	*Cellosize* grade 09	300	QP4400	52000	100M
0.01	65.8	65.7	66.4	66.3	65.9	66.1
0.1	65.3	65.4	65.8	65.3	65.4	65.4
1.0	64.4	65.1	65.5	65.8	66.1	66.3
2.0	64.2	65.0	66.3	67.3	—	—
5.0	64.1	64.7	—	—	—	—
10.0	64.4	65.9	—	—	—	—

Viscosity (dynamic): hydroxyethyl cellulose is available in a wide range of viscosity types, e.g. *Cellosize* is manufactured in eleven regular viscosity grades. Hydroxyethyl cellulose grades differ principally in their aqueous solution viscosities which range from 2-20 000 mPa s for a 2% w/v aqueous solution. Two types of *Cellosize* are produced, a WP-type, which is a normal-dissolving material, and a QP-type, which is a rapid-dispersing material. The lowest viscosity grade (02) is available only in the WP-type. Five viscosity grades (09, 3, 40, 300 and 4400) are produced in both WP- and QP-types. Five high-viscosity grades (10000, 15000, 30000, 52000, and 100M) are produced only in the QP-type. Table II shows the standard *Cellosize* grades and types available and their respective viscosity ranges in aqueous solution.

Natrosol 250 has a degree of substitution of 2.5 and is produced in ten viscosity types. The suffix 'R' denotes that *Natrosol* has been surface treated with glyoxal to aid in solution preparation, *see* Table III.

Aqueous solutions made using a rapidly dispersing material may be prepared by dispersing the hydroxyethyl cellulose in mildly agitated water at 20-25°C. When the hydroxyethyl cellulose has been thoroughly wetted the temperature of the solution may be increased to 60-70°C to increase the rate of dispersion. Making the solution slightly alkaline also increases the dispersion process. Typically, complete dispersion may be achieved in approximately an hour by controlling the temperature, pH and rate of stirring.

Normally dispersing grades of hydroxyethyl cellulose require more careful handling to avoid agglomeration during dispersion; the water should be vigorously stirred. Alternatively, a slurry of hydroxyethyl cellulose may be prepared in a nonaqueous solvent, such as ethanol, prior to dispersion in water.

See also Section 11 for information on solution stability.

Table II: Approximate viscosities of various grades of aqueous *Cellosize* (Amerchol Corp) solutions at 25°C.

Type	Grade	Concentration (% w/v)	Viscosity (mPa s)* Low	High
WP	02	5	7-14	14-20
WP &	09	5	60-100	100-140
QP	3	5	220-285	285-350
	40	2	70-110	110-150
	300	2	250-325	325-400
	4400	2	4200-4700	4700-5200
QP	10000	2	5700	6500
	15000	2	15000-18000	18000-21000
	30000	1	950-1230	1230-1500
	52000	1	1500-1800	1800-2100
	100M	1	2500	3000

* *Cellosize* viscosity grades are available in narrower ranges, as noted by the Low and High designation.

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Table III: Approximate viscosities of various grades of aqueous *Natrosol 250* (Aqualon) solutions at 25°C.

Type	Viscosity (mPa s) for varying concentrations (% w/v). 1%	2%	5%
HHR	3400-5000	—	—
H4R	2600-3300	—	—
HR	1500-2500	—	—
MHR	800-1500	—	—
MR	—	4500-6500	—
KR	—	1500-2500	—
GR	—	150-400	—
ER	—	25-105	—
JR	—	—	150-400
LR	—	—	75-150

	HPE Laboratory Project Data Method	Lab#	Results
Particle Friability			
Natrosol 250L	PF-1	36	0.050%
Natrosol 250HHR	PF-1	36	0.008%
Viscosity			
Natrosol 250L (5%)	VIS-4	6	150-225 mPa s
Natrosol 250MR (1%)	VIS-4	6	190-375 mPa s
Natrosol 250MR (2%)	VIS-4	6	4250-7250 mPa s
Natrosol 250HHR (1%)	VIS-4	6	3275-5875 mPa s

Supplier: Aqualon.

11. Stability and Storage Conditions

Hydroxyethyl cellulose powder is a stable, though hygroscopic, material.

Aqueous solutions of hydroxyethyl cellulose are relatively stable between pH 2-12 with the viscosity of solutions being largely unaffected. However, solutions are less stable below pH 5 due to hydrolysis. At high pH, oxidation may occur.

Increasing temperature reduces the viscosity of aqueous hydroxyethyl cellulose solutions. However, on cooling, the original viscosity is restored. Solutions may be subjected to freeze-thawing, high temperature storage or boiling without precipitation or gelation occurring.

Hydroxyethyl cellulose is subject to enzymatic degradation, with consequent loss in viscosity of its solutions.[5] Enzymes which catalyze this degradation are produced by many bacteria and fungi present in the environment. For prolonged storage, an antimicrobial preservative should therefore be added to aqueous solutions. Aqueous solutions of hydroxyethyl cellulose may also be sterilized by autoclaving.

Hydroxyethyl cellulose powder should be stored in a well-closed container, in a cool, dry, place.

12. Incompatibilities

Hydroxyethyl cellulose is insoluble in most organic solvents.

Hydroxyethyl cellulose is incompatible with zein and partially compatible with the following water-soluble compounds: casein; gelatin; methylcellulose; polyvinyl alcohol and starch.

Hydroxyethyl cellulose can be used with a wide variety of water-soluble antimicrobial preservatives. However, sodium pentachlorophenate produces an immediate viscosity increase when added to hydroxyethyl cellulose solutions.

Hydroxyethyl cellulose has good tolerance for dissolved electrolytes although it may be salted out of solution when mixed with certain salt solutions, e.g. the following salt solutions will precipitate a 10% w/v solution of *Cellosize WP-09* and a 2% w/v solution of *Cellosize WP-4400*: sodium carbonate 50% and saturated solutions of aluminum sulfate; ammonium sulfate; chromic sulfate; disodium phosphate; magnesium sulfate; potassium ferrocyanide; sodium sulfate; sodium sulfite; sodium thiosulfate and zinc sulfate.

Natrosol is soluble in most 10% salt solutions, except sodium carbonate and sodium sulfate, and many 50% salt solutions except: aluminum sulfate; ammonium sulfate; diammonium phosphate; disodium phosphate; ferric chloride; magnesium sulfate; potassium ferrocyanide; sodium metaborate; sodium nitrate; sodium sulfite; trisodium phosphate and zinc sulfate. *Natrosol 150* is generally more tolerant of dissolved salts than *Natrosol 250*.

Hydroxyethyl cellulose is also incompatible with certain fluorescent dyes or optical brighteners, and certain quaternary disinfectants which will increase the viscosity of aqueous solutions.

13. Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose which is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with ethylene oxide, to produce a series of hydroxyethyl cellulose ethers.

The manner in which ethylene oxide is added to cellulose can be described by two terms: the degree of substitution (DS) and the molar substitution (MS). The degree of substitution designates the average number of hydroxyl positions on the anhydroglucose unit that have been reacted with ethylene oxide. Since each anhydroglucose unit of the cellulose molecule has three hydroxyl groups, the maximum value for DS is 3. Molar substitution is defined as the average number of ethylene oxide molecules that have reacted with each anhydroglucose unit. Once a hydroxyethyl group is attached to each unit, it can further react with additional groups in an end-to-end formation. This reaction can continue and, theoretically, there is no limit for molar substitution.

14. Safety

Hydroxyethyl cellulose is primarily used in ophthalmic and topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant material.[6,7]

Acute and subacute oral toxicity studies, in rats, have shown no toxic effects attributable to hydroxyethyl cellulose consumption, the hydroxyethyl cellulose being neither absorbed nor hydrolyzed in the rat gastrointestinal tract. However, although used in oral pharmaceutical formulations hydroxyethyl cellulose has not been approved for direct use in food products, *see* Section 16.

Glyoxal-treated hydroxyethyl cellulose is not recommended for use in oral pharmaceutical formulations or topical preparations which may be used on mucous membranes. Hydroxyethyl cellulose is also not recommended for use in parenteral products.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxyethyl cellulose dust may be irritant to the eyes and therefore eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosions. Hydroxyethyl cellulose is combustible.

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16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral syrups and tablets, otic and topical preparations). Included in nonparenteral medicines licensed in the UK.

Hydroxyethyl cellulose is not currently approved for use in food products in Europe or the US although it is permitted for use in indirect applications such as packaging. This restriction is due to the high levels of ethylene glycol residues which are formed during the manufacturing process.

17. Pharmacopeias

Br, Eur, Fr, Ger, Gr, Hung, It, Neth, Port, Swiss and USPNF.

18. Related Substances

Ethylcellulose; Hydroxypropyl Cellulose; Hydroxypropyl Methylcellulose; Methylcellulose.

19. Comments

The limited scope for the use of hydroxyethyl cellulose in foodstuffs is in stark contrast to its widespread application as an excipient in oral pharmaceutical formulations.

20. Specific References

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2. Gauger LJ. Hydroxyethylcellulose gel as a dinoprostone vehicle. Am J Hosp Pharm 1984; 41: 1761-1762.
3. Delonca H, Joachim J, Mattha A. Influence of temperature on disintegration and dissolution time of tablets with a cellulose component as binder [in French]. J Pharm Belg 1978; 33: 171-178.
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5. Wirick MG. Study of the substitution pattern of hydroxyethyl cellulose and its relationship to enzymic degradation. J Polymer Sci 1968; 6(Part A-1): 1705-1718.
6. Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropyl methylcellulose and cellulose gum. J Am Coll Toxicol 1986; 5(3): 1-60.
7. Durand-Cavagna G, Delort P, Duprat P, Bailly Y, Plazonnet B, Gordon LR. Corneal toxicity studies in rabbits and dogs with hydroxyethyl cellulose and benzalkonium chloride. Fundam Appl Toxicol 1989; 13: 500-508.

21. General References

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Aqualon. Technical literature: *Natrosol*, hydroxyethyl cellulose, 1993.

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Haugen P, Tung MA, Runikis JO. Steady shear flow properties, rheological reproducibility and stability of aqueous hydroxyethylcellulose dispersions. Can J Pharm Sci 1978; 13: 4-7.

Klug ED. Some properties of water-soluble hydroxyalkyl celluloses and their derivatives. J Polymer Sci 1971; 36(Part C): 491-508.

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22. Authors

USA: RJ Harwood, JL Johnson.

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Hydroxypropyl Cellulose

1. Nonproprietary Names

BP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulosum
USPNF: Hydroxypropyl cellulose

2. Synonyms

Cellulose, hydroxypropyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*; oxypropylated cellulose.

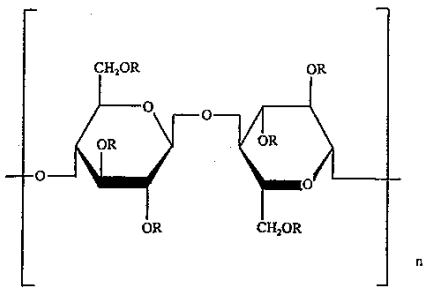
3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4. Empirical Formula Molecular Weight

The USPNF XVII describes hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or some other suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades which have different solution viscosities. Molecular weight ranges from 50 000-1 250 000, *see also* Section 10.

5. Structural Formula



Where R is H or $[-CH_2-CH(CH_3)-O]_mH$

6. Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating and extended release matrix former. Concentrations of between 2-6% w/w of hydroxypropyl cellulose may be used as a binder in either wet granulation or dry, direct compression tableting processes.[1-5] Concentrations of between 15-35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.[6] The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the hydroxypropyl cellulose viscosity and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Either aqueous solutions, containing hydroxypropyl cellulose along with some methylcellulose, or ethanolic solutions may be used.[7-9] Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant, *see* Section 18.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.[10-12]

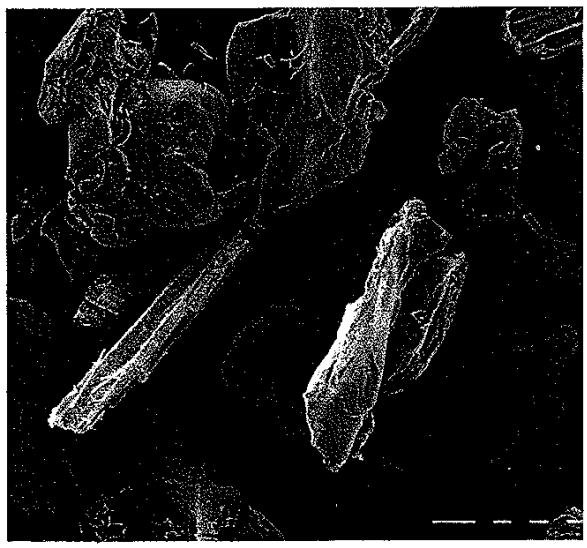
Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Use	Concentration (%)
Extended release matrix former	15-35
Tablet binder	2-6
Tablet film coating	5

8. Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. *See also* Sections 4 and 5.

SEM: 1
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 60x



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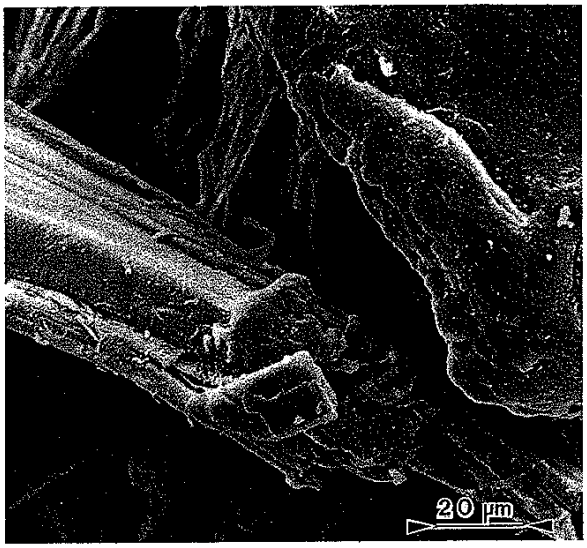
SEM: 2
Excipient: Hydroxypropyl cellulose (*Klucel*)
Manufacturer: Aqualon
Magnification: 600x



9. Pharmacopeial Specifications

Test	PhEur 1992	USPNF XVII (Suppl 6)
Identification	+	+
Apparent viscosity	+	+
Appearance of solution	+	—
pH (1 in 100)	5.0-8.5	5.0-8.0
Loss on drying	≤ 7.0%	≤ 5.0%
Residue on ignition	—	≤ 0.2%
Sulfated ash	≤ 1.6%	—
Arsenic	—	≤ 3 ppm
Chlorides	≤ 0.5%	—
Lead	—	≤ 0.001%
Heavy metals	≤ 20 ppm	≤ 0.004%
Silica	≤ 0.6%	≤ 0.6%
Organic volatile impurities	—	+
Assay of hydroxypropoxy groups	—	≤ 80.5%

10. Typical Properties

Acidity/alkalinity:
pH = 5.0-8.5 for a 1% w/v aqueous solution.
Density (bulk): ≈ 0.5 g/cm^3
Interfacial tension: 12.5 mN/m for a 0.1% w/v aqueous solution versus mineral oil.
Melting point: softens at 130°C; chars at 260-275°C.
Moisture content: hydroxypropyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content, and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are: 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity. *See also* HPE Data.
Molecular weight:
for *Klucel EF* ≈ 80 000
for *Klucel LF* ≈ 95 000
for *Klucel JF* ≈ 140 000
for *Klucel GF* ≈ 370 000
for *Klucel MF* ≈ 850 000
for *Klucel HF* ≈ 1 150 000.
Particle size distribution: for *Klucel* (regular grind), 95% through a US #30 mesh (590 µm) and 99% through a US #20 mesh (840 µm); for *Klucel* (X-grind), 100% through a US #60 mesh (250 µm) and 80% through a US #100 mesh (149 µm).
Refractive index:
n_D^{20} = 1.3353 for a 2% w/v aqueous solution.
Solubility: soluble 1 in 10 parts dichloromethane, 1 in 2.5 parts ethanol, 1 in 2 parts methanol, 1 in 5 parts propan-2-ol, 1 in 5 parts propylene glycol and 1 in 2 parts water; practically insoluble in aliphatic hydrocarbons, aromatic hydrocarbons, carbon tetrachloride, petroleum distillates, glycerin and oils.
Hydroxypropyl cellulose is freely soluble in water below 38°C forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40-45°C.
Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as: dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol; methanol; propan-2-ol (95%) and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids which are borderline solvents, such as: acetone; butyl acetate; cyclohexanol; dichloromethane; lactic acid; methylacetate; methylethyl ketone; propan-2-ol (99%) and *tert*-butanol. The higher viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5-15%) of a cosolvent. For example, dichloromethane is a borderline solvent for *Klucel HF* and solutions have a granular texture, but by adding 10% methanol a smooth solution may be produced.
Hydroxypropyl cellulose is compatible with a number of high molecular weight, high boiling waxes and oils, and can be used to modify certain properties of these materials. Examples of materials that are good solvents for hydroxypropyl cellulose at an elevated temperature are: acetylated monoglycerides; glycerides; pine oil; polyethylene glycol and polypropylene glycol.
Specific gravity: 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.
Surface tension: *see* Table I.

Table I: Surface tension (mN/m) of aqueous solutions of *Nisso HPC* (Nippon Soda Co Ltd) at 20°C.

Grade	Surface tension at 20°C (mN/m) Concentration			
	0.01%	0.1%	1.0%	10.0%
Nisso HPC-L	51.0	49.1	46.3	45.8
Nisso HPC-M	54.8	49.7	46.3	—

Viscosity (dynamic): a wide range of viscosity types are commercially available, *see* Table II and HPE Data. Solutions should be prepared by gradually adding the hydroxypropyl

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cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity. *See also* Section 11 for information on solution stability.

Table II: Viscosity of aqueous solutions of *Klucel* (Aqualon) at 25°C.

Grade	Viscosity (mPa s) of various aqueous solutions Concentration			
	1%	2%	5%	10%
Klucel HF	1500-3000	—	—	—
Klucel MF	—	4000-6500	—	—
Klucel GF	—	150-400	—	—
Klucel JF	—	—	150-400	—
Klucel LF	—	—	75-150	—
Klucel EF	—	—	—	200-600

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content			
*Type LH-21**	MC-7	14	3.81% [a]
Klucel HF	MC-7	14	4.27% [b]
Klucel MF	MC-7	14	1.52% [b]
Klucel GF	MC-7	14	1.67% [b]
Klucel JF	MC-7	14	1.44% [b]
Klucel LF	MC-7	14	2.21% [b]
Klucel EF	MC-7	14	0.59% [b]
Klucel	EMC-1	15	*See* Fig. 1. [b]
*Type LH-11**	SDI-1	14	*See* Fig. 2. [a]
Klucel HF	SDI-1	14	*See* Fig. 2. [b]
Klucel MF	SDI-1	14	*See* Fig. 2. [b]
Klucel EF	SDI-1	14	*See* Fig. 3. [b]
Klucel GF	SDI-1	14	*See* Fig. 3. [b]
Klucel JF	SDI-1	14	*See* Fig. 3. [b]
Klucel LF	SDI-1	14	*See* Fig. 3. [b]
Particle friability	PF-1	36	0.125% [c]
Solubility [c]			
Ethanol (95%) at 25°C	SOL-7	32	0.14 mg/mL
Ethanol (95%) at 37°C	SOL-7	32	0.24 mg/mL
Hexane at 25°C	SOL-7	32	1.0 mg/mL
Hexane at 37°C	SOL-7	32	1.0 mg/mL
Propylene glycol at 25°C	SOL-7	32	1.0 mg/mL
Propylene glycol at 37°C	SOL-7	32	1.0 mg/mL
Water at 25°C	SOL-7	32	500 mg/mL
Water at 37°C	SOL-7	32	500 mg/mL
Viscosity [b]			
Klucel EF (10% w/v)	VIS-1	6	410-740 mPa s
Klucel GF (2% w/v)	VIS-1	6	360-615 mPa s
Klucel GF (3% w/v)	VIS-1	6	1350-1625 mPa s
Klucel HF (1% w/v)	VIS-1	6	1800-3250 mPa s
Klucel HF (2% w/v)	VIS-1	6	2325-3300 mPa s

Supplier: a. Biddle Sawyer Corporation; b. Aqualon; c. Shin-Etsu Chemical Co Ltd.

* Note that *Type LH-11* and *LH-21* are low-substituted grades of hydroxypropyl cellulose, *see also* Section 18.

11. Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material although it is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable between pH 6.0-8.0 with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, which causes chain scission and hence a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration. At high pH, alkali-catalyzed oxidation may degrade the polymer and result in a decrease in viscosity of solutions. This degradation can occur due to the presence of dissolved oxygen or oxidizing agents in a solution.

Increasing temperature causes the viscosity of aqueous solutions to gradually decrease until the viscosity drops

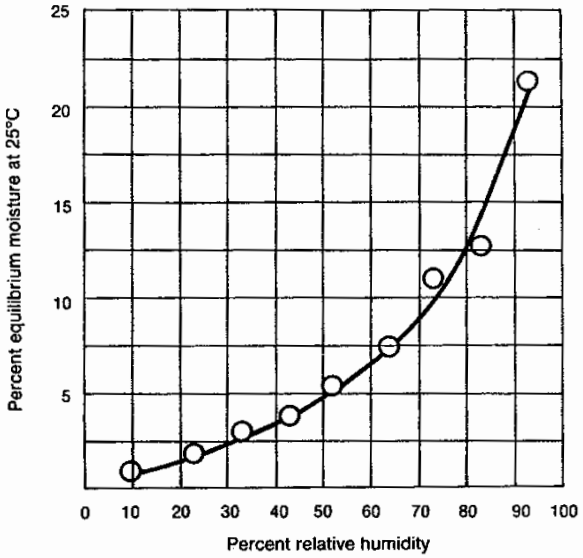

Fig. 1: Equilibrium moisture content of hydroxypropyl cellulose (*Klucel*).

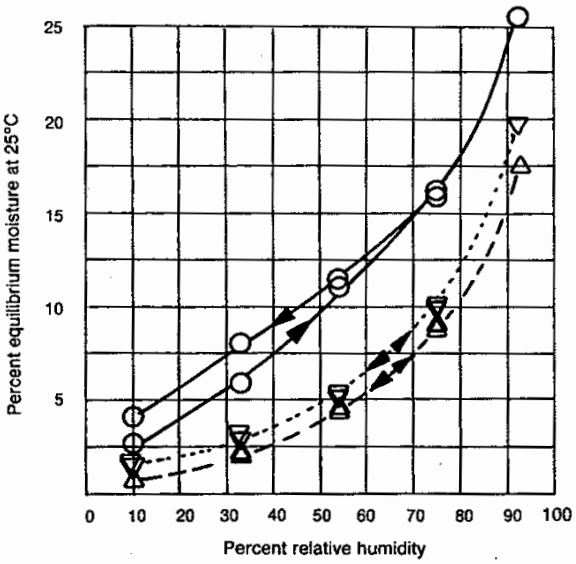

Fig. 2: Equilibrium moisture content of various grades of hydroxypropyl cellulose.
○ *Type LH-11* (Biddle Sawyer Corporation, Lot #8069).
△ *Klucel HF* (Aqualon, Lot #1061).
▽ *Klucel MF* (Aqualon, Lot #1294).
Note that *Type LH-11* is a low-substituted grade of hydroxypropyl cellulose.

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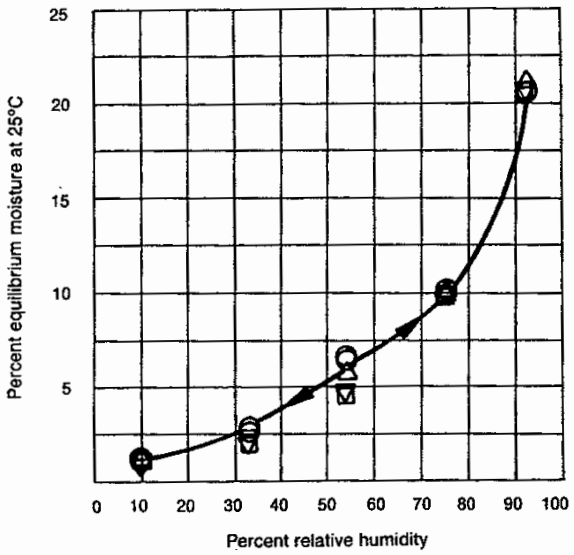

Fig. 3: Equilibrium moisture content of various grades of hydroxypropyl cellulose.
○ *Klucel GF* (Aqualon, Lot #4996).
△ *Klucel JF* (Aqualon, Lot #4753).
▽ *Klucel LF* (Aqualon, Lot #4965).
□ *Klucel EF* (Aqualon, Lot #1223).

suddenly at about 45°C due to the limited solubility of hydroxypropyl cellulose. However, this process is reversible and on cooling the original viscosity is restored.

The high level of substitution of hydroxypropyl cellulose improves the resistance of the polymer to degradation by molds and bacteria.[9] However, aqueous solutions are susceptible to degradation under severe conditions and a viscosity decrease may thus occur. Certain enzymes, produced by microbial action, will degrade hydroxypropyl cellulose in solution.[13] For prolonged storage, an antimicrobial preservative should therefore be added to aqueous solutions. Solutions of hydroxypropyl cellulose in organic solvents do not generally require preservatives.

Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore slightly decrease in viscosity if exposed to light for several months.

Aqueous hydroxypropyl cellulose solutions thus have optimum stability when the pH is maintained between pH 6.0-8.0 and the solution is protected from light, heat and the action of microorganisms.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration, *see* Table III; hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials. The balance of the hydrophilic-lipophilic properties of the polymer, which a required for dual solubility, reduces its ability to hydrate wi water and it therefore tends to be salted out in the presence high concentrations of other dissolved materials.

The precipitation temperature of hydroxypropyl cellulose lower in the presence of relatively high concentrations of oth dissolved materials that compete for the water in the systen *see* Table IV.

Table III: Compatibility of hydroxypropyl cellulose (*Nisso HPC*) with inorganic salts in aqueous solutions.

Salt	Concentration of salt (% w/w)						
	2	3	5	7	10	30	50
Aluminum sulfate	S	S	I	I	I	I	I
Ammonium nitrate	S	S	S	S	S	I	I
Ammonium sulfate	S	S	I	I	I	I	I
Calcium chloride	S	S	S	S	S	T	I
Dichromic acid	S	S	S	S	S	S	S
Disodium hydrogenphosphate	S	S	I	I	I	I	I
Ferric chloride	S	S	S	S	S	I	I
Potassium ferrocyanide	S	S	S	I	I	I	I
Silver nitrate	S	S	S	S	S	S	T
Sodium acetate	S	S	S	S	I	I	I
Sodium carbonate	S	S	I	I	I	I	I
Sodium chloride	S	S	S	S	I	I	I
Sodium nitrate	S	S	S	S	S	I	I
Sodium sulfate	S	S	I	I	I	I	I
Sodium sulfite	S	S	I	I	I	I	I
Sodium thiosulfate	T	T	T	I	I	I	I

S: completely soluble T: turbid white I: insoluble

Table IV: Variation in precipitation temperature of hydroxypropyl cellulose (*Klucel H*) in the presence of other materials.

Ingredients and concentrations	Precipitation temperature (°C)
1% *Klucel H*	41
1% *Klucel H* + 1.0% NaCl	38
1% *Klucel H* + 5.0% NaCl	30
0.5% *Klucel H* + 10% Sucrose	41
0.5% *Klucel H* + 30% Sucrose	32
0.5% *Klucel H* + 40% Sucrose	20
0.5% *Klucel H* + 50% Sucrose	7

13. Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose which is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with propylene oxide at elevated temperature and pressure. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. Etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the propylene oxide, and 'chaining-out' may take place. This results in the formation of side chains containing more than one mole of combined propylene oxide.

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14. Safety

Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also extensively used in cosmetics and food products.

Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material.[14] However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare but have included a report, in a single patient, of allergic contact dermatitis due to hydroxypropyl cellulose in a transdermal estradiol patch.[15] The WHO has not specified an acceptable daily intake for hydroxypropyl cellulose since the levels consumed were not considered to represent a hazard to health.[16] Excessive consumption of hydroxypropyl cellulose may however have a laxative effect.

LD_{50} (mouse, IP): > 25 g/kg[17]
LD_{50} (mouse, IV): > 0.5 g/kg
LD_{50} (mouse, oral): > 5 g/kg
LD_{50} (rat, IP): > 25 g/kg
LD_{50} (rat, IV): 0.25 g/kg
LD_{50} (rat, oral): 10.2 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Eur, Fr, Ger, Hung, It, Jpn, Neth, Port, Swiss and USPNF.

18. Related Substances

Hydroxyethyl Cellulose; Hydroxypropyl Methylcellulose; low-substituted hydroxypropyl cellulose.

Low-substituted hydroxypropyl cellulose:
CAS number: [78214-41-2]
Synonyms: cellulose, 2-hydroxypropyl ether (low-substituted); *L-HPC*.
Pharmacopeias: Jpn and USPNF.
Angle of repose:
49° for *L-HPC Type LH-11*;
45° for *L-HPC Type LH-21*.
Density (bulk):
0.34 g/cm^3 for *L-HPC Type LH-11*;
0.40 g/cm^3 for *L-HPC Type LH-21*.
Density (tapped):
0.57 g/cm^3 for *L-HPC Type LH-11*;
0.65 g/cm^3 for *L-HPC Type LH-21*.
Moisture content: ≤ 5.0% w/w
Particle size distribution: average particle size for *L-HPC Type LH-11* is 50.6 μm; for *L-HPC Type LH-21* it is 41.7 μm.[18]
Solubility: insoluble in water but swells.
Specific gravity: 1.46
Specific surface area:[18]
L-HPC Type LH-11 = 2.70 m^2/g;
L-HPC Type LH-21 = 3.20 m^2/g;
L-HPC Type LH-31 = 5.24 m^2/g;
L-HPC Type LH-41 = 31.60 m^2/g.
Safety: LD_{50} (rat, oral): > 15 g/kg[17]
Comments: a low-substituted hydroxypropyl cellulose containing 5-16% of hydroxypropoxy groups. Used as a sustained release tablet matrix former and as a tablet disintegrant.[18,19]

19. Comments

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

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22. Authors

USA: RJ Harwood, JL Johnson.

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Hydroxypropyl Methylcellulose

1. Nonproprietary Names

BP: Hypromellose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

2. Synonyms

Cellulose, hydroxypropyl methyl ether; *Culminal MHPC*; E464; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*.

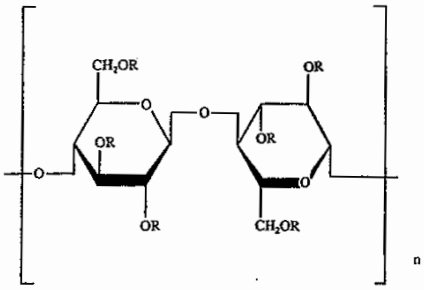
3. Chemical Name and CAS Registry Number

Cellulose, 2-Hydroxypropyl methyl ether
[9004-65-3]

4. Empirical Formula Molecular Weight

The PhEur 1992 describes hydroxypropyl methylcellulose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades which 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. Hydroxypropyl methylcellulose defined in the USP XXII specifies the substitution type by appending a four digit number to the nonproprietary name, e.g. hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

5. Structural Formula



Where R is H, CH_3 or $[CH_3CH(OH)CH_2]$.

6. Functional Category

Coating agent; film-former; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.

In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder,[1] in film-coating[2-7] and as an extended release tablet matrix.[8-12] Concentrations of between 2-5% 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 water-soluble drugs from a matrix.

Depending upon the viscosity grade, concentrations between 2-10% w/w are used as 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.

Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye-drops and artificial tear solutions.

Hydroxypropyl methylcellulose is also 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, hydroxypropyl methylcellulose is used 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.

8. Description

Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

9. Pharmacopeial Specifications

Test	PhEur 1992	USP XXII (Suppl 2)
Identification	+	+
Appearance of solution	+	—
pH (1% w/w solution)	5.5-8.0	—
Apparent viscosity	+	+
Loss on drying	⩽ 10.0%	⩽ 5.0%
Residue on ignition		
for viscosity grade > 50 mPa s	—	⩽ 1.5%
for viscosity grade ⩽ 50 mPa s	—	⩽ 3.0%
for type 1828 of all viscosities	—	⩽ 5.0%
Sulfated ash	⩽ 1.0%	—
Arsenic	—	⩽ 3 ppm
Chlorides	⩽ 0.5%	—
Heavy metals	⩽ 20 ppm	⩽ 0.001%
Methoxy content		
Type 1828	—	16.5-20.0%
Type 2208	—	19.0-24.0%
Type 2906	—	27.0-30.0%
Type 2910	—	28.0-30.0%
Hydroxypropoxy content		
Type 1828	—	23.0-32.0%
Type 2208	—	4.0-12.0%
Type 2906	—	4.0-7.5%
Type 2910	—	7.0-12.0%

10. Typical Properties

Acidity/alkalinity:
pH = 5.5-8.0 for a 1% w/w aqueous solution.

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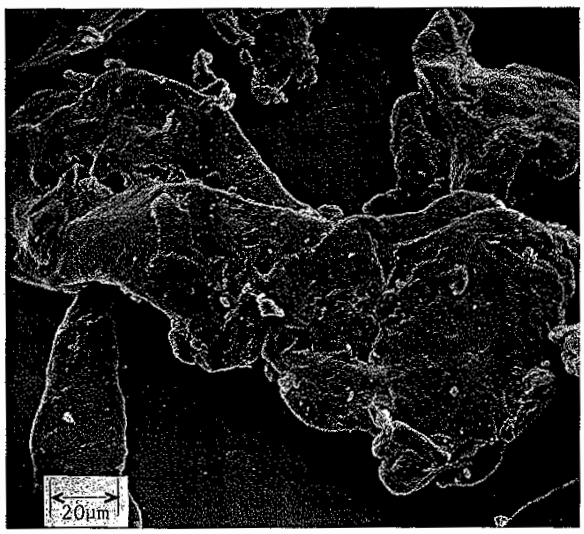
SEM: 1
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Shin-Etsu Chemical Co Ltd
Lot No.: 83214
Magnification: 60x
Voltage: 10kV

SEM: 2
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Shin-Etsu Chemical Co Ltd
Lot No.: 83214
Magnification: 600x
Voltage: 10kV



Ash: 1.5-3.0%, depending upon the grade.
Autoignition temperature: 360°C
Density (tapped): 0.50-0.70 g/cm^3 for *Pharmacoat*.
Melting point: browns at 190-200°C; chars at 225-230°C. Glass transition temperature is 170-180°C.
Moisture content: hydroxypropyl methylcellulose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air. *See also* HPE Data.
Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, and mixtures of methanol and dichloromethane. Certain grades of hydroxypropyl methylcellulose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. *See also* Section 11.
Specific gravity: 1.26
Viscosity (dynamic): a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared although hydroxypropyl methylcellulose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hydroxypropyl methylcellulose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions, *see* Table I.

To prepare an aqueous solution, it is recommended that hydroxypropyl methylcellulose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90°C then the remaining hydroxypropyl methylcellulose added. Cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hydroxypropyl methylcellulose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to 1 part of hydroxypropyl methylcellulose. Cold water is then added to produce the required volume.

Table I: Dynamic viscosity (mPa s) of *Pharmacoat 603* (Shin-Etsu Chemical Co Ltd) solutions in various solvents at 20°C.

Solvent	Viscosity (mPa s) at 20°C Concentration (% w/w)			
	2	6	10	14
Dichloromethane: ethanol (50:50)	4	28	150	580
Ethanol: water (50:50)	8	32	120	350
Water	3	15	45	100

	HPE Laboratory Project Data		
	Method	Lab #	Results
Moisture content	MC-20	15	2.10% [a]
Moisture content	MC-20	15	3.10% [b]
Moisture content	EMC-1	15	*See* Fig. 1. [a]

Supplier: a. Dow Chemical Company; b. Aqualon.

11. Stability and Storage Conditions

Hydroxypropyl methylcellulose powder is a stable material although it is hygroscopic after drying.

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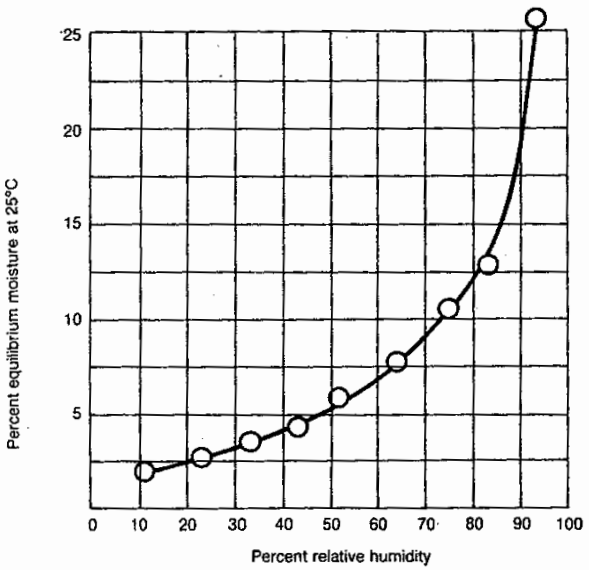

Fig. 1: Equilibrium moisture content of hydroxypropyl methylcellulose, *Methocel E15* (Dow Chemical Company, Lot No.: QP0502-801-E).

Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solutions: Hydroxypropyl methylcellulose undergoes a reversible sol to gel transformation upon heating and cooling respectively. The gel point is 50-90°C, depending upon the grade of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.[13] However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. When used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used for this purpose. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hydroxypropyl methylcellulose powder should be stored in a well-closed container, in a cool, dry, place.

12. Incompatibilities

Hydroxypropyl methylcellulose is incompatible with some oxidizing agents. Since it is nonionic, hydroxypropyl methylcellulose will not complex with metallic salts and ionic organics to form insoluble precipitates.

13. Method of Manufacture

A purified form of cellulose, obtained from cotton waste or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose which is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methylhydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14. Safety

Hydroxypropyl methylcellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl methylcellulose is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect.[14] The WHO has not specified an acceptable daily intake for hydroxypropyl methylcellulose since the levels consumed were not considered to represent a hazard to health.[15]

LD_{50} (mouse, IP): 5 g/kg[16]

LD_{50} (rat, IP): 5.2 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl methylcellulose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosions. Hydroxypropyl methylcellulose is combustible.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral capsules, suspensions, syrups and tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Br, Eur, Fr, Gr, It, Jpn, Neth, Port, Swiss and US.

18. Related Substances

Hydroxyethyl Cellulose; Hydroxypropyl Cellulose; Hydroxypropyl Methylcellulose Phthalate.

19. Comments

Powdered or granular, surface-treated grades of hydroxypropyl methylcellulose are also available which are dispersible in cold water. The dissolution rate of these materials can be controlled by a shift in pH and they are thus useful for slow-release or enteric coated formulations.

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22. Authors

USA: RJ Harwood, JL Johnson.

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Lecithin

1. Nonproprietary Names

USPNF: Lecithin
See also Section 4.

2. Synonyms

E322; egg lecithin; *Epikuron*; *Espholip*; *LSC*; mixed soybean phosphatides; ovolecithin; *Ovothin*; soybean lecithin; soybean phospholipids; vegetable lecithin.

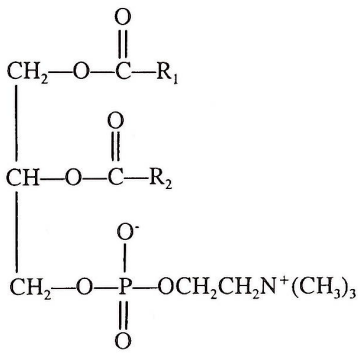
3. Chemical Name and CAS Registry Number

Lecithin [8002-43-5]
The chemical nomenclature and CAS registry numbering of lecithin is complex. The commercially available lecithin, used in cosmetics, pharmaceuticals and food products, although a complex mixture of phospholipids and other materials, may be referred to in some literature sources as 1,2-diacyl-*sn*-glycero-3-phosphocholine (trivial chemical name, phosphatidylcholine). This material is the principal constituent of egg lecithin and has the same CAS registry number. The name lecithin and the CAS registry number above are thus used to refer to both lecithin and phosphatidylcholine in some literature sources.
See also Section 4.

4. Empirical Formula Molecular Weight

The USPNF XVII describes lecithin as a complex mixture of acetone-insoluble phosphatides, which consist chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids and carbohydrates as separated from a crude vegetable oil source.
The composition of lecithin and hence its physical properties varies enormously depending upon the source of the lecithin and the degree of purification. Egg lecithin, for example, contains 69% phosphatidylcholine and 24% phosphatidylethanolamine, whilst soybean lecithin contains 21% phosphatidylcholine, 22% phosphatidylethanolamine and 19% phosphatidylinositol, along with other components.[1]

5. Structural Formula



α-phosphatidylcholine
Where, R_1 and R_2 are fatty acids which may be different or identical.

Lecithin is a complex mixture of materials, *see* Section 4. The structure above shows phosphatidylcholine, the principal component of egg lecithin, in its α-form. In the β-form the phosphorus containing group and the R_2 group exchange positions.

6. Functional Category

Emollient; emulsifying agent; solubilizing agent.

7. Applications in Pharmaceutical Formulation or Technology

Lecithins are used in a wide variety of pharmaceutical applications. They are also used in cosmetics[2] and food products.
Lecithins are mainly used in pharmaceutical products as dispersing, emulsifying and stabilizing agents and are included in intramuscular and intravenous injections, parenteral nutrition formulations and topical products, such as creams and ointments.
Lecithins are also used in suppository bases,[3] to reduce the brittleness of suppositories and have been investigated for their absorption enhancing properties in an intranasal insulin formulation.[4] Lecithins are also commonly used as a component of enteral and parenteral nutrition formulations.
Liposomes in which lecithin is included as a component of the bilayer have been used to encapsulate drug substances and their potential as novel delivery systems has been investigated.[5]
Therapeutically, lecithin and derivatives have been used as a pulmonary surfactant in the treatment of neonatal respiratory distress syndrome.

Use	Concentration (%)
Aerosol inhalation	0.1
IM injection	0.3-2.3
Oral suspensions	0.25-10.0

8. Description

Lecithins vary greatly in their physical form, from viscous semiliquids to powders, depending upon the free fatty acid content. They may also vary in color from brown to light yellow, depending upon whether they are bleached or unbleached.
Lecithins have practically no odor. Those derived from vegetable sources have a bland or nut-like taste, similar to soybean oil.

9. Pharmacopeial Specifications

Test	USPNF XVII (Suppl 6)
Water	≤ 1.5%
Arsenic	≤ 3 ppm
Lead	≤ 0.001%
Heavy metals	≤ 0.004%
Acid value	≤ 36
Hexane-insoluble matter	≤ 0.3%
Acetone-insoluble matter	≥ 50.0%

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10. Typical Properties

Density:
0.97 g/cm^3 for liquid lecithin;
0.5 g/cm^3 for powdered lecithin.
Iodine number:
95-100 for liquid lecithin;
82-88 for powdered lecithin.
Isoelectric point: ≈ 3.5
Saponification value: 196
Solubility: lecithins are soluble in aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, mineral oil and fatty acids. They are practically insoluble in cold vegetable and animal oils, polar solvents and water. When mixed with water however, lecithins hydrate to form emulsions.

11. Stability and Storage Conditions

Lecithins decompose at extreme pH. They are also hygroscopic and subject to microbial degradation. When heated, lecithins oxidize, darken and decompose. Temperatures of 160-180°C will cause degradation within 24 hours.
Fluid, or waxy, lecithin grades should be stored at room temperature or above; temperatures below 10°C may cause separation.
All lecithin grades should be stored in well-closed containers protected from light.

12. Incompatibilities

Incompatible with esterases due to hydrolysis.

13. Method of Manufacture

Lecithins are essential components of cell membranes and may thus in principle be obtained from a wide variety of living matter. In practice however, lecithins are usually obtained from vegetable products such as soybean, peanut, cottonseed, sunflower, rapeseed, corn or groundnut oil. Soybean lecithin is the most commercially important vegetable lecithin. Lecithin obtained from eggs is also commercially important and was the first lecithin to be discovered.
Vegetable lecithins are obtained as a by-product in the vegetable oil refining process. Polar lipids are extracted with hexane and after removal of the solvent a crude vegetable oil obtained. Lecithin is then removed from the crude oil by water extraction. Following drying the lecithin may then be further purified.[1]
With egg lecithin, a different manufacturing process must be used since the lecithin in egg yolks is more tightly bound to proteins than in vegetable sources. Egg lecithin is thus obtained by solvent extraction from liquid egg yolks using acetone or from freeze dried egg yolks using ethanol.[1]
Synthetic lecithins may also be produced.

14. Safety

Lecithin is a component of cell membranes and is therefore consumed as a normal part of the diet. Although excessive consumption may be harmful, oral doses of up to 80 g daily have been used therapeutically in the treatment of tardive dyskinesia.[6] When used in topical formulations lecithin is generally regarded as a nonirritant and nonsensitizing material.[2]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Lecithins may be irritant to the eyes; eye protection and gloves are recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, IM and IV injections, oral capsules, suspensions and tablets, rectal, topical and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Mex and USPNF.

18. Related Substances

-

19. Comments

Lecithins contain a variety of unspecified materials and care should therefore be exercised in the use of unpurified lecithin in injectable or topical dosage forms as interaction with the active substance or other excipients may occur. Unpurified lecithins may also have a greater potential for irritancy in formulations.
Supplier's literature should be consulted for information on the different grades of lecithin available and their applications in formulations.

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Hanin I, Pepeu G, editors. Phospholipids: biochemical, pharmaceutical and analytical considerations. New York: Plenum, 1990.

22. Authors

USA: W Han.

Magnesium Stearate

1. Nonproprietary Names

BP: Magnesium stearate
PhEur: Magnesii stearas
USPNF: Magnesium stearate

2. Synonyms

E572; *HyQual*; magnesium octadecanoate; stearic acid magnesium salt.

3. Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4. Empirical Formula Molecular Weight

$C_{36}H_{70}MgO_4$ 591.27
(for pure material)

The USPNF XVII describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids obtained from fats and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The BP 1993 and PhEur 1983 describe magnesium stearate as consisting mainly of magnesium stearate with variable proportions of magnesium palmitate and magnesium oleate ($C_{36}H_{66}MgO_4$).

5. Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6. Functional Category

Tablet and capsule lubricant.

7. 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 0.25-5.0%.

8. Description

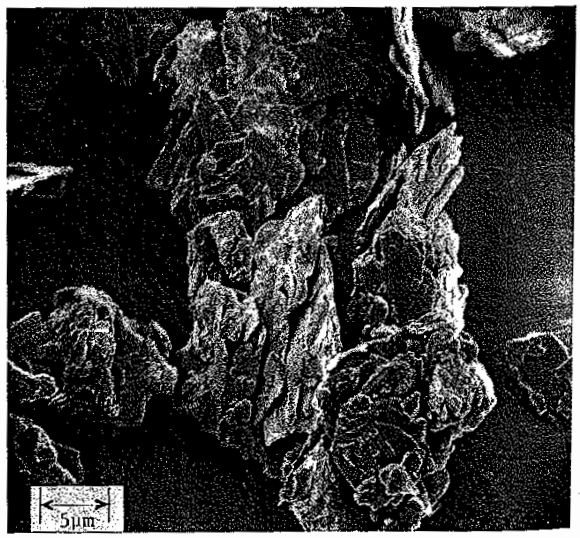
Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to the touch and readily adheres to the skin.

9. Pharmacopeial Specifications

Test	PhEur 1983	USPNF XVII (Suppl 9)
Identification	+	+
Microbial limits	—	+
Acidity or alkalinity	+	—
Color of solution	+	—
Acid value of the fatty acids	195-210	—
Clarity and color of solution of the fatty acids	+	—
Loss on drying	⩽ 6.0%	⩽ 4.0%
Heavy metals	⩽ 20 ppm	—
Lead	—	⩽ 0.001%
Organic volatile impurities	—	+
Chloride	⩽ 250 ppm	—
Sulfate	⩽ 0.5%	—
Assay (dried basis, as Mg)	3.8-5.0%	—
Assay (as MgO)	—	6.8-8.3%

SEM: 1
Excipient: Magnesium stearate
Magnification: 600x

SEM: 2
Excipient: Magnesium stearate
Magnification: 2400x



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10. Typical Properties

Compressibility: *see* HPE Data.
Density: 1.03-1.08 g/cm^3, *see also* HPE Data.
Density (tapped): 0.30 g/cm^3, *see also* HPE Data.
Flash point: 250°C
Flowability: poorly flowing, cohesive powder.
Melting point: 88.5°C
Moisture content: *see* HPE Data.
Polymorphism: a trihydrate, acicular form and a dihydrate, lamellar form have been isolated, with the latter possessing the better lubricating properties.
Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%). *See also* HPE Data.
Specific surface area: 2.45-16.0 m^2/g.

HPE Laboratory Data

	Method	Lab #	Results
Compressibility			
at 63.5-235 MPa	COM-1	21	No compacts [a]
at 500 MPa	COM-7	12	Lamination [b]
Density	DE-1	7	1.06-1.1 g/cm^3 [b]
Density (bulk & tapped)	BTD-2	1	B: 0.143 g/cm^3 [b]
			T: 0.224 g/cm^3 [b]
Density (bulk & tapped)	BTD-7	14	B: 0.160 g/cm^3 [b]
			T: 0.180 g/cm^3 [b]
Moisture content	EMC-1	5	*See* Fig. 1. [c]
Moisture content	MC-12	1	3.85% [b]
Moisture content	MC-12	5	3.00% [c]
Solubility			
Ethanol (95%) at 25°C	SOL-1	1	0.160 mg/mL [b]
n-Hexane at 25°C	SOL-1	1	0.018 mg/mL [b]
Water at 25°C	SOL-1	1	0.040 mg/mL [b]

Supplier:
a. Witco Corporation;
b. Mallinckrodt Speciality Chemicals Co;
c. Penick (Lot No.: 338-NB5-003).

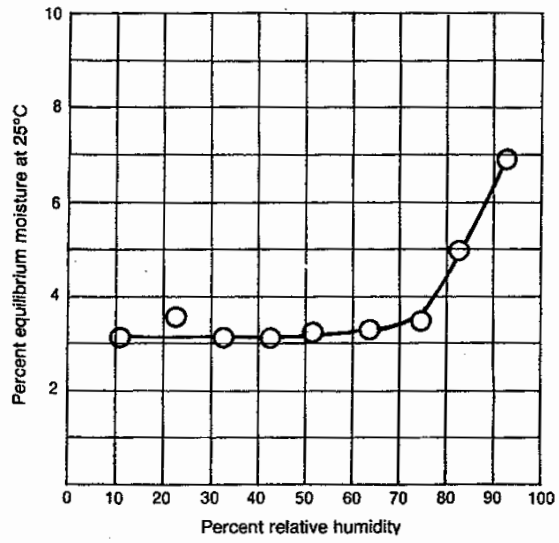

Fig. 1: Equilibrium moisture content of magnesium stearate.

11. Stability and Storage Conditions

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

12. Incompatibilities

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials.

13. Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate, or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures.

14. 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 result in some laxative effect or mucosal irritation. Inhalation of magnesium stearate powder is harmful and has resulted in fatalities, *see also* Section 15.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Belg, Br, Braz, Chin, Cz, Eur, Fr, Ger, Hung, Ind, It, Jpn, Mex, Neth, Nord, Port, Rom, Swiss, Yug and USPNF.

18. Related Substances

Calcium Stearate; Stearic Acid; Zinc Stearate.

19. Comments

Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations.[1-6] Since there may be variation between batches of magnesium stearate, it has not been possible to conclusively correlate the dissolution rate retardation with the observed lubricity.[7] The physical properties of different batches of magnesium stearate, such as specific surface area, have however been correlated with lubricant efficacy.[8-11]
There is evidence to suggest that the hydrophobic nature of magnesium stearate can vary from batch to batch due to the presence of water-soluble, surface-active impurities such as sodium stearate. Batches containing very low concentrations of these impurities have been shown to retard the dissolution of a drug to a greater extent than when using batches which contain higher levels of impurities.
An increase in the coefficient of variation of mixing and a decrease in the dissolution rate has been observed following blending of magnesium stearate with a tablet granulation. Tablet dissolution rate and crushing strength decreased as the time of blending increased; magnesium stearate may also

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increase tablet friability. Blending times with magnesium stearate should thus be carefully controlled.[12-26]

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22. Authors

USA: LV Allen, PE Luner.

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Methylcellulose

1. Nonproprietary Names

BP: Methylcellulose
PhEur: Methylcellulosum
USP: Methylcellulose

2. Synonyms

Benecel; *Celacol*; *Culminal MC*; E461; *Methocel*; *Metolose.*

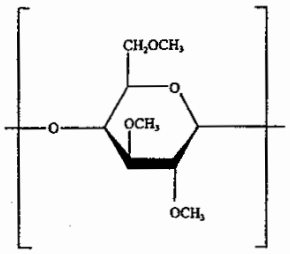
3. Chemical Name and CAS Registry Number

Cellulose methyl ether [9004-67-5]

4. Empirical Formula Molecular Weight

Methylcellulose is a long-chain substituted cellulose in which approximately 27-32% of the hydroxyl groups are in the form of the methyl ether. It contains between 50-1500 anhydroglucose units. The degree of substitution of methylcellulose is defined as the average number of methoxyl (CH_3O) groups attached to each of the anhydroglucose units along the chain and is characteristic of material from a particular source. The degree of substitution also affects the physical properties of methylcellulose, such as its solubility.

5. Structural Formula



Structure shown with complete methoxyl substitution. *See* Section 4.

6. Functional Category

Coating agent; emulsifying agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Methylcellulose is widely used in oral and topical pharmaceutical formulations.

In tablet formulations, low or medium viscosity grades of methylcellulose are used as binding agents, the methylcellulose being added either as a dry powder or in solution.[1-3] High viscosity grades of methylcellulose may also be incorporated in tablet formulations as a disintegrant.[4] Methylcellulose may also be added to a tablet formulation to produce sustained release preparations.[5] The methylcellulose is uniformly incorporated throughout a tablet in a hydrophilic matrix. Upon contact with water the outer tablet skin partially hydrates to form a gel layer. The rate of erosion of this coating or diffusion of an active ingredient through it thus controls the overall dissolution rate.

Tablet cores may also be spray-coated with either aqueous or organic solutions of highly substituted, low viscosity grades of methylcellulose, the coats being used to mask an unpleasant taste or to modify the release of a drug.[6] Methylcellulose coats are also used for sealing tablet cores prior to sugar coating.

Low viscosity grades of methylcellulose are used to emulsify olive, peanut and mineral oils.[7] They are also used as suspending or thickening agents for orally administered liquids, methylcellulose being commonly used in place of sugar-based syrups or other suspension bases.[8] The methylcellulose is used to delay the settling of suspensions and to increase the contact time of drugs, such as antacids, in the stomach.

High viscosity grades of methylcellulose are used to thicken topically applied products such as creams and gels.

In ophthalmic preparations, a 0.5-1.0% w/v solution of a highly substituted, high viscosity grade of methylcellulose has been used as a vehicle for eye-drops.[9] An antimicrobial preservative, such as benzalkonium chloride should also be included. However, hydroxypropyl methylcellulose based formulations are now preferred for ophthalmic preparations.

Therapeutically, methylcellulose is used as a bulk laxative.

Methylcellulose is also widely used in cosmetics and in food products as an emulsifier and stabilizer.

Use	Concentration (%)
Bulk laxative	5-30
Creams, gels and ointments	1-5
Emulsifying agent	1-5
Ophthalmic preparations	0.5-1.0
Suspensions	1-2
Sustained release tablet matrix	5-75
Tablet binder	2-6
Tablet coating	0.5-5
Tablet disintegrant	2-10

8. Description

Methylcellulose occurs as practically odorless and tasteless, white to yellowish-white colored granules or as a powder.

9. Pharmacopeial Specifications

Test	PhEur 1992	USP XXII (Suppl 9)
Identification	+	+
Appearance of solution	+	—
pH (1% w/v solution)	5.5-8.0	—
Apparent viscosity	+	+
Loss on drying	⩽ 10.0%	⩽ 5.0%
Residue on ignition	—	⩽ 1.5%
Sulfated ash	⩽ 1.0%	—
Arsenic	—	⩽ 3 ppm
Chlorides	⩽ 0.5%	—
Heavy metals	⩽ 20 ppm	⩽ 0.001%
Organic volatile impurities	—	+
Assay (of methoxyl groups)	—	27.5-31.5%

10. Typical Properties

Acidity/alkalinity:
pH = 5.5-8.0 for a 1% w/v aqueous suspension.
Angle of repose: 40-50°
Autoignition temperature: ≈ 360°C

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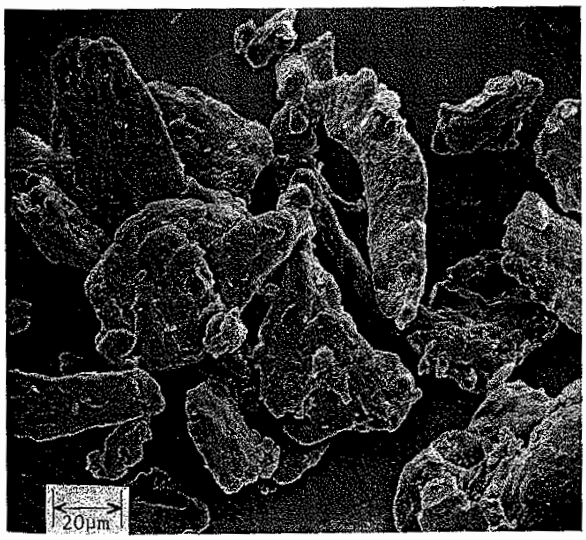
SEM: 1
Excipient: Methylcellulose
Manufacturer: Dow Chemical Company
Lot No.: MM-090271-A
Magnification: 60x
Voltage: 10 kV

SEM: 2
Excipient: Methylcellulose
Manufacturer: Dow Chemical Company
Lot No.: MM-090271-A
Magnification: 600x
Voltage: 10 kV



Degree of substitution: 1.1-2.0 for *Methocel*.
Hygroscopicity: methylcellulose is hygroscopic, *see* HPE Data.
Melting point: begins to char at 280-300°C.
Particle friability: *see* HPE Data.
Solubility: practically insoluble in acetone, chloroform, ethanol, ether, saturated salt solutions, toluene and hot water. Soluble in glacial acetic acid and in a mixture of equal volumes of ethanol and chloroform. In cold water, methylcellulose swells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.
Specific gravity: 1.26-1.31 for powder; 1.0012 for 1% w/v solution; 1.0117 for 5% w/v solution; 1.0245 for 10% w/v solution.
Surface tension: 50-60 mN/m (50-60 dynes/cm) for a 2% w/v solution at 20°C.
Viscosity (dynamic): various grades of methylcellulose are commercially available which produce 2% w/v solutions with viscosities of 10-10 000 mPa s (10-10 000 cP). Individual grades of methylcellulose have a stated, narrowly defined viscosity range measured for a 2% w/v solution. For example, *Metolose SM-15* has a viscosity of 15 mPa s (15 cP), while *Metolose SM-4000* has a viscosity of 4000 mPa s (4000 cP). The viscosity of solutions may be increased by increasing the concentration of methylcellulose. Increased temperatures reduce the viscosity of solutions until gel formation occurs at 50-60°C. The process of thermogelation is reversible, with a viscous solution being reformed on cooling.

	HPE Laboratory Project Data		
	Method	**Lab #**	**Results**
Moisture content	MC-14	28	3.87% [a]
	SI-1	13	*See* Fig. 1.[a]
Particle friability			
Metolose SM-15	PF-1	36	0.261% [b]
Metolose SM-400	PF-1	36	0.323% [b]
Metolose SM-4000	PF-1	36	0.204% [b]

Supplier: a. Dow Chemical Company (Lot No.: MM032364-A); b. Shin-Etsu Chemical Company Ltd.

11. Stability and Storage Conditions

Methylcellulose powder is stable although it is slightly hygroscopic.
Solutions of methylcellulose are stable to alkalis and dilute acids between pH 3-11, at room temperature. At less than pH 3, the viscosity of methylcellulose solutions are reduced.[10] On heating, solution viscosity is reduced until gel formation occurs at approximately 50°C, *see* Section 10.
Methylcellulose solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. Solutions may also be sterilized by autoclaving although this process can decrease the viscosity of a solution.[11,12] The change in viscosity, after autoclaving, is related to solution pH; solutions at less than pH 4 had their viscosities reduced by greater than 20%.[11]
The bulk material should be stored in an airtight container in a cool, dry, place.

12. Incompatibilities

Methylcellulose is reported to be incompatible with: aminacrine hydrochloride; chlorocresol; mercuric chloride; phenol; resorcinol; tannic acid; silver nitrate; cetylpyridinium chloride; *p*-hydroxybenzoic acid; *p*-aminobenzoic acid; methylparaben; propylparaben and butylparaben. Salts of mineral acids and

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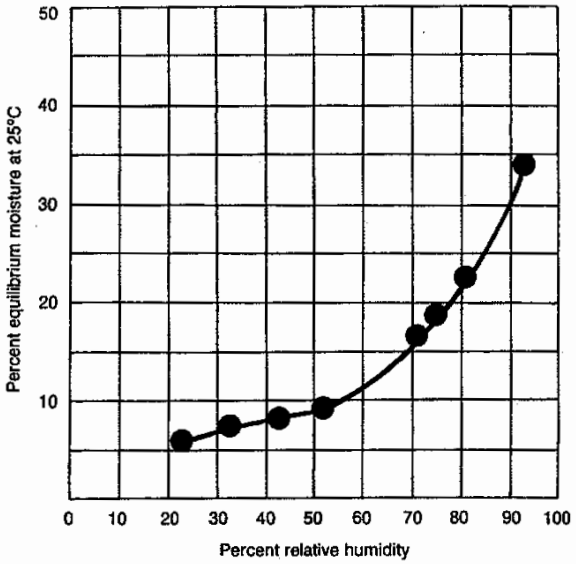

Fig. 1: Moisture sorption isotherm of methylcellulose.

particularly of polybasic acids, phenols and tannins, coagulate solutions of methylcellulose. However, this can be prevented by the addition of ethanol (95%) or glycol diacetate. Complexation of methylcellulose occurs with highly surface-active compounds, such as tetracaine and dibutoline sulfate. High concentrations of electrolytes increase the viscosity of methylcellulose mucilages owing to the salting out of methylcellulose. With very high concentrations of electrolytes, the methylcellulose may be completely precipitated in the form of a discrete or continuous gel.

13. Method of Manufacture

Methylcellulose is prepared from wood pulp by treatment with alkali followed by methylation of the alkali cellulose with chloromethane.

14. Safety

Methylcellulose is widely used in a variety of oral and topical pharmaceutical formulations. It is also extensively used in cosmetics and food products and is generally regarded as a nontoxic, nonallergenic and nonirritant material.[13]

Following oral consumption, methylcellulose is not digested or absorbed and is therefore a noncaloric material. Ingestion of excessive amounts of methylcellulose may temporarily increase flatulence and gastrointestinal distension.

In the normal individual, oral consumption of large amounts of methylcellulose has a laxative action and medium or high viscosity grades are therefore used as bulk laxatives; divided, oral, daily doses of 1-6 g of methylcellulose in the form of granules or tablets, administered with plenty of fluid, are used. In certain individuals however, consumption of methylcellulose may aggravate obstructive gastrointestinal diseases. Oesophageal obstruction may also occur if methylcellulose is swallowed with an insufficient quantity of fluid. Consumption of large quantities of methylcellulose may additionally interfere with the normal absorbtion of some minerals. However, this and the other adverse effects discussed above relate mainly to the use of methylcellulose as a bulk laxative and are not significant factors when methylcellulose is used as an excipient in oral preparations.

Methylcellulose is not commonly used in parenteral products although it has been used in intra-articular and intramuscular injections. Studies, in rats, have suggested that parenterally administered methylcellulose may cause glomerulonephritis and hypertension.

The WHO has not specified an acceptable daily intake of methylcellulose since the level of use in foods was not considered to be a hazard to health.[14]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dust may be irritant to the eyes and eye protection should therefore be worn. Excessive dust generation should be avoided to minimize the risk of explosions. Methylcellulose is combustible.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (buccal tablets, IM injections, ophthalmic preparations, oral capsules, suspensions and tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Braz, Cz, Eur, Fr, Hung, It, Jpn, Neth, Port, Rom, Swiss, US and Yug.

18. Related Substances

Ethylcellulose.

19. Comments

Methylcellulose is best dissolved in water by one of three methods, the most suitable being chosen for a particular application. The most commonly used method is to add methylcellulose initially to hot water. The appropriate quantity of methylcellulose, to produce a solution of required viscosity, is mixed with water at 70°C; about half the desired final volume of water is used. Cold, or ice water, is then added to the hot methylcellulose slurry in order to cool it to below 20°C. A clear, aqueous methylcellulose solution is obtained.

Alternatively, methylcellulose powder may be either dry blended with another powder prior to mixing with cold water or methylcellulose powder may be moistened with an organic solvent such as ethanol (95%) prior to the addition of water.

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22. Authors

USA: RI Senderoff.

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Mineral Oil

1. Nonproprietary Names

BP: Liquid paraffin
PhEur: Paraffinum liquidum
USP: Mineral oil

2. Synonyms

905 (mineral hydrocarbons); *Avatech*; *Citation*; heavy liquid petrolatum; heavy mineral oil; liquid petrolatum; paraffin oil; white mineral oil.

3. Chemical Name and CAS Registry Number

Mineral oil [8012-95-1]

4. Empirical Formula Molecular Weight

Mineral oil is a mixture of refined liquid saturated hydrocarbons obtained from petroleum.

5. Structural Formula

See Section 4.

6. Functional Category

Emollient; solvent; tablet and capsule lubricant; therapeutic agent; oleaginous vehicle.

7. Applications in Pharmaceutical Formulation or Technology

Mineral oil is used primarily as an excipient in topical pharmaceutical formulations where its emollient properties are exploited as an ingredient in ointment bases. It is additionally used in oil-in-water emulsions,[1-5] as a solvent, and as a lubricant in capsule and tablet formulations, and to a limited extent, as a mold release agent for cocoa butter suppositories.

Therapeutically, mineral oil is used in ophthalmic formulations for its lubricant properties and has been used in the treatment of constipation, *see* Section 14. Mineral oil is also used in cosmetics and food products.[6]

Use	Concentration (%)
Ophthalmic ointments	3.0-60.0
Otic preparations	0.5-3.0
Topical emulsions	1.0-32.0
Topical lotions	1.0-20.0
Topical ointments	0.1-95.0

8. Description

Mineral oil is a transparent, colorless, viscous liquid, free from fluorescence in daylight. It is practically tasteless and odorless when cold, and has a faint odor when heated.

9. Pharmacopeial Specifications

Test	PhEur 1983	USP XXII
Specific gravity	0.827-0.890	0.845-0.905
Viscosity (kinematic) at 40°C	—	⩾ 34.5 cSt
Viscosity (dynamic) at 20°C	110-230 mPa s	—
Acidity or alkalinity	+	—
Neutrality	—	+
Readily carbonizable substances	+	+
Limit of polynuclear compounds	+	+
Solid paraffin	+	+

10. Typical Properties

Boiling point: > 360°C
Flash point: 210-224°C
Pour point: -12.2 to -9.4°C
Refractive index: n_D^{20} = 1.4756-1.4800
Surface tension: ≈ 35 mN/m (dynes/cm) at 25°C.
Solubility: practically insoluble in ethanol (95%), glycerin, and water; soluble in acetone, benzene, chloroform, carbon disulfide, ether, and petroleum ether. Miscible with volatile oils and fixed oils, with the exception of castor oil. The addition of a small amount of a suitable surfactant may promote miscibility/solubilization.
Viscosity (dynamic): 110-230 mPa s at 20°C. *See also* HPE Data.

HPE Laboratory Project Data

Sample	Method	Lab #	Results
Kaydol	VIS-1	27	163 ± 2.0 mPa s [a]
Primol 355	VIS-1	27	158 ± 2.0 mPa s [b]

Supplier: a. Witco Corporation; b. Exxon.

11. Stability and Storage Conditions

Mineral oil undergoes oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an 'induction period'. Under ordinary conditions, the induction period may take months or years. However, once a trace of peroxide is formed, further oxidation is autocatalytic and proceeds very rapidly. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. Stabilizers may be added to retard oxidation; butylated hydroxyanisole, butylated hydroxytoluene and α-tocopherol being the most commonly used antioxidants.

Mineral oil may be sterilized by dry heat.

Mineral oil should be stored in an airtight container, protected from light, in a cool, dry, place.

12. Incompatibilities

Incompatible with strong oxidizing agents.

13. Method of Manufacture

Mineral oil is obtained by distillation of petroleum. The lighter hydrocarbons are first removed by distillation and the residue then redistilled between 330-390°C. The distillate is chilled and the solid fractions removed by filtration. The filtrate is then further purified and decolorized by high pressure hydrogenation or sulfuric acid treatment; the purified filtrate is then filtered through adsorbents. The liquid portion obtained is

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distilled and the portion boiling below 360°C discarded. A suitable stabilizer may be added to the mineral oil, *see* Section 11.

14. Safety

Mineral oil is used as an excipient in a wide variety of pharmaceutical formulations, *see* Section 16. It is also used extensively in cosmetics and in some food products.[6]

Therapeutically, mineral oil has been used in the treatment of constipation since it acts as a lubricant and stool softener when taken orally. Daily doses of up to 45 mL have been administered orally while doses of up to 120 mL have been used as an enema. However, excessive dosage of mineral oil, either orally or rectally can result in anal seepage and irritation and its oral use as a laxative is not considered desirable.

Chronic oral consumption of mineral oil may impair the appetite and interfere with the absorption of fat-soluble vitamins and prolonged use should be avoided. Mineral oil is absorbed to some extent when emulsified and can lead to granulomatous reactions. Similar reactions also occur upon injection of the oil;[7] injection may also cause vasospasm.

The most serious adverse reaction to mineral oil is lipoid pneumonia caused by aspiration of the oil.[8,9] With the reduction in the use of mineral oil in nasal formulations the number of instances of lipoid pneumonia has been greatly reduced. However, lipoid pneumonia has also been associated with the use of mineral oil-containing cosmetics[10] and ophthalmic preparations[11] in addition to the chronic ingestion of mineral oil. It is therefore recommended that mineral oil-containing products not be used in very young children, the elderly or persons with debilitating illnesses.

Given its widespread use in many topical products, mineral oil has been associated with few instances of allergic reactions.

The WHO has not specified an acceptable daily intake of mineral oil given the low concentration consumed in foods.[12]

LD_{50} (mouse, oral): 22 g/kg[13]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Inhalation of mineral oil vapors may be harmful. In the UK, the recommended occupational exposure limit for mineral oil mist is 5 mg/m^3 long-term (8-hour TWA) and 10 mg/m^3 short-term.[14]

Mineral oil is combustible.

16. Regulatory Status

GRAS listed. Accepted in the UK for use in certain food applications. Included in the FDA Inactive Ingredients Guide (dental preparations, IV injections, ophthalmic preparations, oral capsules and tablets, otic, topical, transdermal, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Belg, Br, Braz, Chin, Cz, Egypt, Eur, Fr, Ger, Gr, Hung, Ind, It, Jpn, Mex, Neth, Nord, Port, Rom, Rus, Swiss, Turk, US and Yug. Also in BP Vet.

18. Related Substances

Light Mineral Oil; Mineral Oil and Lanolin Alcohols; Paraffin; Petrolatum.

19. Comments

Mineral oil, in completely filled soft plastic tubes, showed bubbles of gas after gamma irradiation. The bubbles were larger at higher levels of radiation. The iodine value also increased after high and low levels of irradiation.

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22. Authors

USA: GE Reier, DA Wadke.

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Light Mineral Oil

1. Nonproprietary Names

BP: Light liquid paraffin
PhEur: Paraffinum perliquidum
USPNF: Light mineral oil

2. Synonyms

905 (mineral hydrocarbons); *Citation*; light liquid petrolatum; light paraffin oil.

3. Chemical Name and CAS Registry Number

Light mineral oil

4. Empirical Formula Molecular Weight

Light mineral oil is a mixture of refined liquid saturated hydrocarbons obtained from petroleum. It is less viscous and has a lower specific gravity than mineral oil.

5. Structural Formula

See Section 4.

6. Functional Category

Emollient; solvent; tablet and capsule lubricant; therapeutic agent; oleaginous vehicle.

7. Applications in Pharmaceutical Formulation or Technology

Light mineral oil is used in applications similar to mineral oil. It is used primarily as an excipient in topical pharmaceutical formulations where its emollient properties are exploited as an ingredient in ointment bases.[1,2] It is also used in ophthalmic formulations.[3] Light mineral oil is additionally used as a solvent and lubricant in capsules and tablets; as a solvent and penetration enhancer in transdermal preparations;[4] and as the oily medium used in the microencapsulation of many drugs.[5-13]
Light mineral oil is also used in cosmetics and certain food products.

Use	Concentration (%)
Ophthalmic ointments	⩽ 15
Otic preparations	⩽ 50
Topical emulsions	1-20
Topical lotions	7-16
Topical ointments	0.2-23

8. Description

Light mineral oil is a transparent, colorless liquid, free from fluorescence in daylight. It is practically tasteless and odorless when cold, and has a faint odor when heated.

9. Pharmacopeial Specifications

Test	PhEur 1983	USPNF XVII
Specific gravity	0.810-0.875	0.818-0.880
Viscosity (kinematic) at 40°C	—	⩽ 33.5 cSt
Viscosity (dynamic) at 20°C	25-80 mPa s	—
Acidity or alkalinity	+	—
Neutrality	—	+
Readily carbonizable substances	+	+
Limit of polynuclear compounds	+	+
Solid paraffin	+	+

10. Typical Properties

Solubility: soluble in chloroform, ether, and hydrocarbons; sparingly soluble in ethanol (95%); practically insoluble in water.

11. Stability and Storage Conditions

Light mineral oil undergoes oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an 'induction period'. Under typical storage conditions, the induction period may take months or years. However, once a trace of peroxide is formed, further oxidation is autocatalytic and proceeds very rapidly. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. The USPNF XVII permits the addition of suitable stabilizers to retard oxidation, butylated hydroxyanisole, butylated hydroxytoluene and α-tocopherol being the most commonly used antioxidants.
Light mineral oil may be sterilized by dry heat.
Light mineral oil should be stored in an airtight container, protected from light, in a cool, dry, place.

12. Incompatibilities

Incompatible with strong oxidizing agents.

13. Method of Manufacture

Light mineral oil is obtained by the distillation of petroleum. A suitable stabilizer may be added to the oil, *see* Section 11.
See also Mineral Oil for further information.

14. Safety

Light mineral oil is used in applications similar to mineral oil. Oral ingestion of large doses of light mineral oil or chronic consumption may be harmful. Aspiration of light mineral oil may cause lipoid pneumonia.
See Mineral Oil for further information.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Inhalation of mineral oil vapors may be harmful. In the UK, the recommended occupational exposure limit for mineral oil mist is 5 mg/m^3 long-term (8-hour TWA) and 10 mg/m^3 short-term.[14] Light mineral oil is combustible.

16. Regulatory Status

Mineral oil is GRAS listed and accepted in the UK for use in certain food applications.
Light mineral oil is included in the FDA Inactive Ingredients Guide (ophthalmic preparations, oral capsules and tablets,

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otic, rectal, topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Belg, Br, Eur, Fr, Ger, Gr, Ind, It, Jpn, Neth, Port, Swiss and USPNF. Also in BP Vet.

18. Related Substances

Mineral Oil; Mineral Oil and Lanolin Alcohols; Paraffin; Petrolatum.

19. Comments

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20. Specific References

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See also Mineral Oil.

21. General References

See Mineral Oil.

22. Authors

USA: R Abramowitz, GE Reier, DA Wadke.

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Poloxamer

1. Nonproprietary Names

USPNF: Poloxamer

2. Synonyms

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

3. Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymer
[9003-11-6]

4. Empirical Formula Molecular Weight

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula:

$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$

The grades included in the USPNF XVII are shown below:

Poloxamer	Physical form	a	b	Average molecular weight
124	liquid	12	20	2090-2360
188	solid	80	27	7680-9510
237	solid	64	37	6840-8830
338	solid	141	44	12700-17400
407	solid	101	56	9840-14600

5. Structural Formula

See Section 4.

6. Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Poloxamers are nonionic polyoxyethylene-polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents.[1-6] The polyoxyethylene segment is hydrophilic whilst the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface active properties vary over a wide range and a number of different types are commercially available, *see* Sections 4, 9, 10 and 19.

Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents, in ointments, suppository bases, gels,[7-9] and as tablet binders and coatings.

Poloxamer 188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes.[10,11]

Therapeutically, poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation; it is usually used in combination with a laxative such as danthron. Poloxamers may also be used therapeutically as wetting agents in eye-drop formulations, in the treatment of kidney stones and as skin wound cleansers.

Use	Concentration (%)
Fat emulsifier	0.3
Flavor solubilizer	0.3
Fluorocarbon emulsifier	2.5
Gelling agent	15-50
Spreading agent	1
Stabilizing agent	1-5
Suppository base	4-6 or 90
Tablet coating	10
Tablet excipient	5-10
Wetting agent	0.01-5

8. Description

Poloxamers generally occur as white-colored, waxy, free flowing prilled granules or as cast solids. They are practically odorless and tasteless. At room temperature, poloxamer 124 occurs as a colorless liquid.

9. Pharmacopeial Specifications

Test	USPNF XVII (Suppl 8)
Average molecular weight	+
Weight percent oxyethylene	
For poloxamer 124	46.7 ± 1.9
For poloxamer 188	81.8 ± 1.9
For poloxamer 237	72.4 ± 1.9
For poloxamer 407	73.2 ± 1.7
pH (1 in 40 solution)	5.0-7.5
Unsaturation (mEq/g)	
For poloxamer 124	0.020 ± 0.008
For poloxamer 188	0.026 ± 0.008
For poloxamer 237	0.034 ± 0.008
For poloxamer 407	0.048 ± 0.017
Heavy metals	⩽ 0.002%
Free ethylene oxide, propylene oxide and 1,4-dioxane	⩽ 5 ppm

10. Typical Properties

Acidity/alkalinity:
pH = 6.0-7.4 for a 2.5% w/v aqueous solution.
Cloud point: > 100°C for a 1% w/v aqueous solution, and a 10% w/v aqueous solution of poloxamer 188.
Density: 1.06 g/cm^3 at 25°C
Flash point: 260°C
Flowability: solid poloxamers are free flowing.
HLB value: 0.5-30; 29 for poloxamer 188.
Melting point:
16°C for poloxamer 124;
52°C for poloxamer 188;
49°C for poloxamer 237;
57°C for poloxamer 338;
56°C for poloxamer 407.
Moisture content: poloxamers generally contain less than 0.5% w/w water and are hygroscopic only at greater than 80% relative humidity. *See also* HPE Data.
Solubility: solubility varies according to the poloxamer type, *see* Table I.

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Table I: Solubility at 25°C for various types of poloxamer in different solvents.

Type	Solvent				
	Ethanol (95%)	Propan-2-ol	Propylene glycol	Water	Xylene
Poloxamer 124	freely soluble	freely soluble	freely soluble	freely soluble	freely soluble
Poloxamer 188	freely soluble	—	—	freely soluble	—
Poloxamer 237	freely soluble	sparingly soluble	—	freely soluble	sparingly soluble
Poloxamer 338	freely soluble	—	sparingly soluble	freely soluble	—
Poloxamer 407	freely soluble	freely soluble	—	freely soluble	—

Surface tension: 19.8 mN/m (19.8 dynes/cm) for a 0.1% w/v aqueous poloxamer 188 solution at 25°C; 24.0 mN/m (24.0 dynes/cm) for a 0.01% w/v aqueous poloxamer 188 solution at 25°C; 26.0 mN/m (26.0 dynes/cm) for a 0.001% w/v aqueous poloxamer solution at 25°C.
Viscosity (dynamic):
1000 mPa s (1000 cP) as a melt at 77°C.

	HPE Laboratory Project Data*		
	Method	Lab #	Results
Moisture content	MC-3	32	0.33%
Moisture content	EMC-1	15	*See* Fig. 1.
Solubility			
Ethanol (95%) at 25°C	SOL-7	32	398 mg/mL
Ethanol (95%) at 37°C	SOL-7	32	396 mg/mL
Hexane at 25°C	SOL-7	32	0.05 mg/mL
Hexane at 37°C	SOL-7	32	0.09 mg/mL
Propylene glycol at 25°C	SOL-7	32	1.0 mg/mL
Propylene glycol at 37°C	SOL-7	32	1.0 mg/mL
Water at 25°C	SOL-7	32	500 mg/mL
Water at 37°C	SOL-7	32	500 mg/mL

* For poloxamer 188.
Supplier: BASF Corp (*Pluronic F-68*, Lot No.: WPEA535B).

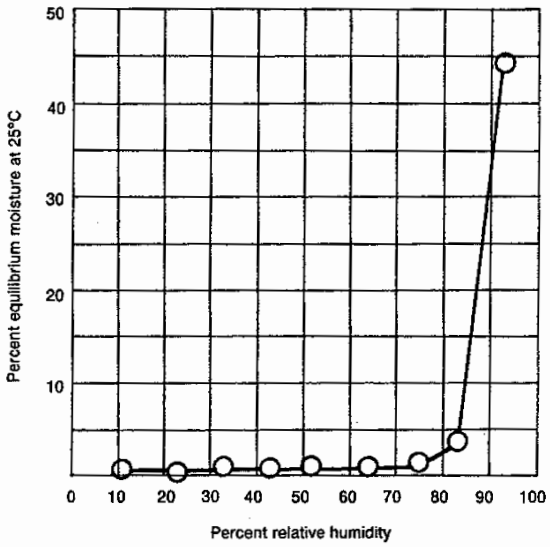

Fig. 1: Equilibrium moisture content of poloxamer 188 (*Pluronic F-68*).

11. Stability and Storage Conditions

Poloxamers are stable materials. Aqueous solutions are stable in the presence of acids, alkalis and metal ions. However, aqueous solutions do support mold growth.
The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

Depending on the relative concentrations, poloxamer 188 is incompatible with phenols and parabens.

13. Method of Manufacture

Poloxamer polymers are prepared by reacting propylene oxide with propylene glycol to form polyoxypropylene glycol. Ethylene oxide is then added to form the block copolymer.

14. Safety

Poloxamers are used in a variety of oral, parenteral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body.
Animal toxicity studies, with dogs and rabbits, have shown poloxamers to be nonirritant and nonsensitizing when applied, in 5% w/v and 10% w/v concentration, to the eyes, gums and skin.

In a 14-day study of intravenous administration to rabbits, at concentrations up to 0.5 g/kg/day, no overt adverse effects were noted. A similar study with dogs also showed no adverse effects at dosage levels up to 0.5 g/kg/day. In a longer term study, rats fed 3% w/w or 5% w/w of poloxamer in food, for up to two years, did not exhibit any significant symptoms of toxicity. However, rats receiving 7.5% w/w of poloxamer in their diet showed some decrease in growth rate.
No hemolysis of human blood cells was observed over 18 hours at 25°C, with 0.001-10% w/v poloxamer solutions.
Acute animal toxicity data for poloxamer 188:[12]
LD_{50} (mouse, IV): 1 g/kg
LD_{50} (mouse, oral): 15 g/kg
LD_{50} (mouse, SC): 5.5 g/kg
LD_{50} (rat, IV): 7.5 g/kg
LD_{50} (rat, oral): 9.4 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (IV injections, inhalations, ophthalmic preparations, oral powders, solutions,

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suspensions and syrups, also topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

USPNF.

18. Related Substances

–

19. Comments

Although the USPNF XVII contains specifications for 5 poloxamer grades many more different poloxamers are commercially available which vary in their molecular weight and the proportion of oxyethylene present in the polymer. A series of poloxamers with greatly varying physical properties are thus available.

The nonproprietary name 'poloxamer' is followed by a number, the first 2 digits of which, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene portion of the copolymer and the third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene portion.

Similarly, with many of the trade names used for poloxamers, e.g. *Pluronic F-68* (BASF Corp), the first digit arbitrarily represents the molecular weight of the polyoxypropylene portion and the second digit represents the weight percent of the oxyethylene portion. The letters 'L', 'P', and 'F', stand for the physical form of the poloxamer, either liquid, paste or flakes, *see also* Table II.

Note that in the US the trade name *Pluronic* is used by BASF Corp for pharmaceutical and industrial grade poloxamers, whilst in the UK and Europe the trade name *Lutrol* is used for the pharmaceutical grade material.

Table II: Nonproprietary name and corresponding commercial grade.

Nonproprietary name	Commercial grade
Poloxamer 124	L-44
Poloxamer 188	F-68
Poloxamer 237	F-87
Poloxamer 338	F-108
Poloxamer 407	F-127

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Chi SC, Jun HW. Release rates of ketoprofen from poloxamer gels in a membraneless diffusion cell. J Pharm Sci 1991; 80: 280-283.

Johnston TP, Miller SC. Toxicological evaluation of poloxamer vehicles for intramuscular use. J Parenter Sci Technol 1985; 39: 83-88.

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Tait CJ, Houston JB, Attwood D, Collett JH. Pharmacokinetics of cimetidine following delivery from implanted poloxamer gels in rats. J Pharm Pharmacol 1987; 39(Suppl): 57P.

22. Authors

UK: JH Collett, PJ Weller.

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Polyethylene Glycol

1. Nonproprietary Names

BP: Macrogol 300
Macrogol 400
Macrogol 1000
Macrogol 1540
Macrogol 4000

PhEur: Macrogolum 300
Macrogolum 400
Macrogolum 1000

USPNF: Polyethylene glycol

2. Synonyms

Breox PEG; *Carbowax*; *Hodag PEG*; *Lutrol E*; PEG; polyoxyethylene glycol; *Renex*.

3. Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxy-poly(oxy-1,2-ethanediyl)
[25322-68-3]

4. Empirical Formula Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$

Where m represents the average number of oxyethylene groups.

Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where n is a number 1 more than the value of m in the previous formula.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number which follows PEG indicates the average molecular weight of the polymer.

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	m	Average molecular weight
PEG 200	4.2	190-210
PEG 300	6.4	285-315
PEG 400	8.7	380-420
PEG 540 (blend)	—	500-600
PEG 600	13.2	570-613
PEG 900	15.3	855-900
PEG 1000	22.3	950-1050
PEG 1450	32.5	1300-1600
PEG 1540	28-36	1300-1600
PEG 2000	40-50	1800-2200
PEG 3000	60-75	2700-3300
PEG 3350	75.7	3000-3700
PEG 4000	69-84	3000-4800
PEG 4600	104.1	4400-4800
PEG 8000	181.4	7000-9000

5. Structural Formula

See Section 4.

6. Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations.

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin, *see* Section 14. Although they do not readily penetrate the skin, polyethylene glycols are water soluble and as such are easily removed from the skin by washing; they are therefore useful as ointment bases.[1] Solid grades are generally employed in topical ointments with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases[2] where they have the following advantages over fats: the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; physical stability on storage is better; suppositories are readily miscible with rectal fluids. Disadvantages of using polyethylene glycols are: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.[3] However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations,[4-6] a mixture of the powdered constituents with 10-15% w/w PEG 6000 is heated to 70-75°C. The mass becomes paste-like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.[7] Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film forming polymers.[8] The presence of polyethylene glycols, especially liquid grades, in film coats tends to increase their water permeability and may reduce protection against low pH in enteric coating films. Polyethylene glycols are useful as plasticizers in micro-encapsulated products to avoid rupture

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Table II: Pharmacopeial specifications of polyethylene glycol.

Test	BP 1993 (Ad 1994) & PhEur 1993					USPNF XVII (Suppl 8)
	PEG 300	PEG 400	PEG 1000	PEG 1540	PEG 4000	
Appearance of solution	+	+	+	+	+	+
Freezing point	—	—	35-40°C	42-46°C	53-56°C	—
Viscosity	+	+	+	+	+	*See* Table III
Average molecular weight	+	+	+	+	+	*See* Table III
Acidity/alkalinity	+	+	+	—	—	—
pH (5% w/v solution)	—	—	—	4.0-7.0	4.5-7.5	4.5-7.5
Hydroxyl value	340-394	264-300	107-118	70-86	30-36	—
Reducing substances	+	+	+	—	—	—
Residue on ignition	—	—	—	—	—	⩽ 0.1%
Sulfated ash	⩽ 0.2%	⩽ 0.2%	⩽ 0.2%	⩽ 0.1%	⩽ 0.1%	—
Arsenic	—	—	—	—	—	⩽ 3 ppm
Limit of ethylene glycol and diethylene glycol	⩽ 0.4%	⩽ 0.4%	—	—	—	⩽ 0.25%
Ethylene oxide	⩽ 1 ppm	⩽ 1 ppm	⩽ 1 ppm	—	—	⩽ 0.02%
Heavy metals	⩽ 20 ppm	⩽ 20 ppm	⩽ 20 ppm	—	—	⩽ 5 ppm
Water	⩽ 2.0%	⩽ 2.0%	⩽ 2.0%	—	—	—

of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An anti-adherent effect is also exerted, again subject to the avoidance of over-heating.

In addition, polyethylene glycols have been used in the preparation of urethane hydrogels which are used as controlled release agents.

8. Description

The USPNF XVII describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200-600 are liquids whilst grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200-600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight, but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG ⩾ 1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free flowing milled powders.

9. Pharmacopeial Specifications

See Table II.

Table III: Specification for viscosity of polyethylene glycol of nominal molecular weight at 98.9°C ± 0.3°C from the USPNF XVII (Suppl 8).

Nominal average molecular weight	Viscosity range in mm^2/s (cSt)
200	3.9-4.8
300	5.4-6.4
400	6.8-8.0
500	8.3-9.6
600	9.9-11.3
700	11.5-13.0
800	12.5-14.5

Table III: *Continued*

Nominal average molecular weight	Viscosity range in mm^2/s (cSt)
900	15.0-17.0
1000	16.0-19.0
1100	18.0-22.0
1200	20.0-24.5
1300	22.0-27.5
1400	24-30
1450	25-32
1500	26-33
1600	28-36
1700	31-39
1800	33-42
1900	35-45
2000	38-49
2100	40-53
2200	43-56
2300	46-60
2400	49-65
2500	51-70
2600	54-74
2700	57-78
2800	60-83
2900	64-88
3000	67-93
3250	73-105
3350	76-110
3500	87-123
3750	99-140
4000	110-158
4250	123-177
4500	140-200
4750	155-228
5000	170-250
5500	206-315
6000	250-390
6500	295-480
7000	350-590
7500	405-735
8000	470-900

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10. Typical Properties

Density:
1.11-1.14 g/cm^3 at 25°C for liquid PEGs;
1.15-1.21 g/cm^3 at 25°C for solid PEGs.
Flash point:
182°C for PEG 200;
213°C for PEG 300;
238°C for PEG 400;
250°C for PEG 600.
Freezing point:
< -65°C PEG 200 sets to a glass;
-15 to -8°C for PEG 300;
4-8°C for PEG 400;
15-25°C for PEG 600.
Melting point:
37-40°C for PEG 1000;
44-48°C for PEG 1500;
40-48°C for PEG 1540;
45-50°C for PEG 2000;
48-54°C for PEG 3000;
50-58°C for PEG 4000;
55-63°C for PEG 6000;
60-63°C for PEG 8000;
60-63°C for PEG 20000.
Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g. PEG 4000 and above, are not hygroscopic. *See also* HPE Data.
Refractive index:
n_D^{25} = 1.459 for PEG 200;
n_D^{25} = 1.463 for PEG 300;
n_D^{25} = 1.465 for PEG 400;
n_D^{25} = 1.467 for PEG 600.
Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher molecular weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils and mineral oil. *See also* HPE Data.
Surface tension: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.
Viscosity (kinematic): *see also* HPE Data and Table III.

Grade	Viscosity in mm^2/s (cSt) 25°C	99°C
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000	solid	19.5
PEG 2000	solid	47
PEG 4000	solid	180
PEG 6000	solid	580
PEG 20000	solid	6900

	HPE Laboratory Project Data		
	Method	Lab #	Results
Bulk/tap density			
PEG 4000 (flakes)	BTD-3	1	B: 0.485 g/cm^3 [c] T: 0.575 g/cm^3
PEG 4000 (powder)	BTD-1	1	B: 0.581 g/cm^3 [c] T: 0.704 g/cm^3
PEG 4000 (powder)	BTD-7	14	B: 0.610 g/cm^3 [c] T: 0.750 g/cm^3
PEG 6000 (flakes)	BTD-3	1	B: 0.476 g/cm^3 [c] T: 0.562 g/cm^3
PEG 6000 (powder)	BTD-1	1	B: 0.481 g/cm^3 [c] T: 0.581 g/cm^3
PEG 6000 (powder)	BTD-7	14	B: 0.510 g/cm^3 [c] T: 0.570 g/cm^3
Density			
PEG 4000 (prilled)	DE-1	31	1.043 g/cm^3 [a]
PEG 4000 (powder)	DE-1	31	1.205 g/cm^3 [c]
PEG 6000 (powder)	DE-1	31	1.122 g/cm^3 [c]
Moisture content			
PEG 1540	MC-3	28	0.585% [c]
PEG 4000 (flakes)	MC-19	1	0.290% [c]
PEG 4000 (powder)	MC-19	1	0.290% [c]
PEG 4000 (powder)	MC-20	2	0.300% [b]
PEG 4000	EMC-1	2	*See* Fig. 1. [b]
PEG 4000 (powder)	SDI-2	26	*See* Fig. 2. [c]
PEG E-4000	SDI-2	26	*See* Fig. 2. [a]
PEG 6000 (flakes)	MC-19	1	0.120% [c]
PEG 6000 (powder)	MC-19	1	0.150% [c]
PEG 6000 (powder)	SDI-2	26	*See* Fig. 3. [c]
PEG E-6000	SDI-2	26	*See* Fig. 3. [a]
Particle size			
PEG 4000 (flakes)	PSD-1	1	*See* Fig. 4. [c]
PEG 4000 (powder)	PSD-1	1	*See* Fig. 5. [c]
PEG 6000 (flakes)	PSD-1	1	*See* Fig. 6. [c]
PEG 6000 (powder)	PSD-1	1	*See* Fig. 7. [c]
Solubility in ethanol (95%) at 25°C			
PEG 4000 (flakes)	SOL-2	1	0.575 mg/mL [c]
PEG 4000 (powder)	SOL-2	1	0.575 mg/mL [c]
PEG 6000 (flakes)	SOL-2	1	0.500 mg/mL [c]
PEG 6000 (powder)	SOL-2	1	0.420 mg/mL [c]
Solubility in *n*-hexane at 25°C			
PEG 4000 (flakes)	SOL-1	1	0.006 mg/mL [c]
PEG 4000 (powder)	SOL-1	1	0.013 mg/mL [c]
PEG 6000 (flakes)	SOL-1	1	0.011 mg/mL [c]
PEG 6000 (powder)	SOL-1	1	0.055 mg/mL [c]
Solubility in water at 25°C			
PEG 4000 (flakes)	SOL-2	1	2100 mg/mL [c]
PEG 4000 (powder)	SOL-2	1	2100 mg/mL [c]
PEG 6000 (flakes)	SOL-2	1	1900 mg/mL [c]
PEG 6000 (powder)	SOL-2	1	1900 mg/mL [c]
Viscosity			
PEG 4000 (flakes)	VIS-1	27	1.26 ± 0.1 mPa s [a]
PEG 4000 (flakes)	VIS-1	27	1.26 ± 0.1 mPa s [b]
PEG 4000 (powder)	VIS-1	27	1.26 ± 0.1 mPa s [b]

Supplier: a. BASF; b. McKesson; c. Union Carbide Corporation.

11. Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, nor do they become rancid.
Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration or gamma

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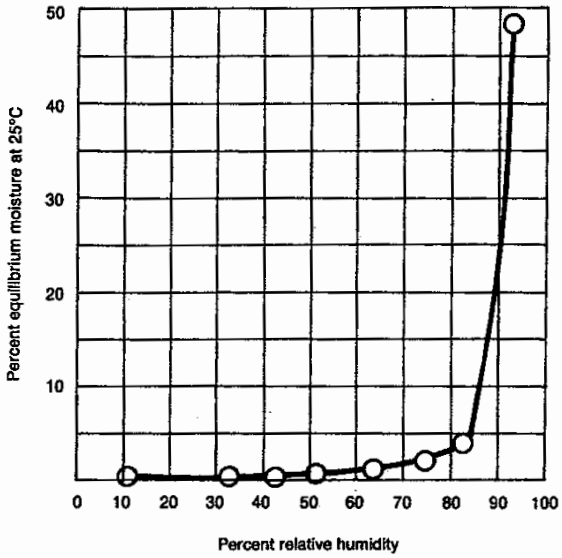

Fig. 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot #B192-8209) at 25°C.

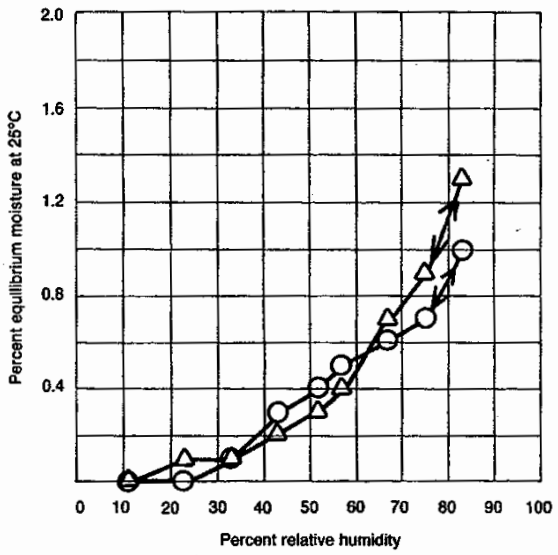

Fig. 3: Equilibrium moisture content of PEG 6000 at 25°C.
○ PEG 6000 powder (Union Carbide Corporation, Lot #B-507).
△ PEG E-6000 (BASF, Lot #WPNY-124B).

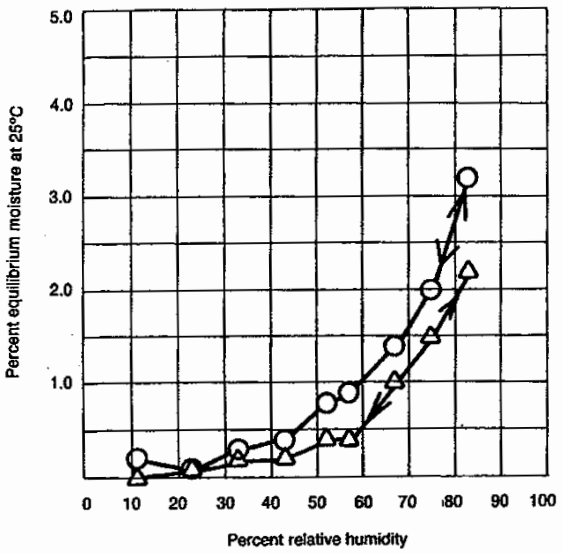

Fig. 2: Equilibrium moisture content of PEG 4000 at 25°C.
○ PEG 4000 powder (Union Carbide Corporation, Lot #B-251).
△ PEG E-4000 (BASF, Lot #WPYA-575B).

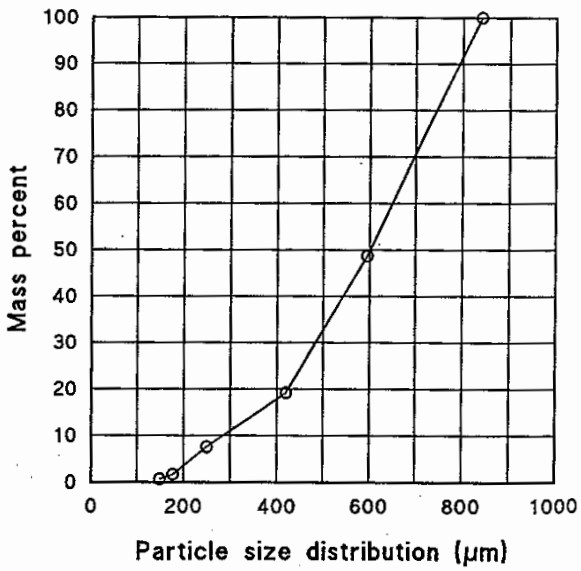

Fig. 4: Particle size distribution of PEG 4000 flakes.

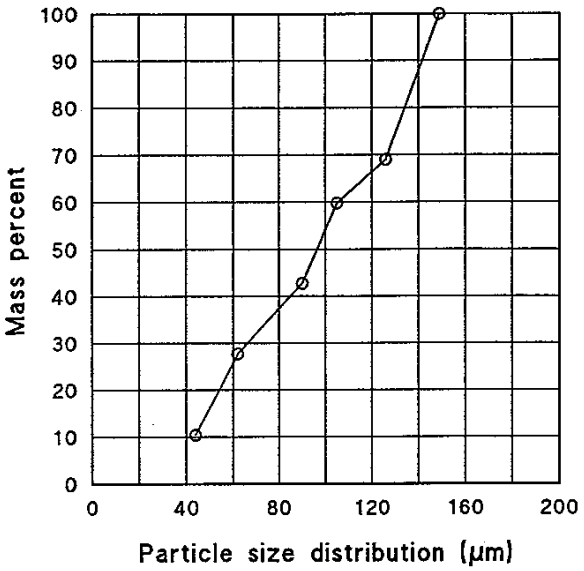

Fig. 5: Particle size distribution of PEG 4000 powder.

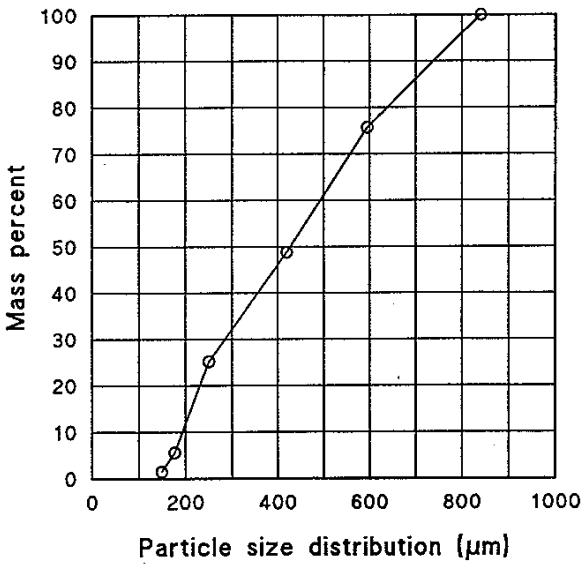

Fig. 6: Particle size distribution of PEG 6000 flakes.

irradiation.[9] Sterilization of solid grades by dry heat at 150°C for one hour may induce oxidation, darkening and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

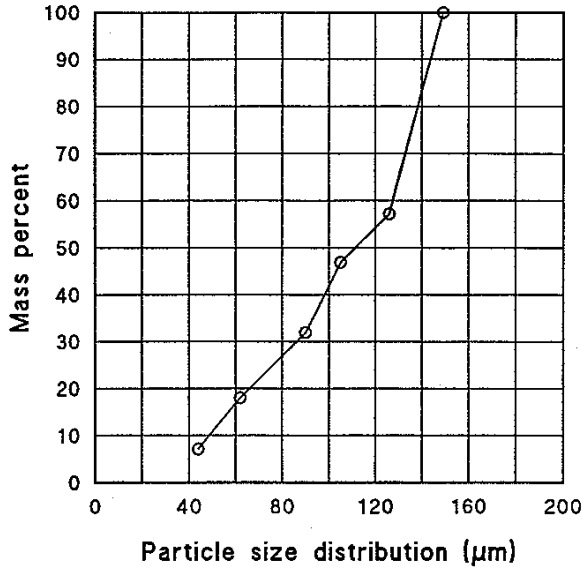

Fig. 7: Particle size distribution of PEG 6000 powder.

Polyethylene glycols should be stored in well-closed containers in a cool, dry, place. Stainless steel, aluminum, glass or lined steel containers are preferred for the storage of liquid grades.

12. Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity due to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some colors.

The antibacterial activity of certain antibiotics, particularly penicillin and bacitracin, is reduced in polyethylene glycol bases. The preservative efficacy of the parabens may also be impaired due to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures.

Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

13. Method of Manufacture

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14. Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.[10-12] However, adverse reactions to polyethylene glycols have been reported and although of relatively low toxicity, any toxicity appears to be greatest with polyethylene glycols of low molecular weight.

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Table IV: Animal toxicity data (LD_{50}) for various grades of polyethylene glycol.[17]

PEG grade	LD_{50} in g/kg									
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (SC)	Rat (IP)	Rat (IV)	Rat (oral)	Rat (SC)
PEG 200	—	7.5	—	38.3	19.9	—	—	—	28.9	—
PEG 300	19.6	—	—	—	17.3	—	17	—	27.5	—
PEG 400	15.7	10.0	8.6	28.9	26.8	—	9.7	7.3	30.2	—
PEG 810	—	—	—	—	—	—	—	13	—	16
PEG 1000	22.5	20	—	—	—	—	—	—	42	—
PEG 1540	—	—	—	—	—	—	15.4	—	51.2	—
PEG 4000	50.9	—	16	—	76	18	11.6	—	50	—
PEG 6000	50	—	—	—	—	—	6.8	—	50	—

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically, including urticaria and delayed allergic reactions, have also been reported.[13] However, the most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis and renal failure following the topical use of polyethylene glycols in burn patients.[14] Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 6 L of an aqueous mixture of electrolytes and high molecular weight polyethylene glycol is consumed by patients undergoing bowel cleansing.[15]

Liquid polyethylene glycols may be absorbed when taken orally, but the higher molecular weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.[16]

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v since hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data *see* Table IV.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, ophthalmic preparations, oral capsules, solutions, syrups and tablets, rectal, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Arg, Aust, Belg, Br, Braz, Cz, Eur, Fr, Ger, Hung, It, Jpn, Neth, Nord, Pol, Port, Rom, Swiss, USPNF and Yug.

Some pharmacopeias, such as the USPNF XVII, have a single monograph describing various different grades; other pharmacopeias have individual monographs. The BP 1993 (Ad 1994) for example has separate monographs for PEG 300, PEG 400, PEG 1000, PEG 1540 and PEG 4000.

18. Related Substances

Polyoxyethylene Alkyl Ethers; Polyoxyethylene Sorbitan Fatty Acid Esters; Suppository Bases.

19. Comments

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22. Authors

USA: JC Price.

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Polymethacrylates

1. Nonproprietary Names

USPNF: Ammonio methacrylate copolymer
USPNF: Methacrylic acid copolymer
Note that two separate monographs applicable to polymethacrylates are contained in the USPNF, *see* Section 9.

2. Synonyms

Eudragit; polymeric methacrylates.

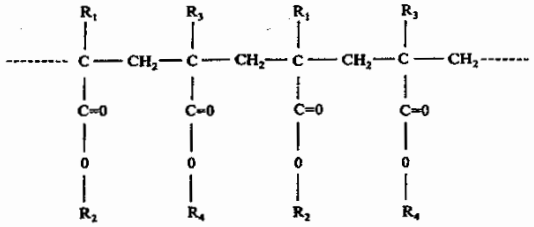
3. Chemical Name and CAS Registry Number

See Table I.

4. Empirical Formula Molecular Weight

The USPNF XVII describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types, type A (*Eudragit L*), type B (*Eudragit S*), and type C (*Eudragit L 30 D-55*), are defined which vary in their methacrylic acid content and solution viscosity. Two additional polymers, type A (*Eudragit RL*) and type B (*Eudragit RS*), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF XVII. *See* Section 9.
Typically, the molecular weight of the polymer is ⩾ 100 000.

5. Structural Formula



For *Eudragit E*:
R_1, R_3 = CH_3
R_2 = $CH_2CH_2N(CH_3)_2$
R_4 = CH_3, C_4H_9
For *Eudragit L* and *S*:
R_1, R_3 = CH_3
R_2 = H
R_4 = CH_3
For *Eudragit RL* and *RS*:
R_1 = H, CH_3
R_2 = CH_3, C_2H_5
R_3 = CH_3
R_4 = $CH_2CH_2N(CH_3)_3^+Cl^-$
For *Eudragit NE 30 D*:
R_1, R_3 = H, CH_3
R_2, R_4 = CH_3, C_2H_5
For *Eudragit L 30 D-55* and *L 100-55*:
R_1, R_3 = H, CH_3
R_2 = H
R_4 = CH_3, C_2H_5

6. Functional Category

Film-former; tablet binder; tablet diluent.

7. Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film coating agents.[1-10] Depending on the type of polymer used, films of different solubility characteristics can be produced, *see* Table III.
Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, *Eudragit L* and *S* types are used as enteric coating agents since they are resistant to gastric fluid. Different types are available which are soluble at different pH values, e.g. *Eudragit L 100* is soluble at > pH 6, *Eudragit S 100* is soluble at > pH 7.
Eudragit RL, *RS* and *NE 30 D* are used to form water-insoluble film coats for sustained release products. *Eudragit RL* films are more permeable than those of *Eudragit RS*, and by mixing the two types together films of varying permeability can be obtained. *Eudragit L 100-55* is a redispersible powder and is an alternative to *Eudragit L 30 D-55* for aqueous enteric coating.
Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5-20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct compression processes in quantities of 10-50%. Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.[11]
See also Section 19.

8. Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, an aqueous dispersion, or as an organic solution. A (60:40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. *See* Tables I and II.
Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to approximately pH 5). *Eudragit E* is available as a 12.5% ready-to-use solution in propan-2-ol/acetone (60:40). It is light yellow in color with the characteristic odor of the solvents. Solvent-free granules contain ⩾ 98% dried weight content of *Eudragit E*.
Eudragit L and *S*, also referred to as methacylic acid copolymers in the USPNF monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in *Eudragit L* and approximately 1:2 in *Eudragit S*. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis, thus affording film coats which are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (*Eudragit L 12.5* and *S 12.5*); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (*Eudragit L 12.5 P* and *S 12.5 P*). Solutions are colorless, with the characteristic odor of the solvent. *Eudragit L-100* and

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Table I: Chemical name and CAS registry number of polymethacrylates.

Chemical name	Trade name	CAS number
Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	*Eudragit E 100* *Eudragit E 12.5*	[24938-16-7]
Poly(ethyl acrylate, methyl methacrylate) 2:1	*Eudragit NE 30 D* (formerly *Eudragit 30 D*)	[9010-88-2]
Poly(methacrylic acid, methyl methacrylate) 1:1	*Eudragit L 100* *Eudragit L 12.5* *Eudragit L 12.5 P*	[25806-15-1]
Poly(methacrylic acid, ethyl acrylate) 1:1	*Eudragit L 30 D-55* *Eudragit L 100-55*	[25212-88-8]
Poly(methacrylic acid, methyl methacrylate) 1:2	*Eudragit S 100* *Eudragit S 12.5* *Eudragit S 12.5 P*	[25086-15-1]
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2	*Eudragit RL 100* *Eudragit RL PO* *Eudragit RL 30 D* *Eudragit RL 12.5*	[33434-24-1]
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1	*Eudragit RS 100* *Eudragit RS PO* *Eudragit RS 30 D* *Eudragit RS 12.5*	[33434-24-1]

Eudragit S-100 are white free flowing powders with at least 95% of dry polymers.

Eudragit RL and *Eudragit RS*, also referred to as ammoniomethacrylate copolymers in the USPNF monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters with *Eudragit RL* (type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol/acetone (60:40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain $\geqslant$ 97% of the dried weight content of the polymer.

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight amine-like odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain $\geqslant$ 97% of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55 is an aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester. The polymer corresponds to USPNF methacrylic acid copolymer, type C. The ratio of free carboxyl groups to ester groups is 1:1. Films dissolve above pH 5.5 forming salts with alkalis, thus affording coatings which are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L 30 D-55*) is a white, free-flowing powder which is redispersible in water to form a latex which has properties similar to *Eudragit L 30 D-55*.

9. Pharmacopeial Specifications

Specifications for methacrylic acid copolymers (*Eudragit L, S* and *L 30 D-55*).

Test	USPNF XVII (Suppl 6)
Identification	+
Viscosity	
Type A	50-200 mPa s
Type B	50-200 mPa s
Type C	100-200 mPa s
Loss on drying	
Type A	$\leqslant$ 5.0%
Type B	$\leqslant$ 5.0%
Type C	$\leqslant$ 3.0%
Residue on ignition	
Type A	$\leqslant$ 0.1%
Type B	$\leqslant$ 0.1%
Type C	$\leqslant$ 0.4%
Arsenic	$\leqslant$ 2 ppm
Heavy metals	$\leqslant$ 0.002%
Monomers	$\leqslant$ 0.3%
Assay of methacrylic acid units (dried basis)	
Type A	46.0-50.6%
Type B	27.6-30.7%
Type C	46.0-50.6%

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Specifications for ammonio methacrylate copolymers (*Eudragit RL* and *RS*).

Test	USPNF XVII (Suppl 4)
Identification	+
Viscosity	
Types A and B	⩽ 15 mPa s
Loss on drying	
Types A and B	⩽ 3.0%
Residue on ignition	
Types A and B	⩽ 0.1%
Arsenic	⩽ 2 ppm
Heavy metals	⩽ 0.002%
Monomers	⩽ 0.3%
Assay of ammonio methacrylate units (dried basis)	
Type A	8.85-11.96%
Type B	4.48-6.77%

10. Typical Properties

Acid value: 315 for *Eudragit L 12.5*, *L 12.5 P*, *L 100*, *L 30 D-55*, and *L 100-55*; 180-200 for *Eudragit S 12.5*, *S 12.5 P*, and *S 100*.

Alkali value:
162-198 for *Eudragit E 12.5* and *E 100*;
23.9-32.3 for *Eudragit RL 12.5*, *RL 100*, and *RL PO*;
27.5-31.7 for *Eudragit RL 30 D*;
12.1-18.3 for *Eudragit RS 12.5*, *RS 100*, and *RS PO*;
16.5-22.3 for *Eudragit RS 30 D*.

Density:
0.81-0.82 g/cm^3 for *Eudragit E*;
0.83-0.85 g/cm^3 for *Eudragit L*, *S 12.5* and *12.5 P*;
0.83-0.85 g/cm^3 for *Eudragit L*, *S 100*;
1.06-1.07 g/cm^3 for *Eudragit L 30 D-55*;
0.82-0.84 g/cm^3 for *Eudragit L 100-55*;
0.815-0.835 g/cm^3 for *Eudragit RL* and *RS 12.5*;
0.815-0.835 g/cm^3 for *Eudragit RL* and *RS PO*;
1.045-1.055 g/cm^3 for *Eudragit RL* and *RS 30 D*.

Refractive index:
n_D^{20} = 1.38-1.385 for *Eudragit E*;
n_D^{20} = 1.39-1.395 for *Eudragit L* and *S*;
n_D^{20} = 1.387-1.392 for *Eudragit L 100-55*;
n_D^{20} = 1.38-1.385 for *Eudragit RL* and *RS*.

Solubility: *see* Table II.

Viscosity (dynamic):
3-12 mPa s for *Eudragit E*;
50-200 mPa s for *Eudragit L* and *S*;
⩽ 50 mPa s for *Eudragit L 30 D-55*;
100-200 mPa s for *Eudragit L 100-55*;
⩽ 15 mPa s for *Eudragit RL* and *RS*;
⩾ 200 mPa s for *Eudragit RL* and *RS D*.

Table II: Solubility of commercially available polymethacrylates (*Eudragit*, Röhm Pharma GmbH) in various solutions.

Type	Solvent						
	Acetone and alcohols[a]	Dichloromethane	Ethyl acetate	1N HCl	1N NaOH	Petroleum ether	Water
Eudragit E 12.5	M	M	M	M	—	M	—
Eudragit E 100	S	S	S	—	—	I	I
Eudragit L 12.5 P	M	M	M	—	M	P	P
Eudragit L 12.5	M	M	M	—	M	P	P
Eudragit L 100-55	S	I	I	—	S	I	I
Eudragit L 100	S	I	I	—	S	I	I
Eudragit L 30 D-55[b]	M[c]	—	—	—	M[d]	—	M
Eudragit S 12.5 P	M	M	M	—	M	P	P
Eudragit S 12.5	M	M	M	—	M	P	P
Eudragit S 100	S	I	I	—	S	I	I
Eudragit RL 12.5	M	M	M	—	—	P	M
Eudragit RL 100	S	S	S	—	—	I	I
Eudragit RL PO	S	S	S	—	I	I	I
Eudragit RL 30 D	M[e]	M	M	—	I	I	M
Eudragit RS 12.5	M	M	M	—	—	P	M
Eudragit RS 100	S	S	S	—	—	I	I
Eudragit RS PO	S	S	S	—	I	I	I
Eudragit RS 30 D	M[e]	M	M	—	I	I	M

Where: S = soluble;
M = miscible;
I = insoluble or immiscible;
P = precipitates.

Note: a. Alcohols including ethanol, methanol and propan-2-ol.
b. Supplied as a milky-white colored aqueous dispersion.
c. A 1:5 mixture forms a clear, viscous, solution.
d. A 1:2 mixture forms a clear or slightly opalescent, viscous liquid.
e. A 1 part of both *Eudragit RL 30 D* and *Eudragit RS 30 D* dissolve completely in 5 parts acetone, ethanol or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1:5 with methanol, *Eudragit RL 30 D* dissolves completely, whereas *Eudragit RS 30 D* only partially.

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11. Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least two years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5-25°C and are stable for at least one year after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

12. Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents and extremes of temperature, *see* Table II. Dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55* and *RS 30 D* are also incompatible with magnesium stearate.

Interactions between polymethacrylates and some drugs can occur although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

13. Method of Manufacture

Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g. butyl ester or dimethylaminoethyl ester.

14. Safety

Polymethacrylate copolymers are widely used as film coating materials in oral pharmaceutical formulations. They are also used to a lesser extent in topical formulations and are generally regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of *Eudragit* (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

See also Section 15.

Table III: Summary of properties and uses of commercially available polymethacrylates (*Eudragit*, Röhm Pharma GmbH).

Type	Supply form	Polymer dry weight content	Recommended solvents or diluents	Solubility	Applications
Eudragit E 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit E 100	Granules	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit L 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100-55	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit L 30 D-55	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit S 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 100	Powder fluid	95%	Acetone, alcohols	Soluble in intestinal from pH 7	Enteric coatings
Eudragit RL 12.5	Organic solution	12.5%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 100	Granules	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL PO	Powder	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 30 D	Aqueous dispersion	30%	Water	High permeability	Sustained release
Eudragit RS 12.5	Organic solution	12.5%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 100	Granules	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS PO	Powder	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 30 D	Aqueous dispersion	30%	Water	Low permeability	Sustained release
Eudragit NE 30 D	Aqueous dispersion	30% or 40%	Water	Swellable, permeable	Sustained release, tablet matrix

Note: Recommended plasticizers for the above types of *Eudragit* polymers include dibutyl phthalate, polyethylene glycols and triethyl citrate. Approximately 20% plasticizer is required for *Eudragit RL 30 D* and *Eudragit RS 30 D*. A plasticizer is not necessary with *Eudragit E 12.5*, *Eudragit E 100* and *Eudragit NE 30 D*.

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15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves and a dust mask or respirator are recommended. Polymethacrylates should be handled in a well-ventilated environment and measures taken to prevent dust formation.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA).[12,13] In the UK, the occupational exposure limit for methyl methacrylate has been set at 410 mg/m^3 (100 ppm) long-term (8-hour TWA), and 510 mg/m^3 (125 ppm) short-term.[14]

See also Section 18.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Fr and USPNF.

18. Related Substances

Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate: $C_5H_8O_2$
Molecular weight: 100.13
CAS number: [80-62-6]
Synonyms: methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.
Comments: methyl methacrylate forms the basis of acrylic bone cements used in orthopaedic surgery.

Poly(methyl methacrylate): $(C_5H_8O_2)_n$
Synonyms: methyl methacrylate polymer; PMMA.
Comments: poly(methyl methacrylate) has been used as a material for intra-ocular lenses, for denture bases and as a cement for dental prostheses.

19. Comments

A number of different polymethacrylates are commercially available which have different applications and properties, *see* Table III.

For spray-coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as: dibutyl sebacate; dibutyl phthalate; glyceryl triacetate and polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

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22. Authors

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Polyoxyethylene Alkyl Ethers

1. Nonproprietary Names

The polyoxyethylene alkyl ethers are a series of polyoxyethylene glycol ethers of *n*-alcohols (lauryl, myristyl, cetyl and stearyl alcohol). Of the large number of different materials commercially available two types are listed in the USPNF XVII, one of which is equivalent to a type listed in the BP 1993.

BP: Cetomacrogol 1000
USPNF: Poloxyl 20 cetostearyl ether
USPNF: Poloxyl 10 oleyl ether

Polyoxyethylene alkyl ethers are extensively employed in cosmetics where the CTFA names laureth-N, myreth-N, ceteth-N and steareth-N are commonly used. In this nomenclature, N is the number of ethylene oxide groups, e.g. steareth-20.

See also Sections 2, 3, 4, 5 and 17.

2. Synonyms

Polyoxyethylene alkyl ethers are nonionic surfactants produced by the polyethoxylation of linear fatty alcohols. Products tend to be mixtures of polymers of slightly varying molecular weights and the numbers used to describe polymer lengths are average values.

Two systems of nomenclature are used to describe these materials. The number '10' in the name '*Texofor A10*' refers to the approximate polymer length in oxyethylene units (i.e. *y*, *see* Section 5). The number '1000' in the name 'cetomacrogol 1000' refers to the average molecular weight of the polymer chain.

Synonyms applicable to polyoxyethylene alkyl ethers are shown below:

Brij; *Cremophor A*; *Cyclogol 1000*; *Empilan KB*; *Empilan KM*; *Ethylan C*; macrogol ethers; *Marlowet*; *Plurafac*; *Procol*; *Texofor A*; *Volpo*.

Table I shows synonyms for specific materials.

Table I: Synonyms of selected polyoxyethylene alkyl ethers.

Name	Synonym
Poloxyl 20 cetostearyl ether	*Atlas G-3713*; cetomacrogol 1000; polyethylene glycol 1000 monocetyl ether.
Poloxyl 2 cetyl ether	*Brij 52*; ceteth-2.
Poloxyl 10 cetyl ether	*Brij 56*; ceteth-10.
Poloxyl 20 cetyl ether	*Brij 58*; ceteth-20.
Poloxyl 4 lauryl ether	*Brij 30*; laureth-4.
Poloxyl 23 lauryl ether	*Brij 35*; laureth-23.
Poloxyl 2 oleyl ether	*Brij 92*; *Brij 93*; oleth-2.
Poloxyl 10 oleyl ether	*Brij 96*; *Brij 97*; oleth-10; polyethylene glycol monooleyl ether.
Poloxyl 20 oleyl ether	*Brij 98*; *Brij 99*; oleth-20.
Poloxyl 2 stearyl ether	*Brij 72*; steareth-2.
Poloxyl 10 stearyl ether	*Brij 76*; steareth-10.
Poloxyl 20 stearyl ether	*Brij 78*; steareth-20.
Poloxyl 100 stearyl ether	*Brij 700*; steareth-100.

3. Chemical Name and CAS Registry Number

Polyethylene glycol monocetyl ether [9004-95-9]
Polyethylene glycol monolauryl ether [9002-92-0]
Polyethylene glycol monooleyl ether [9004-98-2]
Polyethylene glycol monostearyl ether [9005-00-9]

4. Empirical Formula Molecular Weight

See Sections 1, 2 and 5.

5. Structural Formula

$CH_3(CH_2)_x(OCH_2CH_2)_yOH$

Where $(x + 1)$ is the number of carbon atoms in the alkyl chain, typically:

12 lauryl (dodecyl)
14 myristyl (tetradecyl)
16 cetyl (hexadecyl)
18 stearyl (octadecyl)

and y is the number of ethylene oxide groups in the hydrophilic chain, typically 10-60.

The polyoxyethylene alkyl ethers tend to be mixtures of polymers of slightly varying molecular weights, and the numbers quoted are average values. In cetomacrogol 1000, for example, x is 15 or 17, and y is 20-24.

6. Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene alkyl ethers are nonionic surfactants widely used in topical pharmaceutical formulations and cosmetics primarily as emulsifying agents for water-in-oil and oil-in-water emulsions.

Polyoxyethylene alkyl ethers are also used in other applications such as: solubilizing agents for essential oils, perfumery chemicals, vitamin oils and drugs of low water solubility; gelling and foaming agents, e.g. *Brij 72* gives a quick-breaking foam, while *Brij 97* (and others) gives clear gels at 15-20% concentration; anti-dusting agents for powders; wetting and dispersing agents for coarse-particle liquid dispersions; and detergents, especially in shampoos and similar cosmetic cleaning preparations.

8. Description

Polyoxyethylene alkyl ethers vary considerably in their physical appearance from liquids, to pastes, to solid waxy substances. They are colorless, white or cream-colored materials with a slight odor.

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9. Pharmacopeial Specifications

Test	BP 1993 Cetomacrogol 1000	USPNF XVII Poloxyl 20 cetostearyl ether	USPNF XVII Poloxyl 10 oleyl ether
Identification	+	+	+
Water	⩽ 1.0%	⩽ 1.0%	⩽ 3.0%
pH (10% solution)	—	4.5-7.5	—
Alkalinity	+	—	—
Melting point	⩾ 38°C	—	—
Refractive index	1.448-1.452 at 60°C	—	—
Residue on ignition	—	⩽ 0.4%	⩽ 0.4%
Arsenic	—	⩽ 2 ppm	⩽ 2 ppm
Heavy metals	—	⩽ 0.002%	⩽ 0.002%
Acid value	⩽ 0.5	⩽ 0.5	⩽ 1.0
Hydroxyl value	40.0-52.5	42-60	75-95
Iodine value	—	—	23-40
Saponification value	⩽ 1.0	⩽ 2	⩽ 3
Free polyethylene glycols	—	⩽ 7.5%	⩽ 7.5%
Free ethylene oxide	—	⩽ 0.01%	⩽ 0.01%
Average polymer length	—	17.2-25.0	8.6-10.4

10. Typical Properties

See Tables II and III.

11. Stability and Storage Conditions

Polyoxyethylene alkyl ethers are chemically stable in strongly acidic or alkaline conditions. The presence of strong electrolytes may however adversely affect the physical stability of emulsions containing polyoxyethylene alkyl ethers.

On storage, polyoxyethylene alkyl ethers can undergo autoxidation, resulting in the formation of peroxides with an increase in acidity. Many commercially available grades are thus supplied with added antioxidants. Typically, a mixture of 0.01% butylated hydroxyanisole and 0.005% citric acid is used for this purpose.

Polyoxyethylene alkyl ethers should be stored in an airtight container, in a cool, dry, place.

12. Incompatibilities

Discoloration and/or precipitation occurs with iodides, mercury salts, phenolic substances, salicylates, sulfonamides, and tannins. Polyoxyethylene alkyl ethers are also incompatible with benzocaine and oxidizable drugs.[1]

The antimicrobial efficacy of some phenolic preservatives, such as the parabens, is reduced due to hydrogen bonding. Cloud points are similarly depressed by phenols due to hydrogen bonding between ether oxygen atoms and phenolic hydroxyl groups. Salts, other than nitrates, iodides and thiocyanates (which cause an increase), can also depress cloud points.[2]

13. Method of Manufacture

Polyoxyethylene alkyl ethers are prepared by the condensation of linear fatty alcohols with ethylene oxide. The reaction is controlled so that the required ether is formed with the polyethylene glycol of the desired molecular weight.

14. Safety

Polyoxyethylene alkyl ethers are used as nonionic surfactants in a variety of topical pharmaceutical formulations and cosmetics. The polyoxyethylene alkyl ethers form a series of materials with varying physical properties and manufacturers' literature should be consulted for information on the applications and safety of specific materials.

Although generally regarded as essentially nontoxic and nonirritant materials some polyoxyethylene alkyl ethers, particularly when used in high concentration (> 20%), appear to have a greater irritant potential than others.

Animal toxicity studies suggest that polyoxyethylene alkyl ethers have a similar oral toxicity to other surfactants and can be regarded as being moderately toxic. In rats, the oral LD_{50} values range from about 2-4 g/kg body-weight.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

Included in nonparenteral medicines licensed in the US.
Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Name	Pharmacopeia*
Poloxyl 20 cetostearyl ether	Br and USPNF.
Poloxyl 10 oleyl ether	USPNF.

*Polyoxyethylene alkyl ethers are also included in the Japanese Pharmacopeia.

18. Related Substances

Nonionic Emulsifying Wax.

Many other polyoxyethylene ethers, such as diethers and polyethers, are commercially available and are also used as surfactants. In addition to their surfactant properties, the series of polyoxyethylene ethers with alkylauryl side chains, e.g. nonoxynol 10, are also widely used as spermicides.

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Table II: Typical properties of selected commercially available grades of polyoxyethylene alkyl ethers.

Name	Physical form	Acid value	HLB value	Hydroxyl value	Iodine number	Saponification value	Density g/cm^3 at 20°C	Water content (%)	Melting point or pour point (°C)	Cloud point (°C) for 1% aqueous solution
Brij 30	Liquid	⩽ 2	9.7	145-165	—	—	≈ 0.95	⩽ 1.0	—	—
Brij 35	Solid	⩽ 5	16.9	40-60	—	—	≈ 1.05	⩽ 3.0	33	—
Brij 52	Solid	⩽ 1	5.3	160-180	—	—	—	⩽ 1.0	33	—
Brij 56	Solid	⩽ 1	12.9	75-90	—	—	—	⩽ 3.0	31	—
Brij 58	Solid	⩽ 1	15.7	45-60	—	—	—	⩽ 3.0	38	—
Brij 72	Solid	⩽ 1	4.9	150-170	—	—	—	⩽ 1.0	43	—
Brij 76	Solid	⩽ 1	12.4	75-90	—	—	—	⩽ 3.0	38	—
Brij 78	Solid	⩽ 1	15.3	45-60	—	—	—	⩽ 3.0	38	—
Brij 93	—	⩽ 1	4.9	160-180	—	—	—	⩽ 1.0	10	—
Brij 97	—	⩽ 1	12.4	80-95	—	—	—	⩽ 3.0	16	—
Brij 99	—	⩽ 1	15.3	50-65	—	—	—	⩽ 3.0	33	—
Cremophor A6	—	⩽ 1	10-12	115-135	⩽ 1	⩽ 3	0.896-0.906 at 60°C	⩽ 1.0	41-43	—
Cremophor A11	—	⩽ 1	12-14	70-80	⩽ 1	⩽ 1	0.964-0.968 at 60°C	⩽ 1.0	34-36	—
Cremophor A25	—	⩽ 1	15-17	35-45	⩽ 1	⩽ 3	1.020-1.028 at 60°C	⩽ 1.0	44-46	—
Ethosperse 1A4	—	⩽ 2	—	145-160	—	—	0.95	⩽ 0.5	—	—
Ethosperse 1A12	—	⩽ 2	—	72-82	—	—	1.10	⩽ 1.0	—	—
Ethosperse TDA6	—	⩽ 1	—	118-133	—	—	0.98	⩽ 1.0	—	—
Ethosperse S120	—	⩽ 0.5	—	385-430	—	—	1.16	⩽ 1.0	—	—
Ethosperse G26	—	⩽ 2	—	133-142	—	—	1.12 at 38°C	⩽ 0.5	—	—
Ethylan D252	Liquid	—	5.6	—	—	—	0.903	⩽ 0.5	5	Insoluble
Ethylan 253	Liquid	—	7.8	—	—	—	0.930	⩽ 0.5	3	Insoluble
Ethylan 254	Liquid	—	9.8	—	—	—	0.948	⩽ 3.0	5	Insoluble
Ethylan 256	Liquid	—	11.4	—	—	—	0.972	⩽ 0.5	15	43
Ethylan 257	Liquid	—	12.2	—	—	—	0.974 at 40°C	⩽ 0.5	21	49
Ethylan 2512	Solid	—	14.2	—	—	—	1.001	⩽ 0.5	29	92
Ethylan 2560	Solid	—	18.6	—	—	—	—	⩽ 0.5	45	> 100
Plurafac RA20	—	—	—	69-78	—		0.9965	⩽ 0.1	4	—
Plurafac RA30	—	—	—	85-95	—	—	0.976	⩽ 0.1	-6	—
Plurafac RA40	—	—	—	65-75	—	—	0.978	⩽ 0.2	-27	—
Plurafac RA340	—	—	—	73	—	—	0.977	—	-23	—
Renex 30	Cloudy liquid	⩽ 1	14.5	75-85	—	—	1.0	⩽ 3.0	14	18.4
Renex 31	—	⩽ 1	15.4	60-74	—	—	1.0	⩽ 3.0	16	99
Renex 36	—	⩽ 1	11.4	118-133	—	—	1.0	⩽ 1.0	—	< 32
Texofor A1P	Solid	—	16.2	—	—	—	1.025 at 60°C	—	40	> 100
Texofor AP	—	—	—	—	—	—	0.875	—	31	Insoluble
Texofor A6	Solid	—	—	—	—	—	0.140	—	26	Insoluble
Texofor A10	Solid	—	—	—	—	—	0.970	—	30	75
Texofor A14	Solid	—	—	—	—	—	0.995	—	35	100
Texofor A30	Solid	—	—	—	—	—	1.035	—	43	> 100
Texofor A45	Solid	—	—	—	—	—	1.055	—	47	> 100
Texofor A60	Solid	—	—	—	—	—	1.065	—	48	> 100

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Table III: Typical properties of selected commercially available grades of polyoxyethylene alkyl ethers (continued).

Name	Critical micelle concentration (%)	Surface tension of aqueous solution at 20°C (mN/m) (0.05%)	(0.1%)	(0.2%)	Dynamic viscosity at 25°C or pour point (mPa s)	Refractive index at 60°C	Solubility Ethanol	Fixed oils	Propylene glycol	Water
Brij 30	—	—	—	—	30	—	S	S	S	I
Brij 35	0.013	—	—	—	—	—	S	I	S	S
Brij 52	—	—	—	—	—	—	S	S	I	I
Brij 56	—	—	—	—	—	—	S	I	I	I
Brij 58	—	—	—	—	—	—	S	I	I	S
Brij 72	—	—	—	—	—	—	S	S	I	I
Brij 76	—	—	—	—	—	—	S	I	S	I
Brij 78	—	—	—	—	—	—	S	I	I	I
Brij 93	—	—	—	—	30	—	S	S	S	I
Brij 97	—	—	—	—	100	—	S	I	I	S
Brij 99	—	—	—	—	—	—	S	I	S	S
Cremophor A6	—	—	—	—	—	1.4420-1.4424	S	I	—	S
Cremophor A11	—	—	—	—	—	1.4464-1.4474	S	I	—	S
Cremophor A25	—	—	—	—	—	1.4512-1.4520	S	I	—	S
Ethosperse 1A4	—	—	—	—	30	—	S	S	—	S
Ethosperse 1A12	—	—	—	—	1000	—	S	SH	—	S
Ethosperse TDA6	—	—	—	—	80	—	S	I	—	D
Ethosperse S120	—	—	—	—	460	—	S	I	—	S
Ethosperse G26	—	—	—	—	150 at 38°C	—	S	I	—	S
Ethylan D252	—	—	—	—	—	—	—	—	—	I
Ethylan 253	—	—	—	—	—	—	—	—	—	I
Ethylan 254	—	—	—	—	—	—	—	—	—	I
Ethylan 256	—	—	—	—	—	—	—	—	—	S
Ethylan 257	—	—	—	—	—	—	—	—	—	S
Ethylan 2512	—	—	—	—	—	—	—	—	—	S
Ethylan 2560	—	—	—	—	—	—	—	—	—	S
Plurafac RA20	—	—	30.7	—	—	—	—	—	—	—
Plurafac RA30	—	—	28.6	—	—	—	—	—	—	—
Plurafac RA40	—	—	30.3	—	—	—	—	—	—	—
Plurafac RA340	—	—	30.5	—	—	—	—	—	—	—
Renex 30	—	—	—	—	60	—	S	I	—	S
Renex 31	—	—	—	—	130	—	S	I	—	S
Renex 36	—	—	—	—	80	—	S	I	—	D
Texofor A1P	0.006	42.9	—	42.3	—	—	S	—	—	S
Texofor AP	—	—	—	—	—	—	S	—	—	I
Texofor A6	—	—	—	—	—	—	S	—	—	I
Texofor A10	0.004	36.5	—	36.7	—	—	S	—	—	S
Texofor A14	—	36.9	—	36.6	—	—	S	—	—	S
Texofor A30	0.003	46.0	—	46.0	—	—	S	—	—	S
Texofor A45	0.004	47.5	—	47.0	—	—	S	—	—	S
Texofor A60	0.003	48.3	—	48.3	—	—	S	—	—	S

Key S = Soluble I = Insoluble
D = Dispersible SH = Soluble on heating.
Suppliers: ICI Surfactants (*Brij*).

19. Comments

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22. Authors

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Polyoxyethylene Sorbitan Fatty Acid Esters

1. Nonproprietary Names

BP: Polysorbates 20, 60 and 80
PhEur: Polysorbatum 20, 60 and 80
USPNF: Polysorbates 20, 40, 60 and 80

2. Synonyms

Synonyms of selected polysorbates are shown below, *see also* Section 3.

Polysorbate	Synonym
Polysorbate 20	*Armotan PML 20*; *Capmul POE-L*; *Crillet 1*; E432; *Glycosperse L-20*; *Hodag PSML-20*; *Liposorb L-20*; *Liposorb L-20K*; *Montanox 20*; sorbitan monododecanoate poly(oxy-1,2-ethanediyl) derivatives; polyoxyethylene 20 laurate; *Protasorb L-20*; *Tween 20*.
Polysorbate 21	*Crillet 11*; *Hodag PSML-4*; *Protasorb L-5*; *Tween 21*.
Polysorbate 40	*Crillet 2*; E434; *Glycosperse S-20*; *Hodag PSMP-20*; *Liposorb P-20*; *Montanox 40*; *Protasorb P-20*; sorbitan monohexadecanoate poly(oxy-1,2-ethanediyl) derivatives; *Tween 40*.
Polysorbate 60	*Armotan PMS 20*; *Capmul POE-S*; *Crillet 3*; E435; *Glycosperse S-20*; *Hodag PSMS-20*; *Liposorb S-20*; *Liposorb S-20K*; *Montanox 60*; *Polycon T 60 K*; polyoxyethylene 20 stearate; sorbitan monooctadecanoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb S-20*; *Tween 60*.
Polysorbate 61	*Crillet 31*; *Hodag PSMS-4*; *Protasorb S-4*; *Tween 61*.
Polysorbate 65	*Crillet 35*; E436; *Glycosperse TS-20*; *Hodag PSTS-20*; *Liposorb TS-20*; *Liposorb TS-20K*; *Montanox 65*; sorbitan trioctadecanoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb STS-20*; *Tween 65*.
Polysorbate 80	*Armotan PMO 20*; *Capmul POE-O*; *Crillet 4*; *Crillet 50*; E433; *Glycosperse O-20*; *Hodag PSMO-20*; *Liposorb O-20*; *Liposorb O-20K*; *Montanox 80*; polyoxyethylene 20 oleate; (*Z*)-sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb O-20*; *Tween 80*.
Polysorbate 81	*Crillet 41*; *Hodag PSMO-5*; sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb O-5*; *Tween 81*.
Polysorbate 85	*Crillet 45*; *Hodag PSTO-20*; *Liposorb TO-20*; *Montanox 85*; sorbitan tri-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb TO-20*; *Tween 85*.
Polysorbate 120	*Crillet 6*.

3. Chemical Names and CAS Registry Numbers

See Table I.

Table I: Chemical name and CAS registry number of selected polysorbates.

Polysorbate	Chemical name	CAS number
Polysorbate 20	Polyoxyethylene 20 sorbitan monolaurate	[9005-64-5]
Polysorbate 21	Polyoxyethylene (4) sorbitan monolaurate	[9005-64-5]
Polysorbate 40	Polyoxyethylene 20 sorbitan monopalmitate	[9005-66-7]
Polysorbate 60	Polyoxyethylene 20 sorbitan monostearate	[9005-67-8]
Polysorbate 61	Polyoxyethylene (4) sorbitan monostearate	[9005-67-8]
Polysorbate 65	Polyoxyethylene 20 sorbitan tristearate	[9005-71-4]
Polysorbate 80	Polyoxyethylene 20 sorbitan monooleate	[9005-65-6]
Polysorbate 81	Polyoxyethylene (5) sorbitan monooleate	[9005-65-6]
Polysorbate 85	Polyoxyethylene 20 sorbitan trioleate	[9005-70-3]
Polysorbate 120	Polyoxyethylene 20 sorbitan monoisostearate	[66794-58-9]

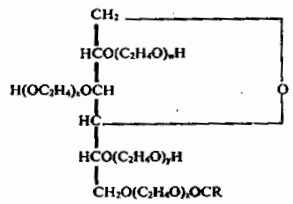
4. Empirical Formula Molecular Weight

Approximate molecular weights for selected polysorbates are shown below in Table II.

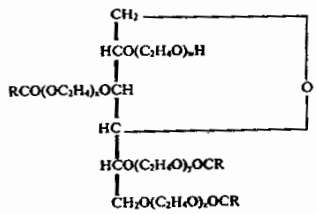
Table II: Empirical formula and molecular weight of selected polysorbates.

Polysorbate	Formula	Molecular weight
Polysorbate 20	$C_{58}H_{114}O_{26}$	1128
Polysorbate 21	$C_{26}H_{50}O_{10}$	523
Polysorbate 40	$C_{62}H_{122}O_{26}$	1284
Polysorbate 60	$C_{64}H_{126}O_{26}$	1312
Polysorbate 61	$C_{32}H_{62}O_{10}$	607
Polysorbate 65	$C_{100}H_{194}O_{28}$	1845
Polysorbate 80	$C_{64}H_{124}O_{26}$	1310
Polysorbate 81	$C_{34}H_{64}O_{11}$	649
Polysorbate 85	$C_{100}H_{188}O_{28}$	1839
Polysorbate 120	$C_{64}H_{126}O_{26}$	1312

5. Structural Formula



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

w+x+y+z = 20 Polysorbate 20, 40, 60, 65, 80 and 85)
w+x+y+z = 5 (Polysorbate 81)
w+x+y+z = 4 (Polysorbate 21 and 61)

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6. Functional Category

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides.

Polysorbates are hydrophilic nonionic surfactants used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as solubilizing agents for a variety of substances including essential oils and oil soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions.

Polysorbates are also widely used in cosmetics and food products.

Use	Concentration (%)
Emulsifying agent	
Used alone in oil-in-water emulsions	1-15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1-10
Used to increase the water holding properties of ointments	1-10
Solubilizing agent	
For poorly soluble active constituents in lipophilic bases	1-10
Wetting agent	
For insoluble active constituents in lipophilic bases	0.1-3

8. Description

Polysorbates have a characteristic odor and a warm, somewhat bitter taste. Their colors and physical forms at 25°C are shown below in Table III.

Table III: Color and physical form of selected polysorbates at 25°C

Polysorbate	Color and form at 25°C
Polysorbate 20	Yellow oily liquid
Polysorbate 21	Yellow oily liquid
Polysorbate 40	Yellow oily liquid
Polysorbate 60	Yellow oily liquid
Polysorbate 61	Tan solid
Polysorbate 65	Tan solid
Polysorbate 80	Yellow oily liquid
Polysorbate 81	Amber liquid
Polysorbate 85	Amber liquid
Polysorbate 120	Yellow liquid

9. Pharmacopeial Specifications

Test	PhEur 1985	USPNF XVII
Identification		
Polysorbate 20	+	+
Polysorbate 40*	—	+
Polysorbate 60	+	+
Polysorbate 80	+	+
Saponification value		
Polysorbate 20	40-50	40-50
Polysorbate 40*	—	41-52
Polysorbate 60	45-55	45-55
Polysorbate 80	45-55	45-55
Hydroxyl value		
Polysorbate 20	96-108	96-108
Polysorbate 40*	—	89-105
Polysorbate 60	81-96	81-96
Polysorbate 80	65-80	65-80
Water		
Polysorbate 20	⩽ 3.0%	⩽ 3.0%
Polysorbate 40*	—	⩽ 3.0%
Polysorbate 60	⩽ 3.0%	⩽ 3.0%
Polysorbate 80	⩽ 3.0%	⩽ 3.0%
Residue on ignition		
Polysorbate 20	—	⩽ 0.25%
Polysorbate 40*	—	⩽ 0.25%
Polysorbate 60	—	⩽ 0.25%
Polysorbate 80	—	⩽ 0.25%
Sulfated ash		
Polysorbate 20	⩽ 0.2%	—
Polysorbate 60	⩽ 0.2%	—
Polysorbate 80	⩽ 0.2%	—
Arsenic		
Polysorbate 20	—	⩽ 1 ppm
Polysorbate 40*	—	⩽ 1 ppm
Polysorbate 60	—	⩽ 1 ppm
Polysorbate 80	—	⩽ 1 ppm
Heavy metals		
Polysorbate 20	⩽ 10 ppm	⩽ 0.001%
Polysorbate 40*	—	⩽ 0.001%
Polysorbate 60	⩽ 10 ppm	⩽ 0.001%
Polysorbate 80	⩽ 10 ppm	⩽ 0.001%
Acid value		
Polysorbate 20	⩽ 2.0	⩽ 2.2
Polysorbate 40*	—	⩽ 2.2
Polysorbate 60	⩽ 2.0	⩽ 2.2
Polysorbate 80	⩽ 2.0	⩽ 2.2
Iodine value		
Polysorbate 20	⩽ 5.0	—
Polysorbate 60	⩽ 5.0	—
Polysorbate 80	18-24	—
Reducing substances		
Polysorbate 20	+	—
Polysorbate 60	+	—
Polysorbate 80	+	—
Specific gravity		
Polysorbate 20	1.10	—
Polysorbate 60	1.10	—
Polysorbate 80	1.08	1.06-1.09
Viscosity at 25°C		
Polysorbate 80	400 mPa s	300-500 mm^2/s

* Note that the BP 1993 and PhEur 1985 contain monographs for polysorbate 20, 60 and 80; the USPNF XVII contains monographs for polysorbate 20, 40, 60 and 80.

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10. Typical Properties

Acid value: *see* Table IV.
Acidity/alkalinity: pH = 6.0-8.0 for a 5% w/v aqueous solution.
Flash point: 149°C
HLB value: *see* Table V.
Hydroxyl value: *see* Table IV.
Moisture content: *see* Table IV.
Saponification value: *see* Table IV.
Solubility: *see* Table VI.
Specific gravity: *see* Table V.
Surface tension: for 0.1% w/v solutions, see table below.

Polysorbate	Surface tension at 20°C (mN/m)
Polysorbate 21	34.7
Polysorbate 40	41.5
Polysorbate 60	42.5
Polysorbate 61	41.5
Polysorbate 80	42.5
Polysorbate 85	41.0

Viscosity (dynamic): *see* Table V.

Table IV: Typical properties of selected polysorbates.

Polysorbate	Acid value	Hydroxyl value	Moisture content (%)	Saponifcation value
Polysorbate 20	2.0	96-108	3.0	40-50
Polysorbate 21	3.0	225-255	3.0	100-115
Polysorbate 40	2.0	90-105	3.0	41-52
Polysorbate 60	2.0	81-96	3.0	45-55
Polysorbate 61	2.0	170-200	3.0	95-115
Polysorbate 65	2.0	44-60	3.0	88-98
Polysorbate 80	2.0	65-80	3.0	45-55
Polysorbate 81	2.0	134-150	3.0	96-104
Polysorbate 85	2.0	39-52	3.0	80-95
Polysorbate 120	2.0	65-85	5.0	40-50

Table V: Typical properties of selected polysorbates (continued).

Polysorbate	HLB value	Specific gravity at 25°C	Viscosity (mPa s)
Polysorbate 20	16.7	1.1	400
Polysorbate 21	13.3	1.1	500
Polysorbate 40	15.6	1.08	500
Polysorbate 60	14.9	1.1	600
Polysorbate 61	9.6	1.06	solid
Polysorbate 65	10.5	1.05	solid
Polysorbate 80	15.0	1.08	425
Polysorbate 81	10.0	—	450
Polysorbate 85	11.0	1.00	300
Polysorbate 120	14.9	—	—

Table VI: Solubilities of selected polysorbates in various solvents.

Polysorbate	Solvent			
	Ethanol	Mineral oil	Vegetable oil	Water
Polysorbate 20	S	I	I	S
Polysorbate 21	S	I	I	D
Polysorbate 40	S	I	I	S
Polysorbate 60	S	I	I	S
Polysorbate 61	SW	SW	SWT	D
Polysorbate 65	SW	SW	DW	D
Polysorbate 80	S	I	I	S
Polysorbate 81	S	S	ST	D
Polysorbate 85	S	I	ST	D
Polysorbate 120	S	I	I	S

D = dispersible; I = insoluble; S = soluble;
T = turbid; W = on warming .

11. Stability and Storage Conditions

Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation.
Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities

Discoloration and/or precipitation occurs with various substances, especially phenols, tannins, tars and/or tar-like materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.[1] *See* Methylparaben.

13. Method of Manufacture

Polysorbates are prepared from sorbitol in a three step process. Water is initially removed from the sorbitol to form a sorbitan (a cyclic sorbitol anhydride). The sorbitan is then partially esterified with a fatty acid, such as oleic or stearic acid, to yield a hexitan ester. Finally, ethylene oxide is then chemically added in the presence of a catalyst to yield the polysorbate.

14. Safety

Polysorbates are widely used in cosmetics, food products and oral, parenteral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. There have however been occasional reports of hypersensitivity to polysorbates following their topical use. Polysorbates have also been associated with serious adverse effects, including some deaths, in low-birthweight infants administered intravenously a vitamin E preparation containing a mixture of polysorbate 20 and 80.[2,3]
The WHO has set an estimated acceptable daily intake for polysorbates 20, 40, 60, 65 and 80, calculated as total polysorbate esters, at up to 25 mg/kg body-weight.[4]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

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16. Regulatory Status

Polysorbates 60, 65 and 80 are GRAS listed. Polysorbates 20, 40, 60, 65 and 80 are accepted as food additives in Europe. Polysorbates 20, 40, 60 and 80 are included in the FDA Inactive Ingredients Guide (IM, IV, oral, rectal, topical and vaginal preparations). Polysorbates are included in parenteral and nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Polysorbate	Pharmacopeia
Polysorbate 20	Aust, Br, Eur, Fr, Ger, Gr, Hung, Ind, It, Neth, Port, Swiss and USPNF.
Polysorbate 40	USPNF.
Polysorbate 60	Aust, Br, Cz, Eur, Fr, Ger, Gr, Hung, It, Neth, Port, Swiss and USPNF.
Polysorbate 80	Aust, Br, Braz, Chin, Cz, Eur, Fr, Ger, Gr, Hung, Ind, It, Jpn, Neth, Nord, Port, Rom, Swiss and USPNF.

18. Related Substances

Sorbitan Esters (Sorbitan Fatty Acid Esters)

19. Comments

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20. Specific References

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22. Authors

UK: RL Leyland.

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Polyoxyethylene Stearates

1. Nonproprietary Names

The polyoxyethylene stearates are a series of polyethoxylated derivatives of stearic acid. Of the large number of different materials commercially available two types are listed in the USPNF XVII.
USPNF: Poloxyl 40 stearate
USPNF: Poloxyl 50 stearate
See also Sections 2, 3, 4, 5 and 17.

2. Synonyms

Polyoxyethylene stearates are nonionic surfactants produced by polyethoxylation of stearic acid. Two systems of nomenclature are used for these materials. The number '8' in the names 'poloxyl 8 stearate' or 'polyoxyethylene 8 stearate' refers to the approximate polymer length in oxyethylene units. The same material may also be designated 'polyoxyethylene glycol 400 stearate' or 'macrogol stearate 400' in which case, the number '400' refers to the average molecular weight of the polymer chain.
Synonyms applicable to polyoxyethylene stearates are shown below:
Ethoxylated fatty acid esters; macrogol stearates; *Marlosol*; PEG fatty acid esters; PEG stearates; polyethylene glycol stearates; poly(oxy-1,2-ethanediyl) α-hydro-ω-hydroxy-octadecanoate; polyoxyethylene glycol stearates.
Table I shows synonyms for specific materials.

Table I: Synonyms of selected polyoxyethylene stearates and distearates.

Name	Synonym
Poloxyl 2 stearate	*Hodag DGS*; PEG-2 stearate.
Poloxyl 4 stearate	*Acconon 200-MS*; *Hodag 20-S*; PEG-4 stearate; polyoxyethylene (4) monostearate; polyethylene glycol 200 monostearate; *Protamate 200-DPS.*
Poloxyl 6 stearate	*Cerasynt 616*; *Kessco PEG 300 Monostearate*; *Lipal 300S*; *Lipo PEG 3-S*; PEG-6 stearate; polyethylene glycol 300 monostearate; *Polystate C*; polyoxyethylene (6) monostearate; *Protamate 300-DPS.*
Poloxyl 8 stearate	*Acconon 400-MS*; *Cerasynt 660*; *Cithrol 4MS*; *Crodet S8*; *Emerest 2640*; *Grocor 400*; *Hodag 40-S*; *Kessco PEG-400 Monostearate*; macrogol stearate 400; *Myrj 45*; PEG-8 stearate; *Pegosperse 400 MS*; polyethylene glycol 400 monostearate; polyoxyethylene (8) monostearate; *Protamate 400-DPS*; *Ritapeg 400 MS.*
Poloxyl 12 stearate	*Hodag 60-S*; *Kessco PEG 600 Monostearate*; *Lipo-PEG 6-S*; PEG-12 stearate; *Pegosperse 600 MS*; polyethylene glycol 600 monostearate; polyoxyethylene (12) monostearate; *Protamate 600-DPS.*
Poloxyl 20 stearate	*Cerasynt 840*; *Hodag 100-S*; *Kessco PEG 1000 Monostearate*; *Lipo-PEG 10-S*; *Myrj 49*; *Pegosperse 1000 MS*; PEG-20 stearate; polyethylene glycol 1000 monostearate; polyoxyethylene (20) monostearate; *Protamate 1000-DPS.*
Poloxyl 30 stearate	*Myrj 51*; PEG-30 stearate; polyoxyethylene (30) stearate.
Poloxyl 40 stearate	*Crodet S40*; E431; *Emerest 2672*; *Hodag POE (40) MS*; *Lipal 395*; macrogol stearate 2000; *Myrj 52*; PEG-40 stearate; polyoxyethylene glycol 2000 monostearate; polyoxyethylene (40) monostearate; *Protamate 2000-DPS.*
Poloxyl 50 stearate	*Atlas G-2153*; *Crodet S50*; *Lipal 505*; *Myrj 53*; PEG-50 stearate; polyoxyethylene (50) monostearate.
Poloxyl 100 stearate	*Myrj 59*; PEG-100 stearate; polyethylene glycol 4400 monostearate; polyoxyethylene (100) monostearate; *Protamate 4400-DPS.*
Poloxyl 150 stearate	*Hodag 600-S*; PEG-150 stearate.
Poloxyl 4 distearate	*Hodag 22-S*; PEG-4 distearate.
Poloxyl 8 distearate	*Hodag 42-S*; *Kessco PEG 400 DS*; PEG-8 distearate; polyethylene glycol 400 distearate; *Protamate 400-DS.*
Poloxyl 12 distearate	*Hodag 62-S*; *Kessco PEG 600 Distearate*; PEG-12 distearate; polyethylene (12) distearate; polyethylene glycol 600 distearate; *Protamate 600-DS.*
Poloxyl 32 distearate	*Hodag 154-S*; *Kessco PEG 1540 Distearate*; PEG-32 distearate; polyethylene glycol 1540 distearate; polyoxyethylene (32) distearate.
Poloxyl 150 distearate	*Hodag 602-S*; *Kessco PEG 6000 DS*; PEG-150 distearate; polyethylene glycol 6000 distearate; polyoxyethylene (150) distearate; *Protamate 6000-DS.*

3. Chemical Name and CAS Registry Number

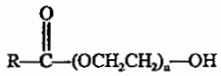
Polyethylene glycol stearate [9004-99-3]
Polyethylene glycol distearate [9005-08-7]

4. Empirical Formula Molecular Weight

Table II: Empirical formula and molecular weight of selected polyoxyethylene stearates.

Name	Empirical formula	Molecular weight
Poloxyl 6 stearate	$C_{30}H_{60}O_8$	548.80
Poloxyl 8 stearate	$C_{34}H_{68}O_{10}$	636.91
Poloxyl 12 stearate	$C_{42}H_{84}O_{14}$	813.12
Poloxyl 20 stearate	$C_{58}H_{116}O_{22}$	1165.55
Poloxyl 40 stearate	$C_{98}H_{196}O_{42}$	2046.61
Poloxyl 50 stearate	$C_{118}H_{236}O_{52}$	2487.15
Poloxyl 100 stearate	$C_{218}H_{436}O_{102}$	4689.80

5. Structural Formula



For the monostearate; where the average value of *n* is 6 for poloxyl 6 stearate, 8 for poloxyl 8 stearate, etc.

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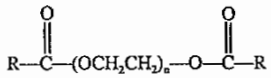

For the distearate; where the average value of n is 12 for poloxyl 12 distearate, 32 for poloxyl 32 distearate, etc.

In both structures, R represents the alkyl group of the parent fatty acid. With stearic acid, R is $CH_3(CH_2)_{16}$. However, it should be noted that stearic acid usually contains other fatty acids, primarily palmitic acid, and consequently a polyoxyethylene stearate may also contain varying amounts of other fatty acid derivatives such as palmitates.

6. Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene stearates are generally used as emulsifiers in oil-in-water type creams and lotions. Their hydrophilicity or lipophilicity depends on the number of ethylene oxide units present: the larger the number, the greater the hydrophilic properties. Poloxyl 40 stearate has also been used as an emulsifying agent in intravenous infusions.[1]

Polyoxyethylene stearates are particularly useful as emulsifying agents when astringent salts or other strong electrolytes are present. They can also be blended with other surfactants to obtain any hydrophilic-lipophilic balance for lotions or ointment formulations.

Use	Concentration (%)
Auxiliary emulsifier for o/w intravenous fat emulsion	0.5-5
Emulsifier for o/w creams or lotions	0.5-10
Ophthalmic ointment	7
Suppository component	1-10
Tablet lubricant	1-2

8. Description

Name	Description
Poloxyl 6 stearate	Soft solid
Poloxyl 8 stearate	Waxy cream
Poloxyl 12 stearate	Pasty solid
Poloxyl 20 stearate	Waxy solid
Poloxyl 40 stearate	Waxy solid, with a faint, bland, fat-like odor, off-white to light tan in color.
Poloxyl 50 stearate	Solid, with a bland, fat-like odor or odorless.
Poloxyl 100 stearate	Solid
Poloxyl 12 distearate	Paste
Poloxyl 32 distearate	Solid
Poloxyl 150 distearate	Solid

9. Pharmacopeial Specifications

Test	USPNF XVII	
	Poloxyl 40 stearate	Poloxyl 50 stearate
Identification	+	+
Congealing range	37-47°C	—
Water	⩽ 3.0%	⩽ 3.0%

Continued

Test	USPNF XVII	
	Poloxyl 40 stearate	Poloxyl 50 stearate
Arsenic	⩽ 3 ppm	⩽ 3 ppm
Heavy metals	⩽ 0.001%	⩽ 0.001%
Acid value	⩽ 2	⩽ 2
Hydroxyl value	25-40	23-35
Saponification value	25-35	20-28
Free polyethylene glycols	17-27%	17-27%

10. Typical Properties

Flash point: > 149°C for poloxyl 8 stearate (*Myrj 45*).

Solubility:

Name	Solvent		
	Ethanol (95%)	Mineral oil	Water
Poloxyl 6 stearate	S	S	DH
Poloxyl 8 stearate	S	I	D
Poloxyl 12 stearate	S	I	S
Poloxyl 20 stearate	S	I	S
Poloxyl 40 stearate	S	I	S
Poloxyl 50 stearate	S	I	S
Poloxyl 100 stearate	S	I	S
Poloxyl 12 distearate	S	—	DH
Poloxyl 32 distearate	S	—	S
Poloxyl 150 distearate	I	—	S

Where,
D = dispersible I = insoluble
S = soluble DH = dispersible (with heat)

See also Table III.

11. Stability and Storage Conditions

Polyoxyethylene stearates are generally stable in the presence of electrolytes and weak acids or bases. Strong acids and bases can cause gradual hydrolysis and saponification.

The bulk material should be stored in a well-closed container, in a dry place, at room temperature.

12. Incompatibilities

Polyoxyethylene stearates are unstable in hot alkaline solutions due to hydrolysis, and will also saponify with strong acids or bases. Discoloration or precipitation can occur with salicylates, phenolic substances, iodine salts and salts of bismuth, silver and tannins.[2-4] Complex formation with preservatives may also occur.[5]

The antimicrobial activity of some materials such as bacitracin, chloramphenicol, phenoxymethylpenicillin, sodium penicillin and tetracycline may be reduced in the presence of polyoxyethylene stearate concentrations greater than 5% w/w.[6,7]

13. Method of Manufacture

Polyoxyethylene stearates are prepared by the direct reaction of fatty acids, particularly stearic acid, with ethylene oxide.

14. Safety

Although polyoxyethylene stearates are primarily used as emulsifying agents in topical pharmaceutical formulations

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Table III: Typical properties of polyoxyethylene stearates.

Name	Acid value	Free ethylene oxide	HLB value	Hydroxyl value	Iodine number	Melting point (°C)	Saponification value	Water content (%)
Poloxyl 6 stearate	⩽ 5.0	⩽ 100 ppm	9.7	—	⩽ 0.5	28-32	95-110	—
Poloxyl 8 stearate	⩽ 2.0	⩽ 100 ppm	11.1	87-105	⩽ 1.0	28-33	82-95	⩽ 3.0
Poloxyl 12 stearate	⩽ 8.5	⩽ 100 ppm	13.6	55-75	⩽ 1.0	≈ 37	62-78	⩽ 1.0
Poloxyl 20 stearate	⩽ 1.0	⩽ 100 ppm	14	50-62	⩽ 1.0	≈ 28	46-56	⩽ 1.0
Poloxyl 30 stearate	⩽ 2.0	—	16	35-50	—	—	30-45	⩽ 3.0
Poloxyl 40 stearate	⩽ 1.0	—	16.9	27-40	—	≈ 38	25-35	⩽ 3.0
Poloxyl 50 stearate	⩽ 2.0	—	17.9	23-35	—	≈ 42	20-28	⩽ 3.0
Poloxyl 100 stearate	⩽ 1.0	⩽ 100 ppm	18.8	15-30	—	≈ 46	9-20	⩽ 3.0
Poloxyl 8 distearate	⩽ 10.0	—	—	⩽ 15	⩽ 0.5	≈ 36	115-124	—
Poloxyl 12 distearate	⩽ 10.0	⩽ 100 ppm	10.6	⩽ 20	⩽ 1.0	≈ 39	93-102	⩽ 1.0
Poloxyl 32 distearate	⩽ 10.0	⩽ 100 ppm	14.8	⩽ 20	⩽ 0.25	≈ 45	50-62	⩽ 1.0
Poloxyl 150 distearate	7-9	⩽ 100 ppm	18.4	⩽ 15	⩽ 0.1	53-57	14-20	⩽ 1.0

certain materials, particularly poloxyl 40 stearate, have also been used in intravenous injections and oral preparations.[1,4] Polyoxyethylene stearates have been extensively tested for toxicity in animals[8-13] and are widely used in pharmaceutical formulations and cosmetics. They are generally regarded as essentially nontoxic and nonirritant materials.

Poloxyl 8 stearate:
LD_{50} (hamster, oral): 27 g/kg[14]
LD_{50} (rat, oral): 64 g/kg
Poloxyl 20 stearate:
LD_{50} (mouse, IP): 0.2 g/kg[14]
LD_{50} (mouse, IV): 0.87 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

Polyoxyethylene stearates that contain greater than 100 ppm of free ethylene oxide may present an explosion hazard when stored in a closed container. This is due to the release of ethylene oxide into the container headspace where it can accumulate, and so exceed the explosion limit.

16. Regulatory Status

Certain polyoxyethylene stearates are accepted for use as food additives in Europe. Included in the FDA Inactive Ingredients Guide (dental solutions, IV injections, ophthalmic preparations, oral capsules and tablets, otic suspensions, topical creams, emulsions, lotions, ointments and solutions, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Name	Pharmacopeia
Poloxyl 8 stearate	Aust, Ger and Swiss.
Poloxyl 40 stearate	Braz, Hung, Jpn, Turk and USPNF.
Poloxyl 50 stearate	USPNF.

18. Related Substances

Polyethylene Glycol; Stearic Acid.

19. Comments

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20. Specific References

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22. Authors

USA: CD Yu.

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Sodium Alginate

1. Nonproprietary Names

BP: Sodium alginate
PhEur: Natrii alginas
USPNF: Sodium alginate

2. Synonyms

Algin; alginic acid, sodium salt; E401; *Kelcosol*; *Keltone*; *Manucol*; *Manugel*; *Pronova*; *Protanal*; *Satialgine-H8*; sodium polymannuronate.

3. Chemical Name and CAS Registry Number

Sodium alginate [9005-38-3]

4. Empirical Formula Molecular Weight

Sodium alginate consists chiefly of the sodium salt of alginic acid, a linear glycuronan polymer consisting of a mixture of β-(1→4)-D-mannosyluronic acid and α-(1→4)-L-gulosyluronic acid residues.

5. Structural Formula

See Section 4.

6. Functional Category

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant.[1] Sodium alginate has also been used in the preparation of sustained release oral formulations since it can delay the dissolution of a drug from tablets[2] and aqueous suspensions.[3]

In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams and gels, and as a stabilizing agent for oil-in-water emulsions. Recently, sodium alginate has been used for the aqueous microencapsulation of drugs,[4] in contrast with the more conventional microencapsulation techniques which use organic solvent systems.

Therapeutically, sodium alginate has been used in combination with an H_2-receptor antagonist in the management of gastroesophageal reflux,[5] and as a hemostatic agent in surgical dressings.[6]

Sodium alginate is also used in cosmetics and food products.

Use	Concentration (%)
Pastes and creams	5-10
Stabilizer in emulsions	1-3
Suspending agent	1-5
Tablet binder	1-3
Tablet disintegrant	2.5-10

8. Description

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

9. Pharmacopeial Specifications

Test	PhEur 1992	USPNF XVII
Identification	+	+
Appearance of solution	+	—
Microbial limits	⩽ 1000/g	⩽ 200/g
Loss on drying	⩽ 15.0%	⩽ 15.0%
Ash	—	18.0-24.0%
Sulfated ash	30.0-36.0%	—
Arsenic	—	⩽ 1.5 ppm
Calcium	⩽ 1.5%	—
Chlorides	⩽ 1.0%	—
Lead	—	⩽ 0.001%
Heavy metals	⩽ 20 ppm	⩽ 0.004%
Assay (dried basis)	—	90.8-106.0%

10. Typical Properties

Acidity/alkalinity:
pH ≈ 7.2 for a 1% w/v aqueous solution.

Solubility: practically insoluble in ethanol, ether and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and acids, in which the pH of the resultant solution is less than pH 3. Slowly soluble in water, forming a viscous colloidal solution.

Viscosity (dynamic): various grades of sodium alginate are commercially available which yield aqueous solutions of varying viscosity. Typically, a 1% w/v aqueous solution, at 20°C, will have a viscosity of 20-400 mPa s (20-400 cP). Viscosity may vary depending upon concentration, pH, temperature or the presence of metal ions. Above pH 10, viscosity decreases, *see also* Alginic Acid and Section 11.

	HPE Laboratory Project Data		
	Method	Lab #	Results
Viscosity (2% w/v aqueous solution)			
	VIS-3	28	2.16 Pa s [a]
	VIS-3	28	2.05 Pa s [a]
	VIS-3	28	2.00 Pa s [b]
	VIS-3	28	3.04 Pa s [b]
Viscosity (3% w/v aqueous solution)			
	VIS-3	28	9.85 Pa s [b]
	VIS-3	28	8.35 Pa s [b]
	VIS-3	28	8.64 Pa s [b]
	VIS-3	28	7.20 Pa s [b]

Supplier: a. Edward Mendell Co Inc; b. Algum.

11. Stability and Storage Conditions

Sodium alginate is a hygroscopic material although it is stable if stored at low relative humidities and a cool temperature.

Aqueous solutions of sodium alginate are most stable between pH 4-10; below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60-80% its original value after storage for two years.[7] Solutions should not be stored in metal containers.

Sodium alginate solutions are susceptible on storage to microbial spoilage which may affect solution viscosity. Solutions are ideally sterilized using ethylene oxide, although

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filtration using a 0.45 μm filter also has only a slight adverse effect on solution viscosity.[8] Autoclaving of solutions can cause a decrease in viscosity which may vary depending upon the nature of any other substances present.[8,9] Gamma irradiation should not be used to sterilize sodium alginate solutions since this process severely reduces solution viscosity.[8,10]

Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol or parabens. If the medium is acidic, benzoic acid may also be used.

The bulk material should be stored in an airtight container in a cool, dry, place.

12. Incompatibilities

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals and ethanol in concentrations greater than 5%. High concentrations of electrolytes cause an increase in viscosity until salting-out of sodium alginate occurs; salting-out occurs if more than 4% of sodium chloride is present.

13. Method of Manufacture

Alginic acid is extracted from brown seaweed and neutralized with sodium bicarbonate to form sodium alginate.

14. Safety

Sodium alginate is widely used in cosmetics, food products and pharmaceutical formulations, such as tablets and topical products, including wound dressings. It is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may be harmful. A study in five healthy male volunteers fed a daily intake of 175 mg/kg body-weight of sodium alginate for 7 days, followed by a daily intake of 200 mg/kg body-weight of sodium alginate for a further 16 days, showed no significant adverse effects.[11]

The WHO has set an estimated acceptable daily intake of alginate salts and alginic acid, used as food additives, at up to 25 mg/kg body-weight, calculated as alginic acid.[12]

Inhalation of alginate dust may be irritant and has been associated with industrially related asthma in workers involved in alginate production. However, it appears that the cases of asthma were linked to exposure to seaweed dust rather than pure alginate dust.[13]

LD_{50} (cat, IP): 0.25 g/kg[14]
LD_{50} (rabbit, IV): 0.1 g/kg
LD_{50} (rat, IV): 1 g/kg
LD_{50} (rat, oral): > 5 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium alginate may be irritant to the eyes or respiratory system if inhaled as dust, *see* Section 14. Eye protection, gloves and a dust respirator are recommended. Sodium alginate should be handled in a well-ventilated environment.

16. Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Guide (oral suspensions and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Eur, Fr, Ger, It, Mex, Neth, Swiss and USPNF.

18. Related Substances

Alginic Acid; calcium alginate; potassium alginate; Propylene Glycol Alginate.

Calcium alginate

CAS number: [9005-35-0]

Synonyms: alginic acid, calcium salt; calcium polymannuronate; calginate; E404.

Comments: calcium alginate is used in applications similarly to sodium alginate, such as in sustained release formulations[15] and hemostatic wound dressings which can be washed off with sterile sodium chloride solution.[6]

Potassium alginate

CAS number: [9005-36-1]

Synonyms: alginic acid, potassium salt; E402; potassium polymannuronate.

19. Comments

A number of different grades of sodium alginate, which have different solution viscosities, are commercially available. Many different alginate salts and derivatives are also commercially available including: ammonium alginate; calcium alginate; magnesium alginate and potassium alginate.

See also Alginic Acid for further information.

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22. Authors

UK: PJ Weller.

Sodium Lauryl Sulfate

1. Nonproprietary Names

BP: Sodium lauryl sulphate
PhEur: Natrii laurilsulfas
USPNF: Sodium lauryl sulfate

2. Synonyms

Dodecyl sodium sulfate; *Elfan 240*; *Empicol LZ*; *Maprofix 563*; *Marlinat DFK30*; *Nutrapon W*; sodium dodecyl sulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; *Stepanol WA 100*.

3. Chemical Name and CAS Registry Number

Sulfuric acid monododecyl ester sodium salt
[151-21-3]

4. Empirical Formula Molecular Weight

$C_{12}H_{25}NaO_4S$ 288.38

The USPNF XVII describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate ($C_{12}H_{25}NaO_4S$). The BP 1993 and PhEur 1993 additionally state that sodium lauryl sulfate should contain not less than 85% of sodium alkyl sulfate calculated as $C_{12}H_{25}NaO_4S$.

5. Structural Formula

$CH_3(CH_2)_{10}CH_2OSO_3Na$
See also Section 4.

6. Functional Category

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

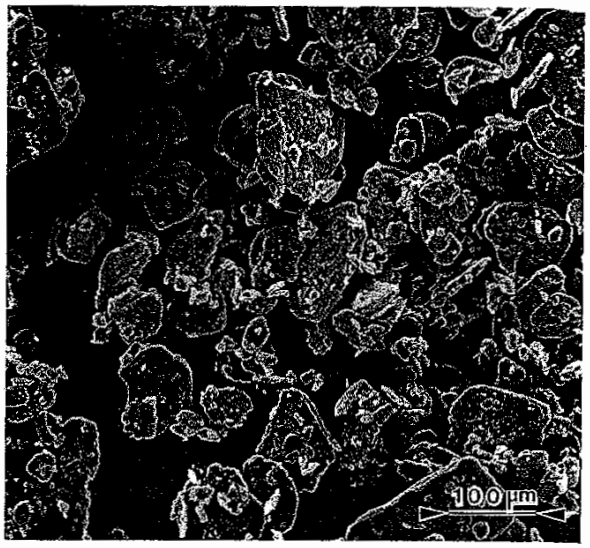
Sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics. It is a detergent and wetting agent effective in both alkaline and acidic conditions.

Use	Concentration (%)
Anionic emulsifier, forms self-emulsifying bases with fatty alcohols	0.5-2.5
Detergent in medicated shampoos	≈ 10
Skin cleanser in topical applications	1
Solubilizer in concentrations greater than critical micelle concentration	> 0.0025
Tablet lubricant	1-2
Wetting agent in dentrifices	1-2

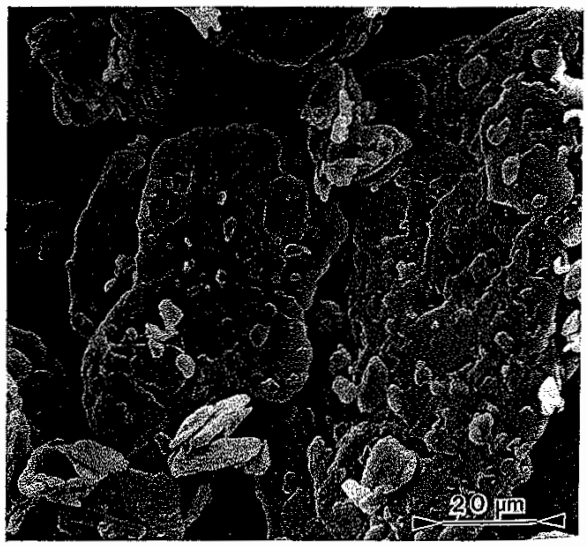
8. Description

Sodium lauryl sulfate consists of white or cream to pale yellow-colored crystals, flakes or powder having a smooth feel, a soapy, bitter taste and a faint odor of fatty substances.

SEM: 1
Excipient: Sodium lauryl sulfate
Manufacturer: Canadian Alcolac Ltd
Magnification: 120x



SEM: 2
Excipient: Sodium lauryl sulfate
Manufacturer: Canadian Alcolac Ltd
Magnification: 600x



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9. Pharmacopeial Specifications

Test	PhEur 1993	USPNF XVII
Identification	+	+
Alkalinity	+	+
Heavy metals	—	≤ 0.002%
Arsenic	—	≤ 3 ppm
Combined sodium chloride and sodium sulfate	≤ 8.0%	≤ 8.0%
Unsulfated alcohols	—	≤ 4.0%
Non-esterified alcohols	≤ 4.0%	—
Total alcohols	—	≥ 59.0%
Assay (as $C_{12}H_{25}NaO_4S$)	≥ 85.0%	—

10. Typical Properties

Acidity/alkalinity:
pH = 7.0-9.5 (1% w/v aqueous solution).
Acid value: 0
Antimicrobial activity: sodium lauryl sulfate has some bacteriostatic action against Gram-positive bacteria, but is ineffective against many Gram-negative microorganisms. It potentiates the fungicidal activity of certain substances such as sulfanilamide and sulfathiazole.
Critical micelle concentration:
8.2 mmol/L (0.23 g/L) at 20°C.
Density: 1.07 g/cm^3 at 20°C
HLB value: ≈ 40
Interfacial tension: 11.8 mN/m (11.8 dynes/cm) for a 0.05% w/v solution (unspecified nonaqueous liquid) at 30°C.
Melting point: 204-207°C (for pure substance).
Moisture content: ≤ 5%; sodium lauryl sulfate is not hygroscopic.
Solubility: freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.
Spreading coefficient:
–7.0 (0.05% w/v aqueous solution) at 30°C.
Surface tension: 25.2 mN/m (25.2 dynes/cm) for a 0.05% w/v aqueous solution at 30°C.
Wetting time (Draize Test):
118 s (0.05% w/v aqueous solution) at 30°C.

11. Stability and Storage Conditions

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e. pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate.
The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry, place.

12. Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions.
Solutions of sodium lauryl sulfate (pH 9.5-10.0) are mildly corrosive to mild steel, copper, brass, bronze and aluminum. Sodium lauryl sulfate is also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

13. Method of Manufacture

Sodium lauryl sulfate is prepared by sulfation of lauryl alcohol, followed by neutralization with sodium carbonate.

14. Safety

Sodium lauryl sulfate is widely used in cosmetics and oral and topical pharmaceutical formulations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract and stomach. Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop. Prolonged inhalation of sodium lauryl sulfate will damage the lungs. Pulmonary sensitization is possible resulting in hyperactive airway dysfunction and pulmonary allergy. Animal studies have shown intravenous administration to cause marked toxic effects to the lung, kidney and liver. Mutagenic testing in bacterial systems has however proven negative.[1]
Adverse reactions to sodium lauryl sulfate in cosmetics and pharmaceutical formulations mainly concern reports of irritation to the skin[2-4] or eyes[5] following topical application.
Sodium lauryl sulfate should not be used in intravenous preparations for humans. The probable human lethal oral dose is 0.5-5 g/kg.
LD_{50} (mouse, IP): 0.25 g/kg[6]
LD_{50} (mouse, IV): 0.12 g/kg
LD_{50} (rat, oral): 1.29 g/kg
LD_{50} (rat, IP): 0.21 g/kg
LD_{50} (rat, IV): 0.12 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Inhalation and contact with the skin and eyes should be avoided; eye protection, gloves and other protective clothing, depending on the circumstances, are recommended. Adequate ventilation should be provided or a dust respirator worn. Prolonged or repeated exposure should be avoided. Sodium lauryl sulfate emits toxic fumes on combustion.

16. Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, and topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Belg, Br, Braz, Cz, Egypt, Eur, Fr, Gr, Hung, Ind, Jpn, Neth, Rom, Swiss, USPNF and Yug.

18. Related Substances

Magnesium lauryl sulfate.

Magnesium lauryl sulfate: $C_{12}H_{26}O_4S.\frac{1}{2}Mg$
CAS number: [3097-08-3]
Comments: a soluble tablet lubricant.[7]

19. Comments

—

20. Specific References

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22. Authors

UK: S Behn.

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Sorbitan Esters (Sorbitan Fatty Acid Esters)

1. Nonproprietary Names

BP: Sorbitan monolaurate
Sorbitan mono-oleate
Sorbitan monostearate

USPNF: Sorbitan monolaurate
Sorbitan monooleate
Sorbitan monopalmitate
Sorbitan monostearate
Sorbitan sesquioleate
Sorbitan trioleate

2. Synonyms

See Table I.

3. Chemical Names and CAS Registry Numbers

See Table II.

Table I: Synonyms of selected sorbitan esters.

Name	Synonym
Sorbitan monoisostearate	1,4-Anhydro-D-glucitol, 6-isooctadecanoate; anhydrosorbitol monoisostearate; *Arlacel 987*; *Crill 6*; sorbitan isostearate.
Sorbitan monolaurate	*Arlacel 20*; *Armotan ML*; *Crill 1*; E493; *Glycomul L*; *Hodag SML*; *Liposorb L*; *Montane 20*; *Protachem SML*; *Sorbester P12*; *Sorbirol L*; sorbitan laurate; *Span 20*.
Sorbitan monooleate	*Arlacel 80*; *Armotan MO*; *Capmul O*; *Crill 4*; *Crill 50*; E494; *Glycomul O*; *Hodag SMO*; *Liposorb O*; *Montane 80*; *Protachem SMO*; *Sorbester P17*; *Sorbirol O*; sorbitan oleate; *Span 80*.
Sorbitan monopalmitate	1,4-Anhydro-D-glucitol, 6-hexadecanoate; *Arlacel 40*; *Armotan MP*; *Crill 2*; E495; *Glycomul P*; *Hodag SMP*; *Liposorb P*; *Montane 40*; *Protachem SMP*; *Sorbester P16*; *Sorbirol P*; sorbitan palmitate; *Span 40*.
Sorbitan monostearate	1,4-Anhydro-D-glucitol, 6-octadecanoate; anhydrosorbitol monostearate; *Arlacel 60*; *Armotan MS*; *Capmul S*; *Crill 3*; E491; *Glycomul S*; *Hodag SMS*; *Liposorb S*; *Liposorb SC*; *Liposorb S-K*; *Montane 60*; *Protachem SMS*; *Sorbester P18*; *Sorbirol S*; sorbitan stearate; *Span 60*.
Sorbitan sesqui-isostearate	*Protachem SQI*.
Sorbitan sesquioleate	*Arlacel C*; *Arlacel 83*; *Crill 43*; *Glycomul SOC*; *Hodag SSO*; *Liposorb SQO*; *Montane 83*; *Protachem SOC*.
Sorbitan trilaurate	*Span 25*.
Sorbitan trioleate	*Arlacel 85*; *Crill 45*; *Glycomul TO*; *Hodag STO*; *Liposorb TO*; *Montane 85*; *Protachem STO*; *Sorbester P37*; *Span 85*.
Sorbitan tristearate	*Crill 35*; *Crill 41*; E492; *Glycomul TS*; *Hodag STS*; *Liposorb TS*; *Liposorb TS-K*; *Montane 65*; *Protachem STS*; *Sorbester P38*; *Span 65*.

Table II: Chemical name and CAS registry number of selected sorbitan esters.

Name	Chemical name	CAS number
Sorbitan di-isostearate	Sorbitan di-isooctadecanoate	[68238-87-9]
Sorbitan dioleate	(Z,Z)-Sorbitan di-9-octadecanoate	[29116-98-1]
Sorbitan monolaurate	Sorbitan monododecanoate	[1338-39-2]
Sorbitan monoisostearate	Sorbitan monoisooctadecanoate	[71902-01-7]
Sorbitan monooleate	(*Z*)-Sorbitan mono-9-octadecenoate	[1338-43-8]
Sorbitan monopalmitate	Sorbitan monohexadecanoate	[26266-57-9]
Sorbitan monostearate	Sorbitan mono-octadecanoate	[1338-41-6]
Sorbitan sesqui-isostearate	Sorbitan sesqui-isooctadecanoate	[71812-38-9]
Sorbitan sesquioleate	(*Z*)-Sorbitan sesqui-9-octadecenoate	[8007-43-0]
Sorbitan sesquistearate	Sorbitan sesqui-octadecanoate	[51938-44-4]
Sorbitan tri-isostearate	Sorbitan tri-isooctadecanoate	[54392-27-7]
Sorbitan trioleate	(*Z*,*Z*,*Z*)-Sorbitan tri-9-octadecenoate	[26266-58-0]
Sorbitan tristearate	Sorbitan tri-octadecanoate	[26658-19-5]

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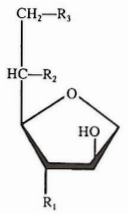
4. Empirical Formula Molecular Weight

Name	Formula	Molecular weight
Sorbitan di-isostearate	$C_{42}H_{80}O_7$	697
Sorbitan dioleate	$C_{42}H_{76}O_7$	693
Sorbitan monoisostearate	$C_{24}H_{46}O_6$	431
Sorbitan monolaurate	$C_{18}H_{34}O_6$	346
Sorbitan monooleate	$C_{24}H_{44}O_6$	429
Sorbitan monopalmitate	$C_{22}H_{42}O_6$	403
Sorbitan monostearate	$C_{24}H_{46}O_6$	431
Sorbitan sesqui-isostearate	$C_{33}H_{63}O_{6.5}$	564
Sorbitan sesquioleate	$C_{33}H_{60}O_{6.5}$	561
Sorbitan sesquistearate	$C_{33}H_{63}O_{6.5}$	564
Sorbitan tri-isostearate	$C_{60}H_{114}O_8$	964
Sorbitan trioleate	$C_{60}H_{108}O_8$	958
Sorbitan tristearate	$C_{60}H_{114}O_8$	964

5. Structural Formula



$R_1 = R_2 = OH$, $R_3 = R$ for sorbitan monoesters,
$R_1 = OH$, $R_2 = R_3 = R$ for sorbitan diesters,
$R_1 = R_2 = R_3 = R$ for sorbitan triesters,
Where R = $(C_{17}H_{35})COO$ for isostearate,
$(C_{11}H_{23})COO$ for laurate,
$(C_{17}H_{33})COO$ for oleate,
$(C_{15}H_{31})COO$ for palmitate,
$(C_{17}H_{35})COO$ for stearate.
The sesqui-esters are equimolar mixtures of monoesters and diesters.

6. Functional Category

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Sorbitan esters are a series of mixtures of partial esters of sorbitol and its mono- and di-anhydrides with fatty acids.
Sorbitan esters are widely used in cosmetics, food products and pharmaceutical formulations as lipophilic nonionic surfactants. They are mainly used in pharmaceutical formulations as emulsifying agents in the preparation of creams, emulsions and ointments for topical application. When used alone, sorbitan esters produce stable water-in-oil emulsions but are frequently used in combination with varying proportions of a polysorbate to produce water-in-oil or oil-in-water emulsions or creams of varying consistencies.
Sorbitan monolaurate, sorbitan monopalmitate and sorbitan trioleate have also been used at a concentration of 0.01-0.05% w/v in the preparation of an emulsion for intramuscular administration.

Use	Concentration (%)
Emulsifying agent	
Used alone in water-in-oil emulsions	1-15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1-10
Used to increase the water-holding properties of ointments	1-10
Solubilizing agent	
For poorly soluble, active constituents in lipophilic bases	1-10
Wetting agent	
For insoluble, active constituents in lipophilic bases	0.1-3

8. Description

Sorbitan esters occur as cream to amber-colored liquids or solids with a distinctive odor and taste, *see* below.

Name	Appearance
Sorbitan monoisostearate	Yellow viscous liquid
Sorbitan monolaurate	Yellow viscous liquid
Sorbitan monooleate	Yellow viscous liquid
Sorbitan monopalmitate	Cream solid
Sorbitan monostearate	Cream solid
Sorbitan sesquioleate	Amber viscous liquid
Sorbitan trioleate	Amber viscous liquid
Sorbitan tristearate	Cream/yellow solid

9. Pharmacopeial Specifications

Test	BP 1993 (Ad 1994)	USPNF XVII (Suppl 9)
Identification	+	+
Acid value		
Sorbitan monolaurate	⩽ 7.0	⩽ 8
Sorbitan monooleate	⩽ 8.0	⩽ 8
Sorbitan monopalmitate	—	⩽ 8
Sorbitan monostearate	⩽ 10.0	⩽ 10
Sorbitan sesquioleate	—	⩽ 14
Sorbitan trioleate	—	⩽ 17
Hydroxyl value		
Sorbitan monolaurate	330-358	330-358
Sorbitan monooleate	193-209	190-215
Sorbitan monopalmitate	—	275-305
Sorbitan monostearate	235-260	235-260
Sorbitan sesquioleate	—	182-220
Sorbitan trioleate	—	50-75
Iodine value		
Sorbitan monooleate	—	62-76
Sorbitan sesquioleate	—	65-75
Sorbitan trioleate	—	77-85
Saponification value		
Sorbitan monolaurate	158-170	158-170
Sorbitan monooleate	149-160	145-160
Sorbitan monopalmitate	—	140-150
Sorbitan monostearate	147-157	147-157
Sorbitan sesquioleate	—	143-165
Sorbitan trioleate	—	169-183
Water		
Sorbitan monolaurate	⩽ 1.5%	⩽ 1.5%
Sorbitan monooleate	⩽ 1.0%	⩽ 1.0%
Sorbitan monopalmitate	—	⩽ 1.5%
Sorbitan monostearate	⩽ 1.5%	⩽ 1.5%

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Continued

Test	BP 1993 (Ad 1994)	USPNF XVII (Suppl 9)
Sorbitan sesquioleate	—	⩽ 1.0%
Sorbitan trioleate	—	⩽ 0.7%
Residue on ignition		
Sorbitan monolaurate	—	⩽ 0.5%
Sorbitan monooleate	—	⩽ 0.5%
Sorbitan monopalmitate	—	⩽ 0.5%
Sorbitan monostearate	—	⩽ 0.5%
Sorbitan sesquioleate	—	⩽ 1.4%
Sorbitan trioleate	—	⩽ 0.25%
Sulfated ash	⩽ 0.5%	—
Heavy metals	⩽ 10 ppm	⩽ 0.001%
Arsenic	⩽ 3 ppm	—
Specific gravity		
Sorbitan monolaurate	0.9-1.03	—
Sorbitan monooleate	0.985-1.005	—
Viscosity		
Sorbitan monolaurate	3.0-5.0 Pa s	—
Sorbitan monooleate	0.9-1.5 Pa s	—
Assay for fatty acids		
Sorbitan monolaurate	—	55.0-63.0%
Sorbitan monooleate	—	72.0-78.0%
Sorbitan monopalmitate	—	63.0-71.0%
Sorbitan monostearate	—	68.0-76.0%
Sorbitan sesquioleate	—	74.0-80.0%
Sorbitan trioleate	—	85.5-90.0%
Assay for polyols		
Sorbitan monolaurate	—	39.0-45.0%
Sorbitan monooleate	—	25.0-31.0%
Sorbitan monopalmitate	—	32.0-38.0%
Sorbitan monostearate	—	27.0-34.0%
Sorbitan sesquioleate	—	22.0-28.0%
Sorbitan trioleate	—	13.0-19.0%

Note: unless otherwise indicated, the above specifications apply to all of the sorbitan esters listed in the BP 1993 or USPNF XVII. The USPNF XVII contains 6 sorbitan ester monographs while the BP 1993 contains 3 monographs, *see* Sections 1 and 17.

10. Typical Properties

Acid value: *see* Table III
Density: *see* Table III
Flash point: > 149°C
HLB value: *see* Table III
Hydroxyl value: *see* Table III
Iodine number: *see* Table III
Melting point: *see* Table III
Moisture content: *see* Table IV
Pour point: *see* Table III
Saponification value: *see* Table IV
Solubility: sorbitan esters are generally soluble or dispersible in oils; they are also soluble in most organic solvents. In water, although insoluble they are generally dispersible.
Surface tension: *see* Table IV
Viscosity (dynamic): *see* Table IV

11. Stability and Storage Conditions

Gradual soap formation occurs with strong acids or bases; sorbitan esters are stable in weak acids or bases.
Sorbitan esters should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

–

13. Method of Manufacture

Sorbitol is dehydrated to form a hexitan (1,4-sorbitan) which is then esterified with the desired fatty acid.

Table III: Typical properties of selected sorbitan esters.

Name	Acid value	Density (g/cm^3)	HLB value	Hydroxyl value	Iodine number	Melting point (°C)	Pour point (°C)
Sorbitan monoisostearate	⩽ 8	—	4.7	220-250	—	—	—
Sorbitan monolaurate	⩽ 7	1.01	8.6	159-169	⩽ 7	—	16-20
Sorbitan monooleate	⩽ 8	1.01	4.3	193-209	—	—	-12
Sorbitan monopalmitate	3-7	1.0	6.7	270-303	⩽ 1	43-48	—
Sorbitan monostearate	5-10	—	4.7	235-260	⩽ 1	53-57	—
Sorbitan sesquioleate	8.5-13	1.0	3.7	188-210	—	—	—
Sorbitan trioleate	10-14	0.95	1.8	55-70	—	—	—
Sorbitan tristearate	⩽ 7	—	2.1	60-80	—	—	—

Table IV: Typical properties of selected sorbitan esters (continued).

Name	Saponification value	Surface tension of 1% aqueous solution (mN/m)	Viscosity at 25°C (mPa s)	Water content (%)
Sorbitan monoisostearate	143-153	—	—	⩽ 1.0
Sorbitan monolaurate	159-169	28	3900-4900	⩽ 0.5
Sorbitan monooleate	149-160	30	970-1080	⩽ 0.5
Sorbitan monopalmitate	142-152	36	Solid	⩽ 1.0
Sorbitan monostearate	147-157	46	Solid	⩽ 1.0
Sorbitan sesquioleate	149-160	—	1500	⩽ 1.0
Sorbitan trioleate	170-190	32	200-250	⩽ 1.0
Sorbitan tristearate	172-185	48	Solid	⩽ 1.0

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14. Safety

Sorbitan esters are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. However, there have been occasional reports of hypersensitive skin reactions following the topical application of products containing sorbitan esters.[1-4]

The WHO has set an estimated acceptable daily intake of sorbitan monopalmitate, monostearate and tristearate,[5] and sorbitan monolaurate and monooleate[6] at up to 25 mg/kg body-weight calculated as total sorbitan esters.

Sorbitan monolaurate LD_{50} (rat, oral): 33.6 g/kg[7]

Sorbitan monostearate LD_{50} (rat, oral): 31 g/kg[7]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

Certain sorbitan esters are accepted as food additives in Europe. Sorbitan esters are included in the FDA Inactive Ingredients guide (inhalations, IM injections, ophthalmic, oral, topical and vaginal preparations). Sorbitan esters are used in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Name	Pharmacopeia
Sorbitan monolaurate	Br, Hung, Mex and USPNF.
Sorbitan monooleate	Br, Mex and USPNF.
Sorbitan monopalmitate	Mex and USPNF.
Sorbitan monostearate	Br and USPNF.
Sorbitan sesquioleate	Jpn, Swiss and USPNF.
Sorbitan trioleate	USPNF.

18. Related Substances

Polyoxyethylene Sorbitan Fatty Acid Esters.

19. Comments

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20. Specific References

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UK: RL Leyland.

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Pregelatinized Starch

1. Nonproprietary Names

BP: Pregelatinised maize starch
USPNF: Pregelatinized starch

2. Synonyms

Compressible starch; *Instastarch*; *Lycatab PGS*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *Starch 1500*; *Sta-Rx 1500*.

3. Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4. Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$
Where n = 300-1000.
Pregelatinized starch is a starch that has been chemically and mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin and 80% unmodified starch. The USPNF XVII does not specify the botanical origin of the original starch but the BP 1993 specifies that corn (maize) starch should be used. *See also* Starch and Section 13.

5. Structural Formula

See Starch.

6. Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent[1] and disintegrant.[2]
In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry compression processes.[3-11] In such processes, pregelatinized starch is self-lubricating. However, when used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.[12]
Pregelatinized starch may also be used in wet granulation processes.[13]

Use	Concentration (%)
Diluent (hard gelatin capsules)	5-75
Tablet binder (direct compression)	5-20
Tablet binder (wet granulation)	5-10
Tablet disintegrant	5-10

8. Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.
Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules. Examination of samples suspended in glycerin show characteristic forms depending upon the method of drying used during manufacture, e.g. either irregular chunks from drum drying or thin plates.

9. Pharmacopeial Specifications

Test	BP 1993	USPNF XVII (Suppl 5)
Identification	+	+
pH (10% w/v slurry)	4.5-7.0	4.5-7.0
Iron	—	⩽ 0.002%
Oxidizing substances	—	+
Sulfur dioxide	—	⩽ 0.008%
Microbial limits	+	+
Loss on drying	⩽ 15.0%	⩽ 14.0%
Residue on ignition	—	⩽ 0.5%
Sulfated ash	⩽ 0.5%	—
Protein	⩽ 0.5%	—

10. Typical Properties

Acidity/alkalinity: pH = 4.5-7.0 for a 10% w/v aqueous dispersion.
Angle of repose: 40.7°[6]
Flowability: 18-23% (Carr compressibility index)[14]
Moisture content: pregelatinized maize starch is hygroscopic,[11,15,16] *see* HPE Data.
Particle size distribution: 30-150 μm, median diameter 52 μm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 μm), and less than 0.5% retained on a US #40 mesh (420 μm).
Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Fully pregelatinized starch conforms to the completeness of solution test in the USP XXII. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold water soluble matter for partially pregelatinized starch is 10-20%.
Specific surface area: 0.21-0.22 m^2/g
Viscosity (dynamic): 8-10 mPa s (8-10 cP) for a 2% w/v aqueous dispersion at 25°C.

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	HPE Laboratory Project Data Method	Lab #	Results*
Bulk/tap density			
Starch 1500	BTD-7	14	B: 0.650 g/cm^3 [a] T: 0.820 g/cm^3
Moisture content	MC-22	2	7.0% [b]
	MC-15	34	8.94% [b]
	EMC-1	2	*See* Fig. 1. [b]
Starch 1500	MC-15	34	11.12% [a]
Starch 1500	MC-15	14	11.30% [a]
Starch 1500	SDI-1	14	*See* Fig. 2. [a]
Wheat (*Paygel 90*)	MC-15	14	6.60% [c]
Wheat (*Paygel 90*)	SDI-1	14	*See* Fig. 2. [c]
Particle size	PSD-2	5	68 μm [b]
Starch 1500	PSD-2	5	80 μm [a]

Supplier: a. Colorcon Ltd; b. National Starch & Chemicals Ltd; c. Henkel Corp.
* Note that results are for pregelatinized corn starch unless otherwise indicated.

11. Stability and Storage Conditions

Pregelatinized starch is a stable, though hygroscopic material, which should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

–

13. Method of Manufacture

Fully pregelatinized starch is prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62-72°C. Chemical additives which may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded or drum-dried. In the latter case, the dried material may be processed to produce a desired particle size range.
Partially pregelatinized starch is prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where partial gelatinization and subsequent drying takes place.

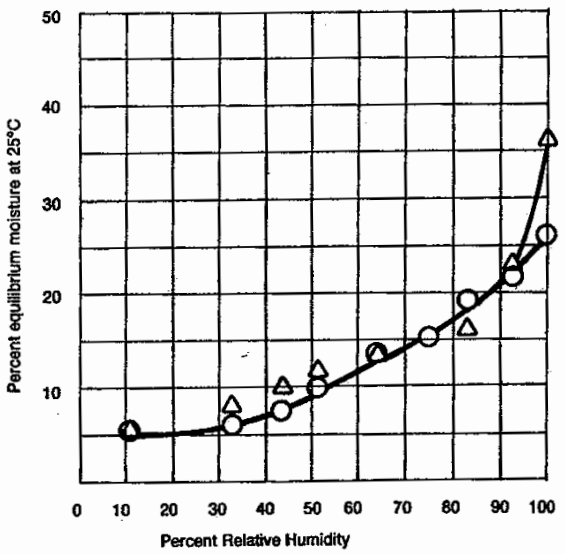

Fig. 1: Equilibrium moisture content of corn starch and pregelatinized starch.
○ Corn starch (National Starch & Chemicals Ltd; Lot #421).
△ Pregelatinized corn starch (National Starch & Chemicals Ltd; Lot #HJW 103).

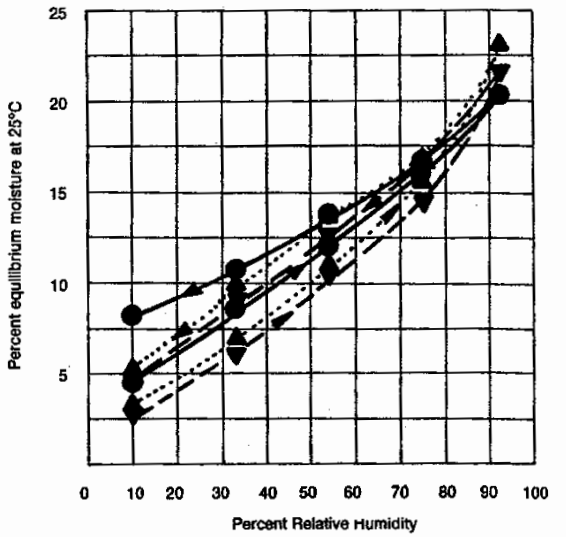

Fig. 2: Sorption-desorption isotherms of pregelatinized corn starch and pregelatinized wheat starch.
● Pregelatinized corn starch, *Sta-Rx 1500* (AE Staley Mfg Co; Lot #977912).
▲ Pregelatinized wheat starch, *Paygel 90* (Henkel Corp; Lot #289D).
▼Pregelatinized corn starch, *Starch 1500* (Colorcon Ltd; Lot #904014)

14. Safety

Pregelatinized starch, and starch, are widely used in oral solid dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of pregelatinized starch may be harmful.
See Starch for further information.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust-mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.
In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are, 10 mg/m^3 for total inhalable dust and 5 mg/m^3 for respirable dust.[17]

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions and tablets). Included in nonparenteral medicines licensed in the UK.

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17. Pharmacopeias

Br and USPNF.

18. Related Substances

Starch; Sterilizable Maize Starch.

19. Comments

A low moisture grade of pregelatinized starch, *Starch 1500 L.M.* (Colorcon Ltd), containing less than 7% of water, is commercially available specifically intended for use as a diluent in capsule formulations.

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5. Bolhuis GK, Lerk CF. Comparative evaluation of excipients for direct compression. Pharm Weekbl 1973; 108: 469-481.
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22. Authors

USA: NG Lordi.

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Stearic Acid

1. Nonproprietary Names

BP: Stearic acid
USPNF: Stearic acid

2. Synonyms

570; *Crodacid*; *Crosterene*; *Glycon S-90*; *Hystrene*; *Industrene*; *Kortacid 1895*; *Pristerene*.

3. Chemical Name and CAS Registry Number

Octadecanoic acid [57-11-4]

4. Empirical Formula Molecular Weight

$C_{18}H_{36}O_2$ 284.47 (for pure material)

The BP 1993 and the USPNF XVII describe stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). The content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%. The USPNF XVII also contains a monograph for purified stearic acid, *see* Section 18.

5. Structural Formula

$CH_3(CH_2)_{16}COOH$

6. Functional Category

Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant[1-3] although it may also be used as a binder,[4] or in combination with shellac as a tablet coating.

In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams.[5,6] The partially neutralized stearic acid forms a creamy base when mixed with 5-15 times its own weight of aqueous liquid, the appearance and plasticity of the cream being determined by the proportion of alkali used.

Stearic acid is also widely used in cosmetics and food products.

Use	Concentration (%)
Ointments and creams	1-20
Tablet lubricant	1-3

8. Description

Stearic acid is a hard, white or faintly yellow colored, somewhat glossy, crystalline solid or a white, or yellowish white, powder. It has a slight odor and taste suggesting tallow. *See also* Section 13.

SEM: 1
Excipient: Stearic acid, 95% (*Emersol 153*)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120x
Voltage: 10 kV

SEM: 2
Excipient: Stearic acid, food grade (*Emersol 6332*)
Manufacturer: Emery Industries
Lot No.: 18895
Magnification: 120x
Voltage: 10kV

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SEM: 3
Excipient: Stearic acid USP (*Hydrofol Acid 1655*)
Manufacturer: Sherex Chemical Company Inc
Lot No.: 9303-M639-521
Magnification: 120x
Voltage: 10kV

SEM: 4
Excipient: Stearic acid (*Hydrofol Acid 1870*)
Manufacturer: Sherex Chemical Company Inc
Lot No.: 9227-M635-421
Magnification: 120x
Voltage: 10kV

9. Pharmacopeial Specifications

Test	BP 1993	USPNF XVII (Suppl 6)
Identification	+	+
Congealing temperature	⩾ 54°C	⩾ 54°C
Residue on ignition	—	⩽ 0.1%
Sulfated ash	⩽ 0.1%	—
Heavy metals	⩽ 20 ppm	⩽ 0.001%
Mineral acid	+	+
Neutral fat or paraffin	—	+
Acid value	200-212	—
Iodine value	⩽ 4.0	⩽ 4.0
Organic volatile impurities	—	+
Assay of stearic acid	⩾ 40.0%	⩾ 40.0%
Assay of both acids	⩾ 90.0%	⩾ 90.0%

10. Typical Properties

Acid value: 200-212
Density (bulk): ≈ 0.8 g/cm^3
Melting point: ⩾ 54°C
Moisture content: contains practically no water.
Saponification value: 200-220
Solubility: freely soluble in benzene, carbon tetrachloride, chloroform and ether; soluble in ethanol, hexane and propylene glycol; practically insoluble in water.
See also Section 18.

11. Stability and Storage Conditions

Stearic acid is a stable material; an antioxidant may also be added to it, *see* Section 13. The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents.
Insoluble stearates are formed with many metals; ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts.
A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs although such laboratory studies that have suggested incompatibilities, e.g. naproxen,[7] may not necessarily be applicable to formulated products.
Stearic acid has been reported to cause pitting in the film-coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.[8]

13. Method of Manufacture

Stearic acid is manufactured by hydrolysis of fat by continuous exposure to a counter-current stream of high-temperature water and fat in a high-pressure chamber. The resultant mixture is purified by vacuum steam distillation and the distillates then separated using selective solvents.
Stearic acid may also be manufactured by hydrogenation of cottonseed and other vegetable oils; by the hydrogenation and subsequent saponification of olein followed by recrystallization from alcohol; and from edible fats and oils by boiling with sodium hydroxide, separating any glycerin and decomposing the resulting soap with sulfuric or hydrochloric acid. The

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Table I: Specifications of different stearic acid grades (Witco Corporation).

Product	Stearic acid content (%)	Titer (°C)	Acid value	Iodine value	Saponification value	Unsaponifiable matter (%)
Hystrene 5016	44	54.5-56.5	206-210	⩽ 0.5	206-211	⩽ 0.2
Hystrene 7018	68.5	61.0-62.5	200-205	⩽ 0.5	200-206	⩽ 0.2
Hystrene 9718	90	66.5-68.0	196-201	⩽ 0.8	196-202	⩽ 0.3
Industrene 7018	65	58-62	200-207	⩽ 1.5	200-208	⩽ 0.5
Industrene 8718	87	64.5-67.5	196-201	⩽ 2.0	196-202	⩽ 1.5

stearic acid is then subsequently separated from any oleic acid by cold expression.
Stearic acid is derived from edible fat sources unless it is intended for external use, in which case nonedible fat sources may be used. Stearic acid may contain a suitable antioxidant such as 0.005% w/w butylated hydroxytoluene.

14. Safety

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful.
LD_{50} (mouse, IV): 23 mg/kg[9]
LD_{50} (rabbit, skin): > 5 g/kg
LD_{50} (rat, IV): 21.5 mg/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Stearic acid dust may be irritant to the skin, eyes and mucous membranes. Eye protection, gloves and a dust respirator are recommended. Stearic acid is combustible.

16. Regulatory Status

GRAS listed. Accepted as a food additive in the UK. Included in the FDA Inactive Ingredients Guide (buccal tablets, oral capsules, solutions, suspensions and tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Belg, Br, Braz, Chin, Cz, Egypt, Fr, Hung, Ind, It, Jpn, Mex, Nord, Rom, Swiss, USPNF and Yug.

18. Related Substances

Calcium Stearate; Magnesium Stearate; palmitic acid; purified stearic acid; Zinc Stearate.

Palmitic acid: $C_{16}H_{32}O_2$
Molecular weight: 256.42
CAS number: [57-10-3]
Synonyms: cetylic acid; hexadecanoic acid; hexadecylic acid.
Appearance: the pure material is a white, crystalline powder.
Boiling point: 215°C
Density: 0.853 g/cm^3 at 62°C
Melting point: 63-64°C
Refractive index: n_D^{80} = 1.4273
Solubility: freely soluble in chloroform; ether, propan-2-ol and hot ethanol (95%); sparingly soluble in ethanol (95%); practically insoluble in water.

Purified stearic acid: $C_{18}H_{36}O_2$
Molecular weight: 284.47
CAS number: [57-11-4]
Synonyms: octadecanoic acid.
Pharmacopeias: USPNF.
Acid value: 195-200
Boiling point: 361°C
Density: 0.847 g/cm^3 at 70°C
Flash point: 196°C
Iodine number: ⩽ 1.5
Melting point: 66-69°C
Refractive index: n_D^{80} = 1.4299
Solubility: soluble 1 in 5 parts benzene, 1 in 6 parts carbon tetrachloride, 1 in 2 parts chloroform, 1 in 15 parts ethanol, 1 in 3 parts ether; practically insoluble in water.
Vapor density (relative): 9.80 (air = 1)
Comments: purified stearic acid contains not less than 96.0% of stearic and palmitic acid, of which, stearic acid constitutes not less than 90.0% of the total.

19. Comments

A wide range of different grades of stearic acid are commercially available which have varying chemical compositions and hence different physical and chemical properties, *see* Table I.[10]

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22. Authors

USA: LV Allen.

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Hydrogenated Vegetable Oil, Type I

1. Nonproprietary Names

USPNF: Hydrogenated vegetable oil, type I
See also Sections 8, 9 and 18.

2. Synonyms

Sterotex
Trade names for materials derived from stated vegetable oils are shown below:
Hydrogenated cottonseed oil: *Lubritab.*
Hydrogenated palm oil: *Dynasan P60*; *Softisan 154.*
Hydrogenated soybean oil: *Sterotex HM.*

3. Chemical Name and CAS Registry Number

Hydrogenated vegetable oil [68334-00-9]
Hydrogenated soybean oil [8016-70-4]

4. Empirical Formula Molecular Weight

—

5. Structural Formula

$R_1COOCH_2-CH(OOCR_2)-CH_2OOCR_3$
Where R_1, R_2 and R_3 are mainly C_{15} and C_{17}.

6. Functional Category

Tablet and capsule diluent; tablet and capsule lubricant; tablet binder.

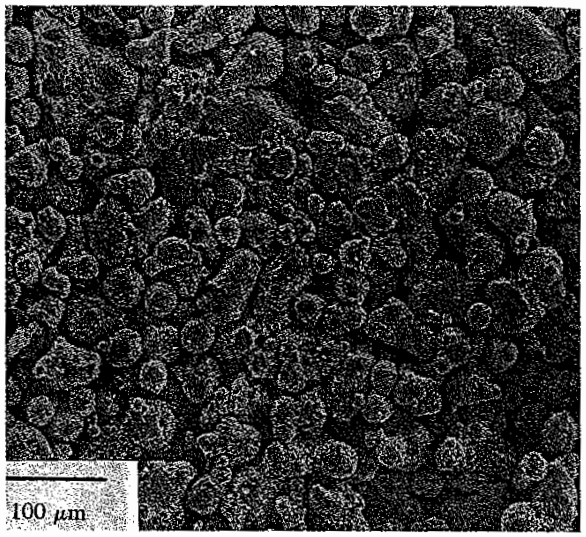
7. Applications in Pharmaceutical Formulation or Technology

Hydrogenated vegetable oil, type I is used as a lubricant in tablet and capsule formulations.[1,2] It is used at concentrations of 1-6% w/w, usually in combination with talc. It may also be used as an auxiliary binder in tablet formulations.
Hydrogenated vegetable oil, type I is additionally used as the matrix forming material in lipophilic based controlled release formulations;[3-6] it may also be used as a coating aid in controlled release formulations.
Other uses of hydrogenated vegetable oil, type I include: as a viscosity modifier in the preparation of oil-based liquid and semi-solid formulations; in the preparation of suppositories, to reduce the sedimentation of suspended components and to improve the solidification process; and in the formulation of liquid and semi-solid fills for hard gelatin capsules.[7]
Fully hydrogenated vegetable oil products may also be used as alternatives to hard waxes in cosmetics and topical pharmaceutical formulations.

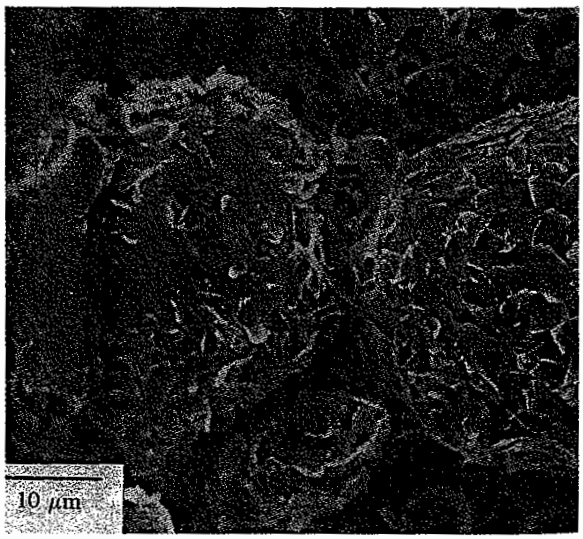
8. Description

Hydrogenated vegetable oil is a mixture of triglycerides of fatty acids. The two types which are defined in the USPNF XVII (Suppl 5) are characterised by their physical properties, *see* Section 9.
Hydrogenated vegetable oil, type I occurs in various forms, e.g. fine powder, flakes or pellets. The color of the material depends on the manufacturing process and the form. In general, the material is white to yellowish-white with the powder grades appearing more white-colored than the coarser grades.

SEM: 1
Excipient: Hydrogenated vegetable oil, type I (*Lubritab*)
Manufacturer: Edward Mendell Co Inc
Magnification: 100x
Voltage: 6 kV



SEM: 2
Excipient: Hydrogenated vegetable oil, type I (*Lubritab*)
Manufacturer: Edward Mendell Co Inc
Magnification: 1000x
Voltage: 6 kV



9. Pharmacopeial Specifications

Test	USPNF XVII (Suppl 5)	
	Type I	Type II
Melting range	57-70°C	20-50°C
Heavy metals	⩽ 10 ppm	⩽ 0.001%
Iodine value	0-5	55-80
Saponification value	175-205	185-200
Loss on drying	⩽ 0.1%	⩽ 0.1%
Acid value	⩽ 4.0	⩽ 4.0
Unsaponifiable matter	⩽ 0.8%	⩽ 0.8%

10. Typical Properties

Density (tapped): 0.57 g/cm^3 for *Lubritab*
Melting point: 61-66°C for *Lubritab*
Particle size distribution: mean size in range 50–70μm for *Lubritab*, by laser diffraction method.
Solubility: soluble in chloroform, petroleum spirit and hot propan-2-ol; practically insoluble in water.

11. Stability and Storage Conditions

Hydrogenated vegetable oil, type I is a stable material; typically it is assigned a three year shelf-life.
The bulk material should be stored in a well-closed container in a cool, dry, place.

12. Incompatibilities

Incompatible with strong oxidizing agents.

13. Method of Manufacture

Hydrogenated vegetable oil, type I is prepared from refined vegetable oils which are hydrogenated using a catalyst.

14. Safety

Hydrogenated vegetable oil, type I is used in food products and oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant excipient.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves, eye protection and a dust mask are recommended when handling fine powder grades.

16. Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral capsules and tablets, and suppositories). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Jpn and USPNF.

18. Related Substances

Hydrogenated Castor Oil; hydrogenated vegetable oil, type II; Medium Chain Triglycerides; Suppository Bases.

Hydrogenated vegetable oil, type II
Comments: hydrogenated vegetable oil, type II includes partially hydrogenated vegetable oils from different sources which have a wide range of applications. In general, type II materials have lower melting ranges and higher iodine values than type I materials. Many type II materials are prepared to meet specific customer requirements for use in cosmetics. Type II materials may also be used in the manufacture of suppositories. *See also* Section 9.

19. Comments

Products from different manufacturers may vary due to differences in the source of the vegetable oil used for hydrogenation.

20. Specific References

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UK: RC Moreton.

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