



Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

Edited by
Ainley Wade and Paul J Weller

American Pharmaceutical Association
Washington

1994

The Pharmaceutical Press
London

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Exhibit 1033
IPR2017-00807
ARGENTUM

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RS 201
E87 H36
1994
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A catalogue record for this book is available from the British Library.

Library of Congress Catalog Card Number: 94-79492.

Edited by
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International Standard Book Number (ISBN) in the UK: 0 85369 305 6
International Standard Book Number (ISBN) in the USA: 0 91730 66 8

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Typeset in Great Britain by Alden Multimedia, Northampton.
Printed and bound in Great Britain by

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requirement has not been clearly defined but is estimated to be 3-20 mg. Absorption from the gastrointestinal tract is dependent upon normal pancreatic function and the presence of bile. Tocopherols are widely distributed throughout the body with some ingested tocopherol metabolized in the liver; excretion of metabolites is via the urine or bile. Individuals with vitamin E deficiency are usually treated by oral administration of tocopherols although intramuscular and intravenous administration may sometimes be used. Tocopherols are well tolerated although large oral doses may cause diarrhea or other gastrointestinal disturbances. Topical application of tocopherols may cause contact dermatitis. The use of tocopherols as antioxidants in pharmaceuticals and food products is unlikely to pose any hazard to human health since the daily intake from such uses is small compared to the intake of naturally occurring tocopherols in the diet. The WHO has set an acceptable daily intake of tocopherol used as an antioxidant at 0.15-2 mg/kg body-weight.⁽⁵⁾

15. Handling Precautions

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

16. Regulatory Status

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

17. Pharmacopeias

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

Note that the nomenclature for tocopherols and tocopherol derivatives is confusing and many pharmacopeias do not specify clearly the isomer or form of the tocopherol.

18. Related Substances

d-Alpha tocopherol; *d*-alpha tocopheryl acetate; *dl*-alpha tocopheryl acetate; *d*-alpha tocopheryl acid succinate; *dl*-alpha tocopheryl acid succinate; beta tocopherol; delta tocopherol; gamma tocopherol; tocopherols excipient.

***d*-Alpha tocopherol:** C₂₉H₅₀O₂

Molecular weight: 430.69

CAS number: [59-02-9]

Synonyms: natural alpha tocopherol; (+)-(2*R*,4'*R*,8'*R*)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol; *d*-α-tocopherol; vitamin E.

Appearance: a practically odorless, clear, yellow or greenish-yellow colored viscous oil.

Solubility: practically insoluble in water; soluble in ethanol (95%). Miscible with acetone, chloroform, ether and vegetable oils.

Comments: this is the naturally occurring form of alpha tocopherol.

***d*-Alpha tocopheryl acetate:** C₃₁H₅₂O₃

Molecular weight: 472.73

CAS number: [58-95-7]

Synonyms: (+)-(2*R*,4'*R*,8'*R*)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chroman-1-yl acetate; *d*-α-tocopheryl acetate; vitamin E.

Appearance: a practically odorless, clear, yellow or greenish-yellow colored viscous oil which may solidify in the cold.

Melting point: 28°C

Solubility: practically insoluble in water; soluble in ethanol (95%). Miscible with acetone, chloroform, ether and vegetable oils.

Specific rotation [α]_D²⁵:

+0.25° (10% w/v solution in chloroform)

Comments: unstable to alkalis.

***dl*-Alpha tocopheryl acetate:** C₃₁H₅₂O₃

Molecular weight: 472.73

CAS number: [7695-91-2]

Synonyms: (±)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol acetate; (±)-(2*RS*,4'*RS*,8'*RS*)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chroman-1-yl acetate; (±)-α-tocopherol acetate; α-tocopheroli acetate; *all-rac*-α-tocopheryl acetate; *dl*-α-tocopheryl acetate; vitamin E.

Appearance: a practically odorless, clear, yellow or greenish-yellow viscous oil.

Density: 0.953 g/cm³

Melting point: -27.5°C

Refractive index: n_D²⁰ = 1.4950-1.4972

Solubility: practically insoluble in water; freely soluble in acetone, chloroform, ethanol, ether and vegetable oils; soluble in ethanol (95%).

Comments: unstable to alkali. However, unlike alpha tocopherol, the acetate is much less susceptible to the effects of air, light or ultraviolet light. Alpha tocopherol acetate concentrate, a powdered form of alpha tocopherol acetate, is described in some pharmacopeias, e.g. BP 1993. The concentrate may be prepared by either dispersing alpha tocopherol acetate in a suitable carrier such as acacia or gelatin, or by adsorbing alpha tocopherol acetate on silicic acid.

***d*-Alpha tocopheryl acid succinate:** C₃₃H₅₄O₅

Molecular weight: 530.8

CAS number: [4345-03-3]

Synonyms: (+)-α-tocopherol hydrogen succinate; *d*-α-tocopheryl acid succinate; vitamin E.

Appearance: a practically odorless white powder.

Melting point: 76-77°C

Solubility: practically insoluble in water; slightly soluble in alkaline solutions; soluble in acetone, ethanol (95%), ether and vegetable oils; very soluble in chloroform.

Comments: unstable to alkalis.

***dl*-Alpha tocopheryl acid succinate:** C₃₃H₅₄O₅

Molecular weight: 530.8

CAS number: [17407-37-3]

Synonyms: (±)-α-tocopherol hydrogen succinate; *dl*-α-tocopherol succinate; *dl*-α-tocopheryl acid succinate; vitamin E.

Appearance: a practically odorless white crystalline powder.

Solubility: practically insoluble in water; slightly soluble in alkaline solutions; soluble in acetone, ethanol (95%), ether and vegetable oils; very soluble in chloroform.

Comments: unstable to alkalis.

Beta tocopherol: C₂₈H₄₈O₂

Molecular weight: 416.66

CAS number: [148-03-8]

Synonyms: cumotocopherol; (±)-3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; 5,8-dimethyltocol; neotocopherol; *dl*-β-tocopherol; vitamin E; *p*-xylotocopherol.

Appearance: a pale yellow colored viscous oil.

Solubility: practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether and vegetable oils.

Specific rotation [α]_D²⁰: +6.37°

Benzalkonium Chloride

1. Nonproprietary Names

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

2. Synonyms

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

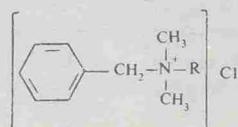
3. Chemical Name and CAS Registry Number

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

4. Empirical Formula Molecular Weight

The USPNF XVII describes benzalkonium chloride as a mixture of alkylbenzyltrimethylammonium 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.

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

Microorganism	MIC ($\mu\text{g/mL}$)
<i>Aerobacter aerogenes</i>	64
<i>Clostridium histolyticum</i>	5
<i>Clostridium oedematiens</i>	5
<i>Clostridium tetani</i>	5
<i>Clostridium welchii</i>	5
<i>Escherichia coli</i>	16
<i>Pneumococcus II</i>	5
<i>Proteus vulgaris</i>	64
<i>Pseudomonas aeruginosa</i>	30
<i>Salmonella enteritidis</i>	30
<i>Salmonella paratyphi</i>	16
<i>Salmonella typhosa</i>	4
<i>Shigella dysenteriae</i>	2
<i>Staphylococcus aureus</i>	1.25
<i>Streptococcus pyrogenes</i>	1.25
<i>Vibrio cholerae</i>	2

Density: $\approx 0.98 \text{ g/cm}^3$ at 20°C

Melting point: $\approx 40^\circ\text{C}$

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.

LD₅₀ (guinea pig, oral): 200 mg/kg⁽¹⁵⁾

LD₅₀ (mouse, IP): 10 mg/kg

LD₅₀ (mouse, IV): 10 mg/kg

LD₅₀ (mouse, oral): 175 mg/kg

LD₅₀ (mouse, SC): 64 mg/kg

LD₅₀ (rat, IP): 14.5 mg/kg

LD₅₀ (rat, IV): 13.9 mg/kg

LD₅₀ (rat, oral): 240 mg/kg

LD₅₀ (rat, SC): 400 mg/kg

LD₅₀ (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 USP NF. Also in BP Vet.

18. Related Substances

Benzethonium Chloride; Cetrimide.

19. Comments

—

20. Specific References

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22. Authors

USA: NM Vemuri.

Carboxymethylcellulose Sodium

1. Nonproprietary Names

BP: Carmellose sodium

PhEur: Carboxymethylcellulosum natricum

USP: Carboxymethylcellulose sodium

2. Synonyms

Akucell; *Blanose*; *Cekol*; cellulose gum; CMC sodium; *Courlose*; E466; *Nymcel*; SMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; *Tylose CB*.

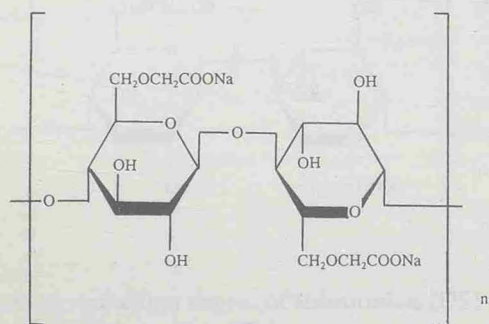
3. Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

4. Empirical Formula Molecular Weight

The USP XXII describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose. Typical molecular weight is 90 000-700 000.

5. Structural Formula



Structure shown with a degree of substitution (DS) of 1.0.

6. Functional Category

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

7. Applications in Pharmaceutical Formulation or Technology

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.⁽¹⁾ Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant,⁽²⁻⁴⁾ and to stabilize emulsions.⁽⁵⁾

Higher concentrations, usually 4-6%, of the medium viscosity grade is used to produce gels which can be used as the base for applications and pastes; glycerin is often included in such gels to prevent drying out. Carboxymethylcellulose sodium is additionally one of the main ingredients of self adhesive ostomy, wound care and dermatological patches where it is

used to absorb wound exudate or transepidermal water and sweat.

Carboxymethylcellulose sodium is also used in cosmetics, toiletries⁽⁶⁾ and food products.

Use	Concentration (%)
Emulsifying agent	0.25-1.0
Gel-forming agent	4.0-6.0
Injections	0.05-0.75
Oral solutions	0.1-1.0
Tablet binder	1.0-6.0

8. Description

Carboxymethylcellulose sodium occurs as a white to almost white colored, odorless, granular powder. *See also* Section 19.

9. Pharmacopeial Specifications

Test	PhEur 1986	USP XXII (Suppl 8)
Identification	+	+
pH (1% w/v solution)	6.0-8.0	6.5-8.5
Appearance of solution	+	—
Viscosity	+	+
Loss on drying	≤ 10.0%	≤ 10.0%
Heavy metals	≤ 20 ppm	≤ 0.004%
Chloride	≤ 0.25%	—
Sodium glycolate	≤ 0.4%	—
Sulfated ash	20.0-33.3%	—
Assay (of sodium)	6.5-10.8%	6.5-9.5%

SEM: 1

Excipient: Carboxymethylcellulose sodium

Manufacturer: Buckeye Cellulose Corp

Lot No.: 9247 AP

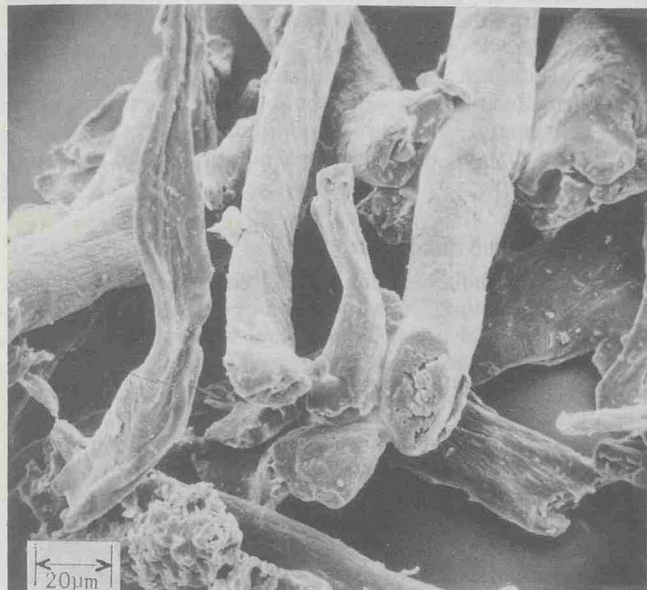
Magnification: 120x

Voltage: 10 kV

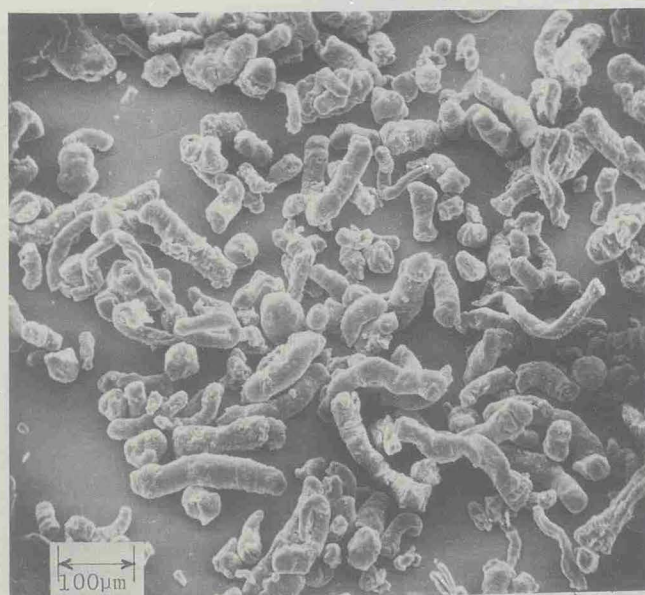


SEM: 2

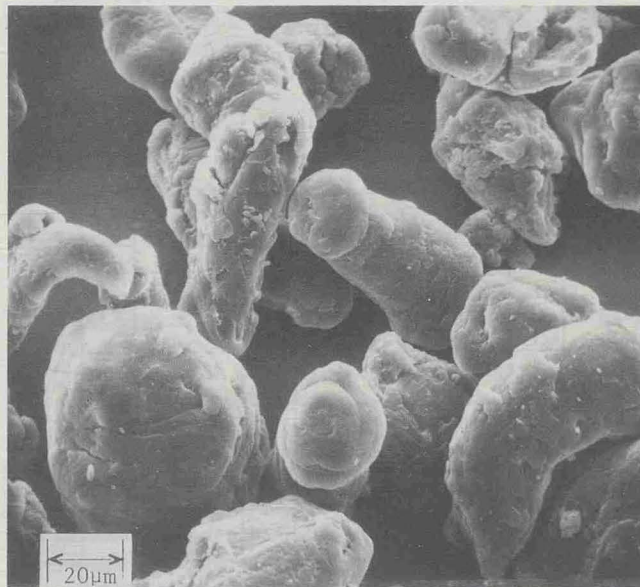
Excipient: Carboxymethylcellulose sodium
 Manufacturer: Buckeye Cellulose Corp
 Lot No.: 9247 AP
 Magnification: 600x
 Voltage: 10 kV

**SEM: 3**

Excipient: Carboxymethylcellulose sodium
 Manufacturer: Hercules Ltd
 Lot No.: 21 A-1 (44390)
 Magnification: 120x
 Voltage: 20 kV

**SEM: 4**

Excipient: Carboxymethylcellulose sodium
 Manufacturer: Hercules Ltd
 Lot No.: 21 A-1 (44390)
 Magnification: 600x
 Voltage: 20 kV

**10. Typical Properties**

Density (bulk): 0.75 g/cm³

Dissociation constant: $pK_a = 4.30$

Melting point: browns at approximately 227°C, chars at approximately 252°C.

Moisture content: typically, contains less than 10% of water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37°C at relative humidities of about 80%. *See also* HPE Data and Section 11.

Solubility: practically insoluble in acetone, ethanol, ether and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS). *See* Section 19.

Viscosity: various grades of carboxymethylcellulose sodium are commercially available which have differing aqueous viscosities; aqueous 1% w/v solutions with viscosities of 5-4000 mPas (5-4000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity.⁽⁶⁾ Viscosities of various grades of carboxymethylcellulose sodium are shown in Table I. *See also* Section 11.

Table I: Viscosity of aqueous carboxymethylcellulose sodium solutions at 25°C.

Grade	Concentration (% w/v)	Viscosity (mPa s)
Low viscosity	4	50-200
Medium viscosity	2	400-800
High viscosity	1	1500-3000

HPE Laboratory Project Data			
Method	Lab #	Results	
Moisture content	MC-10	10	8.5%
Moisture content	MC-7	5	6.5%
Moisture content	EMC-1	10	See Fig. 1.

Supplier: Hercules Ltd (Lot #76493).

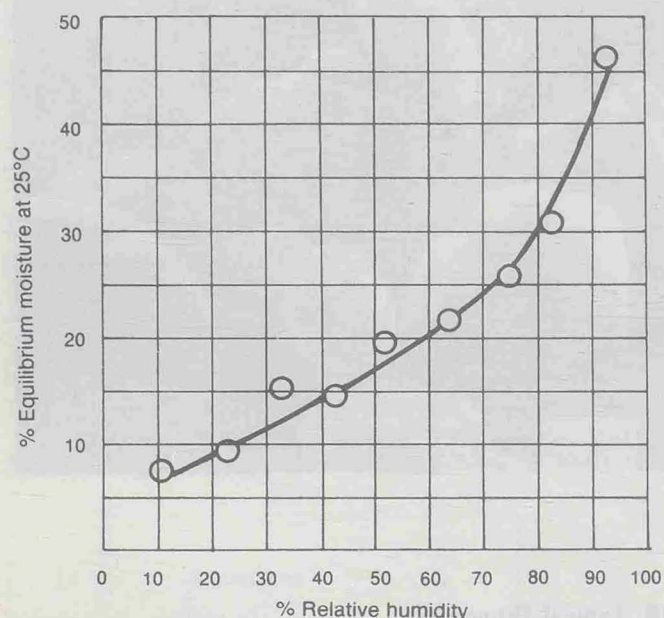


Fig. 1: Equilibrium moisture content of carboxymethylcellulose sodium.

11. Stability and Storage Conditions

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under high humidity conditions carboxymethylcellulose sodium can absorb a large quantity (> 50%) of water. In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time.⁽⁷⁾ Aqueous solutions are stable between pH 2-10; below pH 2 precipitation can occur while above pH 10 solution viscosity rapidly decreases. Generally, solutions exhibit maximum viscosity and stability at pH 7-9.

Carboxymethylcellulose sodium may be sterilized in the dry state by maintaining it at a temperature of 160°C for 1 hour. However, this process results in a significant decrease in viscosity and some deterioration in the properties of solutions prepared from the sterilized material.

Aqueous solutions may similarly be sterilized by heating although this also results in some reduction in viscosity. After autoclaving, viscosity is reduced by about 25% although this reduction is less marked than for solutions prepared from material sterilized in the dry state. The extent of the reduction is dependent on the molecular weight and degree of substitution; higher molecular weight grades generally undergo a greater percentage reduction in viscosity. Sterilization of solutions by gamma irradiation also results in a reduction in viscosity.

Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative.⁽⁸⁾

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

12. Incompatibilities

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury and zinc; it is also incompatible with xanthan gum. Precipitation can occur at pH < 2 and when mixed with ethanol (95%).

Carboxymethylcellulose sodium also forms complex coacervates with gelatin and pectin. It additionally forms a complex with collagen and is capable of precipitating certain positively charged proteins.

13. Method of Manufacture

Alkali cellulose is prepared by steeping cellulose obtained from wood pulp or cotton fibres in sodium hydroxide solution. The alkali cellulose is then reacted with sodium monochloroacetate to produce carboxymethylcellulose sodium. Sodium chloride and sodium glycolate are obtained as by-products of this etherification.

14. Safety

Carboxymethylcellulose sodium is used in oral, topical and some parenteral formulations. It is also widely used in cosmetics, toiletries and food products and is generally regarded as a nontoxic and nonirritant material. However, oral consumption of large amounts of carboxymethylcellulose sodium can have a laxative effect; therapeutically 4-10 g, in daily divided doses, of the medium and high viscosity grades of carboxymethylcellulose sodium have been used as bulk laxatives.

The WHO has not specified an acceptable daily intake for carboxymethylcellulose sodium as a food additive since the levels necessary to achieve a desired effect were not considered to be a hazard to health.⁽⁹⁾

In animal studies, subcutaneous administration of carboxymethylcellulose sodium has been found to cause inflammation and in some cases of repeated injection fibrosarcomas have been found at the injection site.⁽¹⁰⁾

Hypersensitivity and anaphylactic reactions have occurred in cattle and horses which have been attributed to carboxymethylcellulose sodium in parenteral formulations such as vaccines and penicillins.^(11,12)

LD₅₀ (guinea pig, oral): 16 g/kg⁽¹³⁾

LD₅₀ (mouse, oral): > 27 g/kg

LD₅₀ (rabbit, oral): > 27 g/kg

LD₅₀ (rat, oral): 27 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Carboxymethylcellulose sodium may be irritant to the eyes. Eye protection is recommended.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations, inhalations, intra-articular, intrabursal, intradermal, intraleisional, IM, intrasynovial and SC injections, oral capsules, drops, solutions, suspensions, syrups and tablets, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Braz, Cz, Egypt, Eur, Fr, Gr, Hung, Ind, It, Jpn, Mex, Neth, Nord, Rom, Swiss, US and Yug.

18. Related Substances

Carboxymethylcellulose Calcium; Carboxymethylcellulose sodium 12; Croscarmellose Sodium.

Carboxymethylcellulose sodium 12

Pharmacopeias: USPNF.

Comments: carboxymethylcellulose sodium 12 is the sodium salt of a polycarboxymethyl ether of cellulose. Its degree of substitution is between 1.15-1.45, corresponding to a sodium content, calculated on the dry basis, of 10.5-12.0%.

19. Comments

A number of grades of carboxymethylcellulose sodium are commercially available, the most frequently used grade having a degree of substitution (DS) of 0.7. The DS is defined as the average number of hydroxyl groups substituted per anhydroglucose unit and it is this which determines the aqueous solubility of the polymer.

Grades are typically classified as being either low, medium or high viscosity. The degree of substitution and the maximum viscosity of an aqueous solution of stated concentration should be indicated on any carboxymethylcellulose sodium labelling. Carboxymethylcellulose sodium has been reported to give false positive results in the LAL test for endotoxins.⁽¹⁴⁾

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22. Authors

UK: JE Fairbrother, DA Hollingsbee, PJ Weller.

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]

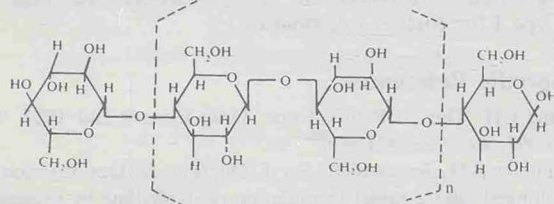
4. Empirical Formula

 $(C_6H_{10}O_5)_n$ Where $n \approx 220$.

Molecular Weight

 $\approx 36\,000$

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.

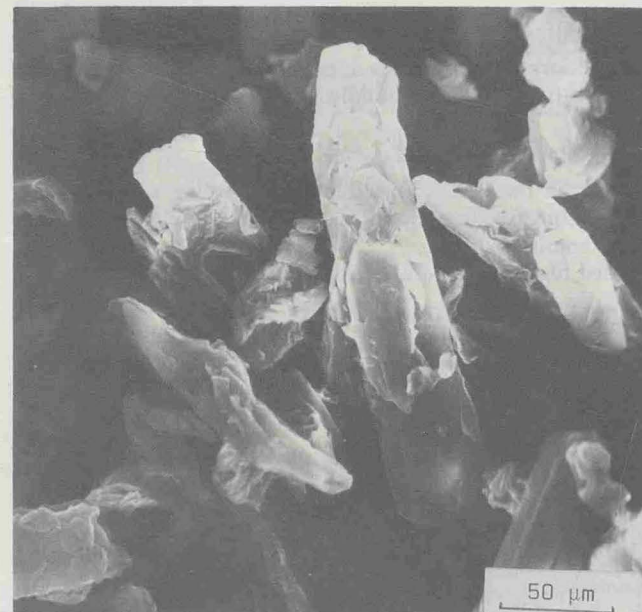
SEM: 1

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/cm³ for *Avicel PH 101*.⁽¹⁰⁾0.29 g/cm³ for *Emcocel 90M*.⁽⁹⁾

Density (tapped):

0.45 g/cm³ for *Avicel PH 101*.⁽¹⁰⁾0.35 g/cm³ 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.

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

Grade	Nominal mean particle size (μm)	Mesh size	Particle size analysis	Moisture content (%)
			Amount retained (%)	
<i>Avicel PH 101</i> ^(a)	50	60	≤ 1.0	≤ 5.0
		200	≤ 30.0	
<i>Avicel PH 102</i> ^(a)	100	60	≤ 8.0	≤ 5.0
		200	≥ 45.0	
<i>Avicel PH 103</i> ^(a)	50	60	≤ 1.0	≤ 3.0
		200	≤ 30.0	
<i>Avicel PH 105</i> ^(a)	20	400	≤ 1.0	≤ 5.0
<i>Avicel PH 112</i> ^(a)	100	60	≤ 8.0	≤ 1.5
		200	≥ 45.0	
<i>Avicel PH 200</i> ^(a)	180	60	≥ 19.0	≤ 5.0
		100	≥ 50.0	
<i>Emcocel 50M</i> ^(b)	51	60	≤ 0.25	≤ 5.0
		200	≤ 30.0	
<i>Emcocel 90M</i> ^(b)	91	60	≤ 8.0	≤ 5.0
		200	≥ 45.0	
<i>Vivacel 101</i> ^(c)	50	50	≥ 35.0	≤ 5.0
		150	≤ 10.0	
<i>Vivacel 102</i> ^(c)	100	50	≥ 50.0	≤ 5.0
		150	≤ 30.0	
<i>Vivacel 12</i> ^(c)	180	50	≥ 70.0	≤ 5.0
		500	≤ 1.0	
<i>Vivacel 20</i> ^(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 m²/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.

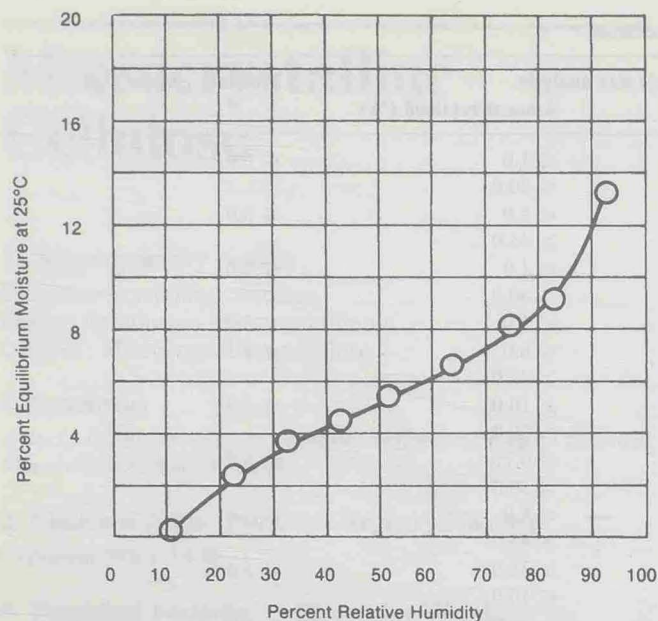


Fig. 1: Equilibrium moisture content of microcrystalline cellulose (Avicel PH 101, Lot #1929).

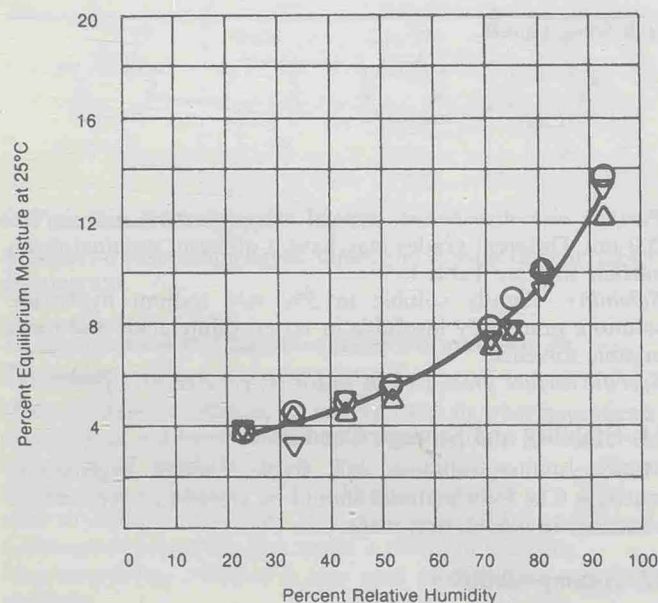


Fig. 2: Equilibrium moisture content of microcrystalline cellulose.

- 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 circumstances 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/m³ long-term (8-hour TWA) for total inhalable dust and 5 mg/m³ for respirable dust; short-term the limit for total inhalable dust has been set at 20 mg/m³.⁽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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22. Authors

USA: L Mathur.

Edetic Acid

1. Nonproprietary Names

USPNF: Edetic acid

2. Synonyms

Edathamil; EDTA; ethylenediaminetetraacetic acid; (ethylenedinitrilo)tetraacetic acid; *Questric acid* 5286; *Sequestrene AA*; *Versene Acid*.

3. Chemical Name and CAS Registry Numbers

N,N'-1,2-Ethanediyldis[*N*-(carboxymethyl)glycine]
[60-00-4]

4. Empirical Formula Molecular Weight

$C_{10}H_{16}N_2O_8$ 292.24

5. Structural Formula

$(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$

6. Functional Category

Chelating agent; therapeutic agent.

7. Applications in Pharmaceutical Formulation or Technology

Edetic acid and edetate salts are used in pharmaceutical formulations, cosmetics and foods as chelating agents; that is, they form stable water-soluble complexes (chelates) with alkaline earth and heavy metal ions. The chelated form has few of the properties of the free ion, and for this reason chelating agents are often described as 'removing' ions from solution; this process is also called sequestering. The stability of the metal-edetate complex depends on the metal ion involved and also on the pH. The calcium chelate is relatively weak and will preferentially chelate heavy metals, such as iron, copper and lead, with the release of calcium ions. For this reason, edetate calcium disodium is used therapeutically in cases of lead poisoning, *see also* Section 19.

Edetic acid and edetates are primarily used as antioxidant synergists by sequestering trace amounts of metal ions, particularly copper, iron and manganese, which might otherwise catalyze autoxidation reactions. Edetic acid and edetates may be used alone or in combination with true antioxidants, the usual concentration employed being in the range 0.005-0.1% w/v. Edetates have been used to stabilize: ascorbic acid; corticosteroids; epinephrine; folic acid; formaldehyde; gums and resins; hyaluronidase; hydrogen peroxide; oxytetracycline; penicillin; salicylic acid and unsaturated fatty acids. Essential oils may be washed with a 2% w/v solution of edetate to remove trace metal impurities.

Edetic acid and edetates possess some antimicrobial activity but are most frequently used in combination with other antimicrobial preservatives due to their synergistic effects. Many solutions used for the cleaning, storage and wetting of contact lenses thus contain disodium edetate. Typically, edetic acid and edetates are used in concentrations of 0.01-0.1% w/v as antimicrobial preservative synergists, *see* Section 10.

Edetic acid and disodium edetate may also be used as water softeners since they will chelate the calcium and magnesium ions present in hard water; edetate calcium disodium is not

effective. Many cosmetic and toiletry products, e.g. soaps, contain edetic acid as a water softener.

Disodium edetate is also used as an anticoagulant since it will chelate calcium and prevent the coagulation of blood *in vitro*. Concentrations of 0.1% w/v are used in small volumes for hematological testing and 0.3% w/v in transfusions.

8. Description

Edetic acid occurs as a white crystalline powder.

9. Pharmacopeial Specifications

Test	USPNF XVII
Identification	+
Residue on ignition	≤ 0.2%
Heavy metals	≤ 0.003%
Nitrilotriacetic acid	≤ 0.3%
Iron	≤ 0.005%
Assay	98.0-100.5%

10. Typical Properties

Acidity/alkalinity:

pH = 2.2 for a 0.2% w/v aqueous solution.

Antimicrobial activity: edetic acid has some antimicrobial activity against Gram-negative microorganisms, *Pseudomonas aeruginosa*, some yeasts and fungi, although this activity is insufficient for edetic acid to be used effectively as an antimicrobial preservative on its own.^(1,2) However, when used with other antimicrobial preservatives edetic acid demonstrates a marked synergistic effect in its antimicrobial activity. Edetic acid and edetates are therefore frequently used in combination with such preservatives as: benzalkonium chloride; bronopol; cetrimide; imidurea; parabens and phenols, especially chloroxylenol. Typically, edetic acid is used at a concentration of 0.1-0.15% w/v. In the presence of some divalent metal ions, such as Ca^{2+} or Mg^{2+} , the synergistic effect may be reduced or lost altogether. The addition of disodium edetate to phenylmercuric nitrate⁽³⁾ and thimerosal^(3,4) has also been reported to reduce the antimicrobial efficacy of the preservative. Edetic acid and iodine form a colorless addition compound which is bactericidal.

Dissociation constant:

$pK_{a1} = 2.00$;

$pK_{a2} = 2.67$;

$pK_{a3} = 6.16$;

$pK_{a4} = 10.26$.

Melting point: melts above 220°C, with decomposition.

Solubility: soluble in solutions of alkali hydroxides; soluble 1 in 500 of water.

11. Stability and Storage Conditions

Although edetic acid is fairly stable in the solid state, edetate salts are more stable than the free acid, which decarboxylates if heated above 150°C. Disodium edetate dihydrate loses water of crystallization when heated to 120°C. Edetate calcium disodium is slightly hygroscopic and should be protected from moisture.

Aqueous solutions of edetic acid or edetate salts may be sterilized by autoclaving, and should be stored in an alkali-free container.

Edetic acid and edetates should be stored in well-closed containers in a cool, dry, place.

12. Incompatibilities

Edetic acid and edetates are incompatible with strong oxidizing agents, strong bases and polyvalent metal ions such as copper, nickel and copper alloy.

Edetic acid and disodium edetate behave as weak acids, displacing carbon dioxide from carbonates and reacting with metals to form hydrogen.

Other incompatibilities include the inactivation of certain types of insulin due to the chelation of zinc, and the chelation of trace metals in TPN solutions following the addition of TPN additives stabilized with disodium edetate. Calcium disodium edetate has also been reported to be incompatible with amphotericin and with hydralazine hydrochloride in infusion fluids.

13. Method of Manufacture

Edetic acid may be prepared by the condensation of ethylenediamine with sodium monochloroacetate in the presence of sodium carbonate. An aqueous solution of the reactants is heated to about 90°C for ten hours, then cooled, and hydrochloric acid added to precipitate the edetic acid.

Edetic acid may also be prepared by the reaction of ethylenediamine with hydrogen cyanide and formaldehyde with subsequent hydrolysis of the tetranitrile, or under alkaline conditions with continuous extraction of ammonia.

See Section 18 for information on the preparation of edetate salts.

14. Safety

Edetic acid and edetates are widely used in topical, oral and parenteral pharmaceutical formulations. They are also extensively used in cosmetics and food products.

Edetic acid is generally regarded as an essentially nontoxic and nonirritant material although it has been associated with dose-related bronchoconstriction when used as a preservative in nebulizer solutions. It has therefore been recommended that nebulizer solutions for bronchodilation should not contain edetic acid.⁽⁵⁾

Edetates, particularly disodium edetate and edetate calcium disodium, are used in a greater number and variety of pharmaceutical formulations than the free acid. Both disodium edetate and edetate calcium disodium are poorly absorbed from the gastrointestinal tract and are associated with few adverse effects when used as excipients in pharmaceutical formulations.

Disodium edetate, trisodium edetate and edetic acid readily chelate calcium and can, in large doses, cause calcium depletion (hypocalcemia) if used over an extended period or if administered too rapidly by intravenous infusion. If used in preparations for the mouth, they can also leach calcium from the teeth. In contrast, edetate calcium disodium does not chelate calcium.

Edetate calcium disodium is nephrotoxic and should be used with caution in patients with renal impairment. Disodium edetate should similarly be used with caution in patients with renal impairment, tuberculosis and impaired cardiac function. The WHO has set an estimated acceptable daily intake for disodium edetate in foodstuffs at up to 2.5 mg/kg body-weight.⁽⁶⁾

See also Section 19.

LD₅₀ (mouse, IP): 0.25 g/kg⁽⁷⁾

LD₅₀ (mouse, oral): 0.03 g/kg

LD₅₀ (rat, IP): 0.397 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Edetic acid and edetates are mildly irritant to the skin, eyes and mucous membranes. Ingestion, inhalation and contact with the skin and eyes should therefore be avoided. Eye protection, gloves and a dust mask are recommended.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (otic, rectal and topical preparations). Included in nonparenteral medicines licensed in the UK.

See also Section 18.

17. Pharmacopeias

Rom and USPNF.

18. Related Substances

Dipotassium edetate; disodium edetate; edetate calcium disodium; sodium edetate; trisodium edetate.

Dipotassium edetate: C₁₀H₁₄K₂N₂O₈

Molecular weight: 368.46

CAS number: [2001-94-7]

Synonyms: dipotassium edathamil; dipotassium ethylenediaminetetraacetate; edathamil dipotassium; edetate dipotassium; edetic acid dipotassium salt; EDTA dipotassium; *N,N'*-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] dipotassium salt; ethylenebis(iminodiacetic acid) dipotassium salt; ethylenediaminetetraacetic acid dipotassium salt; (ethylenedinitrilo)tetraacetic acid dipotassium salt; tetracemate dipotassium.

Appearance: white crystalline powder.

Disodium edetate: C₁₀H₁₄N₂Na₂O₈

Molecular weight: 336.21

CAS number:

[139-33-3] for the anhydrous material;

[6381-92-6] for the dihydrate.

Synonyms: disodium edathamil; disodium ethylenediaminetetraacetate; edathamil disodium; edetate disodium; edetic acid disodium salt; EDTA disodium; *N,N'*-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] disodium salt; ethylenebis(iminodiacetic acid) disodium salt; ethylenediaminetetraacetic acid disodium salt; (ethylenedinitrilo)tetraacetic acid disodium salt; *Questal Di*; *Sequestrene NA2*; tetracemate disodium; *Versene disodium*.

Appearance: odorless white crystalline powder with a slightly acid taste.

Pharmacopeias: Belg, Br, Eur, Fr, Gr, Hung, Ind, It, Jpn, Mex, Neth, Nord, Port, Swiss, Turk, US and Yug.

Acidity/alkalinity: pH = 4.3-4.7 for a 1% w/v solution in carbon dioxide free water.

Freezing point depression:

0.14°C (1% w/v aqueous solution)

Melting point:

decomposition at 252°C for the dihydrate.

Refractive index:

1.335 for a 1% w/v aqueous solution.

Solubility: practically insoluble in chloroform and ether; slightly soluble in ethanol (95%); soluble 1 in 11 of water.

Specific gravity:

1.004 for a 1% w/v aqueous solution.

Viscosity (kinematic): 1.03 mm²/s (1 cSt) for a 1% w/v aqueous solution.

Method of manufacture: disodium edetate may be prepared by the reaction of edetic acid and sodium hydroxide.

Safety: see also Section 14.

LD₅₀ (mouse, IP): 0.26 g/kg⁽⁷⁾

LD₅₀ (mouse, IV): 0.056 g/kg

LD₅₀ (mouse, oral): 2.05 g/kg

LD₅₀ (rabbit, IV): 0.047 g/kg

LD₅₀ (rabbit, oral): 2.3 g/kg

LD₅₀ (rat, oral): 2 g/kg

LD₅₀ (rat, SC): 3.735 g/kg

Regulatory status: GRAS listed. Included in the FDA Inactive Ingredients Guide (inhalations, injections, ophthalmic preparations, oral capsules, solutions, suspensions, syrups and tablets, rectal, topical and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

Comments: in pharmaceutical formulations disodium edetate is used as a chelating agent typically at concentrations between 0.005-0.1% w/v.

Edetate calcium disodium: C₁₀H₁₂CaN₂Na₂O₈

Molecular weight: 374.28

CAS number:

[62-33-9] for the anhydrous material;

[23411-34-9] for the dihydrate.

Synonyms: 385; calcium disodium edetate; calcium disodium ethylenediaminetetraacetate; calcium disodium (ethylenedinitrilo)tetraacetate; edathamil calcium disodium; edetic acid calcium disodium salt; [[N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycinat o]](4-)-N,N',O,O',-O^N,-O^{N'}]calcate(2-)disodium; EDTA calcium; ethylenediaminetetraacetic acid calcium disodium chelate; [(ethylenedinitrilo)tetraacetato] calcate(2-)disodium; sodium calciumedetate; *Versene CA*.

Appearance: white or creamy-white colored, slightly hygroscopic, crystalline powder or granules; odorless, or with a slight odor; tasteless, or with a faint saline taste.

Pharmacopeias: Belg, Br, Cz, Egypt, Eur, Fr, Gr, It, Mex, Neth, Nord, Port, Swiss, Turk, US and Yug. Also in BP Vet. Some pharmacopeias specify that edetate calcium disodium is the dihydrate, others that it is the anhydrous material. The USP XXII specifies that edetate calcium disodium is a mixture of the dihydrate and trihydrate but that the dihydrate predominates.

Acidity/alkalinity:

pH = 4-5 for a 1% w/v aqueous solution.

Density (bulk): 0.69 g/cm³

Solubility: practically insoluble in chloroform, ether and other organic solvents; very slightly soluble in ethanol (95%); soluble 1 in 2 of water.

Method of manufacture: edetate calcium disodium may be prepared by the addition of calcium carbonate to a solution of disodium edetate.

Safety: see also Section 14.

LD₅₀ (dog, oral): 12 g/kg⁽⁷⁾

LD₅₀ (mouse, IP): 4.5 g/kg

LD₅₀ (mouse, oral): 10 g/kg

LD₅₀ (rabbit, IP): 6 g/kg

LD₅₀ (rabbit, oral): 7 g/kg

LD₅₀ (rat, IP): 3.85 g/kg

LD₅₀ (rat, IV): 3.0 g/kg

LD₅₀ (rat, oral): 10 g/kg

Regulatory status: GRAS listed. Accepted for use as a food additive in the UK. Included in the FDA Inactive Ingredients Guide (injections, oral capsules, solutions, suspensions, syrups and tablets).

Comments: used in pharmaceutical formulations as a chelating agent in concentrations between 0.01-0.1% w/v. Usually

edetate calcium disodium is used in pharmaceutical formulations in preference to disodium edetate or sodium edetate to prevent calcium depletion occurring in the body. In food products, edetate calcium disodium may also be used in flavors and as a color retention agent. Edetate calcium disodium occurs as the dihydrate, trihydrate and anhydrous material.

Sodium edetate: C₁₀H₁₂N₂Na₄O₈

Molecular weight: 380.20

CAS number: [64-02-8]

Synonyms: edetate sodium; edetic acid tetrasodium salt; EDTA tetrasodium; N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycine] tetrasodium salt; ethylenebis(iminodiacetic acid) tetrasodium salt; ethylenediaminetetraacetic acid tetrasodium salt; (ethylenedinitrilo)tetraacetic acid tetrasodium salt; *Sequestrene NA4*; tetracemate tetrasodium; tetracemin; tetrasodium edetate; tetrasodium ethylenebis(iminodiacetate); tetrasodium ethylenediaminetetraacetate; *Versene*.

Appearance: white crystalline powder.

Acidity/alkalinity:

pH = 11.3 for a 1% w/v aqueous solution.

Melting point: > 300°C

Solubility: soluble 1 in 1 of water.

Safety: see also Section 14.

LD₅₀ (mouse, IP): 0.33 g/kg⁽⁷⁾

Regulatory status: included in the FDA Inactive Ingredients Guide (inhalations, injections, ophthalmic preparations, oral capsules and tablets, and topical preparations).

Comments: sodium edetate reacts with most divalent and trivalent metallic ions to form soluble metal chelates and is used in pharmaceutical formulations in concentrations between 0.01-0.1% w/v.

Trisodium edetate: C₁₀H₁₂N₂Na₃O₈

Molecular weight: 358.20

CAS number: [150-38-9]

Synonyms: edetate trisodium; edetic acid trisodium salt; EDTA trisodium; N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycine] trisodium salt; ethylenediaminetetraacetic acid trisodium salt; (ethylenedinitrilo)tetraacetic acid trisodium salt; *Sequestrene NA3*; trisodium ethylenediaminetetraacetate; *Versene-9*.

Appearance: white crystalline powder.

Acidity/alkalinity:

pH = 9.3 for a 1% w/v aqueous solution.

Melting point: > 300°C

Method of manufacture: trisodium edetate may be prepared by adding a solution of sodium hydroxide to disodium edetate.

Safety: see also Section 14.

LD₅₀ (mouse, IP): 0.3 g/kg⁽⁷⁾

LD₅₀ (mouse, oral): 2.15 g/kg

LD₅₀ (rat, oral): 2.15 g/kg

Regulatory status: included in the FDA Inactive Ingredients Guide (topical preparations).

Comments: more soluble in water than either the disodium salt or the free acid. Trisodium edetate also occurs as the monohydrate and is used in pharmaceutical formulations as a chelating agent.

Other salts of edetic acid which are commercially available include diammonium, dimagnesium, dipotassium, ferrous sodium and magnesium disodium edetates.

19. Comments

Therapeutically, a dose of 50 mg/kg body-weight of disodium edetate, as a slow infusion over a 24 hour period, with a maximum daily dose of 3 g, has been used as a treatment for hypercalcemia. For the treatment of lead poisoning, a dose of

60-80 mg/kg of edetate calcium disodium, as a slow infusion in two daily doses, for 5 days, has been used.

20. Specific References

1. Richards RME, Cavill RH. Electron microscope study of effect of benzalkonium chloride and edetate disodium on cell envelope of *Pseudomonas aeruginosa*. *J Pharm Sci* 1976; 65: 76-80.
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21. General References

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22. Authors

UK: RS Cook; N Yussuf.



Edetic acid is a hexadentate chelating agent. It is used in the pharmaceutical industry for the treatment of heavy metal poisoning. It is also used in the food industry as a preservative and in the textile industry for dyeing and finishing.

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Property	Value
Molecular weight	292.24
Boiling point	265°C
Melting point	102°C
Density	1.026 g/cm³
Refractive index	1.37
Viscosity	1.026 cP
Surface tension	72.75 dyne/cm
Heat of fusion	10.5 kJ/mol
Heat of vaporization	40.7 kJ/mol
Heat of combustion	-1367 kJ/mol
Standard enthalpy of formation	-1367 kJ/mol
Standard enthalpy of combustion	-1367 kJ/mol
Standard Gibbs free energy of formation	-1367 kJ/mol
Standard Gibbs free energy of combustion	-1367 kJ/mol
Standard entropy of formation	136.7 J/mol·K
Standard entropy of combustion	136.7 J/mol·K
Standard enthalpy of formation (gas)	-1367 kJ/mol
Standard enthalpy of combustion (gas)	-1367 kJ/mol
Standard Gibbs free energy of formation (gas)	-1367 kJ/mol
Standard Gibbs free energy of combustion (gas)	-1367 kJ/mol
Standard entropy of formation (gas)	136.7 J/mol·K
Standard entropy of combustion (gas)	136.7 J/mol·K

Glycerin

1. Nonproprietary Names

BP: Glycerol

PhEur: Glycerolum

USP: Glycerin

2. Synonyms

Croderol; E422; glycerine; *Glycon G-100*; *Kemstrene*; *Pricerine*; 1,2,3-propanetriol; trihydroxypropane glycerol.

3. Chemical Name and CAS Registry Number

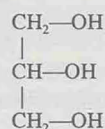
Propane-1,2,3-triol [56-81-5]

4. Empirical Formula Molecular Weight

 $C_3H_8O_3$

92.09

5. Structural Formula



6. Functional Category

Antimicrobial preservative; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.

7. Applications in Pharmaceutical Formulation or Technology

Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical and parenteral preparations. It is also used in cosmetics and as a food additive.

In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. In parenteral formulations glycerin is mainly used as a solvent,⁽¹⁾ whilst in oral solutions glycerin is used as a sweetening agent, antimicrobial preservative and viscosity-increasing agent. Glycerin is also used as a plasticizer of gelatin in the production of soft gelatin capsules and gelatin suppositories. Glycerin is additionally employed as a therapeutic agent in a variety of clinical applications.

Use	Concentration (%)
Antimicrobial preservative	> 20
Emollient	up to 30
Humectant	up to 30
Ophthalmic formulations	0.5-3.0
Plasticizer in tablet film coating	variable
Solvent for parenteral formulations	up to 50
Sweetening agent in alcoholic elixirs	up to 20

8. Description

Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

9. Pharmacopeial Specifications

Test	PhEur 1991	USP XXII (Suppl 7)
Identification	+	+
Specific gravity	—	≥ 1.249
Color	—	+
Appearance of solution	+	—
Acidity or alkalinity	+	—
Refractive index	1.470-1.475	—
Residue on ignition	—	≤ 0.01%
Sulfated ash	≤ 0.01%	—
Chloride	≤ 10 ppm	≤ 0.001%
Sulfate	—	≤ 0.002%
Arsenic	—	≤ 1.5 ppm
Heavy metals	≤ 5 ppm	≤ 5 ppm
Chlorinated compounds (as Cl)	+	≤ 0.003%
Organic volatile impurities	—	+
Aldehydes	+	—
Fatty acids and esters	+	+
Sugars	+	—
Water	≤ 2.0%	—
Assay	98.0-101.0%	95.0-101.0%

10. Typical Properties

Boiling point: 290°C (with decomposition)

Density:

1.2656 g/cm³ at 15°C;

1.2636 g/cm³ at 20°C;

1.2620 g/cm³ at 25°C.

Flash point: 176°C (open cup)

Freezing point:

Concentration of aqueous glycerin solution (% w/w)	Freezing point (°C)
10	-1.6
20	-4.8
30	-9.5
40	-15.4
50	-23
60	-34.7
66.7	-46.5
80	-20.3
90	-1.6

Hygroscopicity: hygroscopic.

Melting point: 17.8°C

Osmolarity: a 2.6% v/v aqueous solution is iso-osmotic with serum.

Refractive index:

$n_D^{15} = 1.4758$;

$n_D^{20} = 1.4746$;

$n_D^{25} = 1.4730$.

Solubility:

Solvent	Solubility at 20°C
Acetone	slightly soluble
Benzene	practically insoluble
Chloroform	practically insoluble
Ethanol (95%)	miscible
Ether	1 in 500
Ethyl acetate	1 in 11
Methanol	miscible
Oils	practically insoluble
Water	miscible

Specific gravity:

Concentration of aqueous glycerin solution (% w/w)	Specific gravity at 20°C
10	1.024
20	1.049
30	1.075
40	1.101
50	1.128
60	1.156

Surface tension:

63.4 mN/m (63.4 dynes/cm) at 20°C.

Vapor density (relative): 3.17 (air = 1)

Viscosity (dynamic): see also HPE Data.

Concentration of aqueous glycerin solution (% w/w)	Viscosity at 20°C (mPa s)
5	1.143
10	1.311
25	2.095
50	6.05
60	10.96
70	22.94
83	111

HPE Laboratory Project Data

	Method	Lab #	Results
Viscosity	VIS-1	27	515 ± 19 mPa s ^(a)
Viscosity	VIS-1	27	1034 ± 19 mPa s ^(b)

Supplier: a. Star; b. Superol.

11. Stability and Storage Conditions

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions, but decomposes on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol and propylene glycol are chemically stable.

Glycerin may crystallize if stored at low temperatures; the crystals do not melt until raised to 20°C.

Glycerin should be stored in an airtight container, in a cool, dry, place.

12. Incompatibilities

Glycerin may explode if mixed with strong oxidizing agents, such as chromium trioxide, potassium chlorate or potassium permanganate. In dilute solution, the reaction proceeds at a slower rate, with several oxidation products being formed. Black discoloration of glycerin occurs, in the presence of light, on contact with zinc oxide or basic bismuth nitrate.

An iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates and tannin.

Glycerin forms a boric acid complex, glyceroboric acid, which is a stronger acid than boric acid.

13. Method of Manufacture

Glycerin is mainly obtained from oils and fats as a by-product in the manufacture of soaps and fatty acids. It may also be obtained from natural sources by fermentation of, for

example, sugar beet molasses in the presence of large quantities of sodium sulfite. Synthetically, glycerin may be prepared by the chlorination and saponification of propylene.

14. Safety

Glycerin occurs naturally in animal and vegetable fats and oils that are consumed as part of a normal diet. Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or is used in the synthesis of body fats.

Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, parenteral and topical preparations. Adverse effects are mainly due to the dehydrating properties of glycerin.

Oral doses are demulcent and mildly laxative in action. Large doses may produce headache, thirst, nausea and hyperglycemia. The therapeutic parenteral administration of very large glycerin doses, 70-80 g over 30-60 minutes in adults to reduce cranial pressure, may induce hemolysis, hemoglobinuria and renal failure.⁽²⁾ Slower administration has no deleterious effects.⁽³⁾

Glycerin may also be used orally in doses of 1.0-1.5 g/kg body-weight to reduce intraocular pressure.

When used as an excipient or food additive, glycerin is not usually associated with any adverse effects and is generally regarded as a nontoxic and nonirritant material.

LD₅₀ (guinea pig, oral): 7.75 g/kg⁽⁴⁾

LD₅₀ (mouse, IP): 8.98 g/kg

LD₅₀ (mouse, IV): 6.2 g/kg

LD₅₀ (mouse, oral): 4.1 g/kg

LD₅₀ (mouse, SC): 0.09 g/kg

LD₅₀ (rat, IP): 8.3 g/kg

LD₅₀ (rat, IV): 5.6 g/kg

LD₅₀ (rat, oral): 12.6 g/kg

LD₅₀ (rat, SC): 0.1 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the recommended long-term (8-hour TWA) exposure limit for glycerin mist is 10 mg/m³.⁽⁵⁾

Glycerin is combustible and may react explosively with strong oxidizing agents, see Section 12.

16. Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, injections, nasal, ophthalmic, oral capsules, solutions, suspensions and tablets, otic, rectal, topical, transdermal and vaginal preparations). Included in nonparenteral and parenteral 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, Swiss, Turk and US. Also in BP Vet.

Glycerin (85%) is also included in the following pharmacopeias: Br; Eur; Fr; Gr; It; Neth; Port; Swiss and Yug. Also in BP Vet.

18. Related Substances

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19. Comments

20. Specific References

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22. Authors

USA: JC Price.

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*; *Pharmaccoat*.

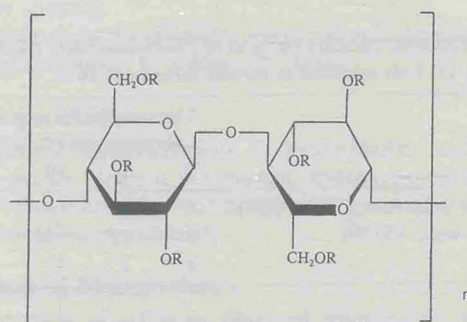
3. Chemical Name and CAS Registry Number

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 (OCH₃). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH₂CHOHCH₃), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

5. Structural Formula



Where R is H, CH₃ or [CH₃CH(OH)CH₂].

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:

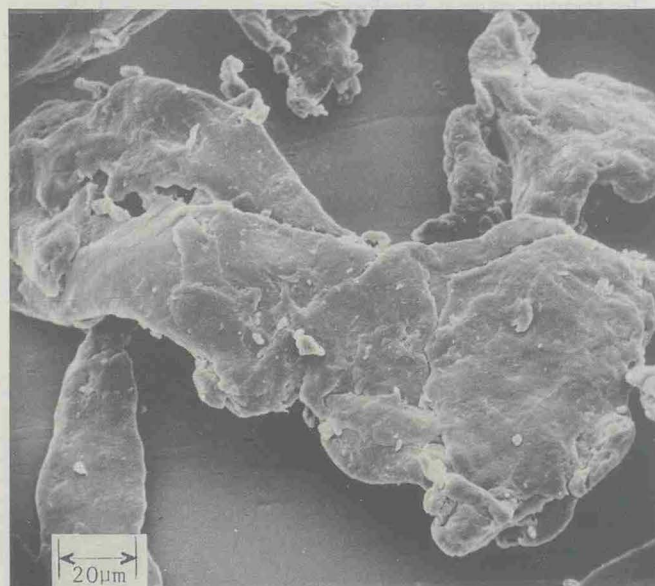
pH = 5.5-8.0 for a 1% w/w aqueous solution.

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/cm³ 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	<i>See Fig. 1.</i> ^(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.

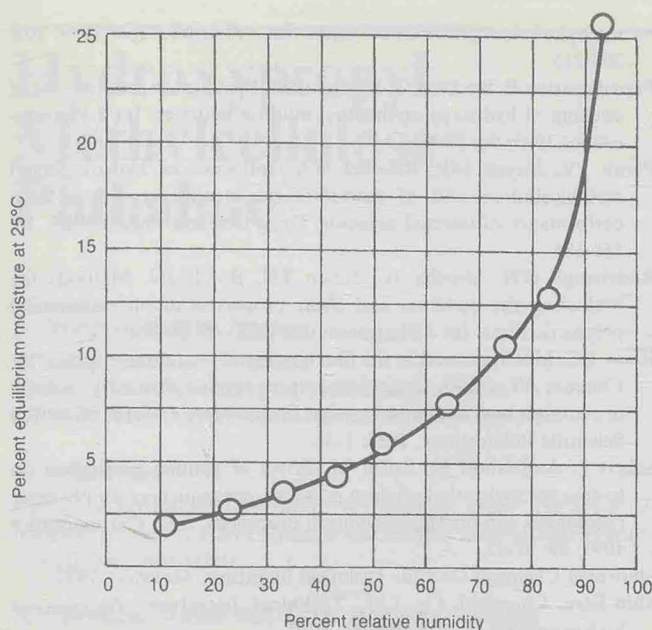


Fig. 1: Equilibrium moisture content of hydroxypropyl methylcellulose, Methocel E15 (Dow Chemical Company, Lot No.: QP0502-801-E).

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⁾

LD₅₀ (mouse, IP): 5 g/kg⁽¹⁶⁾

LD₅₀ (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.

20. Specific References

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- Wan LSC, Heng PWS, Wong LF. The effect of hydroxypropylmethylcellulose on water penetration into a matrix system. *Int J Pharmaceutics* 1991; 73: 111-116.

22. Authors

USA: RJ Harwood, JL Johnson.

Phenylethyl Alcohol

1. Nonproprietary Names

USP: Phenylethyl alcohol

2. Synonyms

Benzeneethanol; benzyl carbinol; benzylmethanol;
 β -hydroxyethyl benzene; phenethanol; β -phenylethyl alcohol;
 2-phenylethyl alcohol; phenylethanol; PEA.

3. Chemical Name and CAS Registry Number

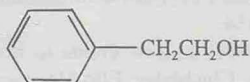
2-Phenylethanol [60-12-8]

4. Empirical Formula Molecular Weight

C₈H₁₀O

122.17

5. Structural Formula



6. Functional Category

Antimicrobial preservative.

7. Applications in Pharmaceutical Formulation or Technology

Phenylethyl alcohol is used as an antimicrobial preservative in parenteral and ophthalmic formulations at 0.25-0.5% v/v concentration; it is generally used in combination with other preservatives.^(1,2) Phenylethyl alcohol has also been used on its own as an antimicrobial preservative at concentrations up to 1% v/v in topical preparations. At this concentration, mycoplasmas are inactivated within 20 minutes although enveloped viruses are resistant.⁽³⁾ Phenylethyl alcohol is also used in flavors and as a perfumery component, especially in rose perfumes.

8. Description

Phenylethyl alcohol is a clear, colorless liquid with an odor of rose oil. It has a burning taste which irritates and then anesthetizes mucous membranes.

9. Pharmacopeial Specifications

Test	USP XXII
Identification	+
Specific gravity	1.017-1.020
Refractive index	1.531-1.534
Residue on ignition	≤ 0.005%
Chlorinated compounds	+
Aldehyde	+

10. Typical Properties

Antimicrobial activity: phenylethyl alcohol has moderate antimicrobial activity although it is relatively slow acting; it is not sufficiently active to be used alone.⁽⁴⁾ Greatest activity occurs at less than pH 5; it is inactive above pH 8. Synergistic

effects have been reported when combined with benzalkonium chloride, chlorhexidine gluconate or diacetate, polymyxin B sulfate and phenylmercuric nitrate.⁽⁵⁻⁹⁾ With either benzalkonium chloride or chlorhexidine, synergistic effects were observed against *Pseudomonas aeruginosa* and apparently additive effects against Gram-positive organisms. With phenylmercuric nitrate, the effect was additive against *Pseudomonas aeruginosa*. Additive effects against *Pseudomonas cepacia* in combination with either benzalkonium chloride or chlorhexidine have also been reported.⁽¹⁰⁾ See also Section 12.

Bacteria: fair activity against Gram-positive bacteria; for *Staphylococcus aureus*, the minimum inhibitory concentration (MIC) may be more than 5 mg/mL. Greater activity is shown against Gram-negative organisms.⁽¹¹⁾ Typical MIC values are: *Salmonella typhi* 1.25 mg/mL; *Pseudomonas aeruginosa* 2.5 mg/mL; *Escherichia coli* 5.0 mg/mL.

Fungi: poor activity against molds and fungi.

Spores: inactive, e.g. at 0.6% v/v concentration, reported to be ineffective against spores of *Bacillus stearothermophilus* at 100°C for 30 minutes.

Boiling point: 219-221°C

Melting point: -27°C

Partition coefficients:

Chloroform: water = 15.2;

Heptane: water = 0.58;

Octanol: water = 21.5.

Flash point: 102°C (open cup)

Solubility:

Solvent	Solubility at 20°C
Benzyl benzoate	very soluble
Chloroform	very soluble
Diethyl phthalate	very soluble
Ethanol (95%)	very soluble
Ether	very soluble
Fixed oils	very soluble
Glycerin	very soluble
Mineral oil	slightly soluble
Propylene glycol	very soluble
Water	1 in 60

11. Stability and Storage Conditions

Phenylethyl alcohol is stable in bulk, but is volatile and sensitive to light and oxidizing agents. It is reasonably stable in both acidic and alkaline solutions. Aqueous solutions may be sterilized by autoclaving. If stored in low density polyethylene containers, phenylethyl alcohol may be absorbed by the containers. Losses to polypropylene containers have been reported to be insignificant over 12 weeks at 30°C. Sorption to rubber closures is generally small.

The bulk material should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities

Incompatible with oxidizing agents and protein, e.g. serum. Phenylethyl alcohol is partially inactivated by polysorbates, although this is not as great as the reduction in antimicrobial activity that occurs with parabens and polysorbates.⁽¹²⁾

13. Method of Manufacture

Phenylethyl alcohol is prepared either by reduction of ethyl phenylacetate with sodium in absolute alcohol; hydrogenation

of phenylacetaldehyde in the presence of a nickel catalyst; or by addition of ethylene oxide or ethylene chlorohydrin to phenylmagnesium bromide, followed by hydrolysis. Phenylethyl alcohol also occurs naturally in a number of essential oils, especially rose oil.

14. Safety

Phenylethyl alcohol is used as an antimicrobial preservative in parenteral, topical and ophthalmic preparations and is generally regarded as a nontoxic and nonirritant material. However, at the concentration used to preserve eye-drops (about 0.5% v/v) or above, eye irritation may occur.⁽¹³⁾

LD₅₀ (mouse, IP): 0.2 g/kg⁽¹⁴⁾

LD₅₀ (mouse, oral): 0.8 g/kg

LD₅₀ (rabbit, skin): 0.79 g/kg

LD₅₀ (rat, oral): 1.79 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 (nasal, ophthalmic, otic, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Nord and US.

18. Related Substances

19. Comments

20. Specific References

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2. Heller WM, Foss NE, Shay DE and Ichniowski CT. Preservatives in solutions. J Am Pharm Assoc (Pract Pharm) 1955; 16: 29-36.

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4. Kohn SR, Gershenfeld L, Barr M. Effectiveness of antibacterial agents presently employed in ophthalmic preparations as preservatives against *Pseudomonas aeruginosa*. J Pharm Sci 1963; 52: 967-974.
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21. General References

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22. Authors

UK: MC Allwood, R Baird.

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]

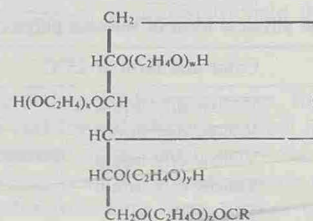
4. Empirical Formula Molecular Weight

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

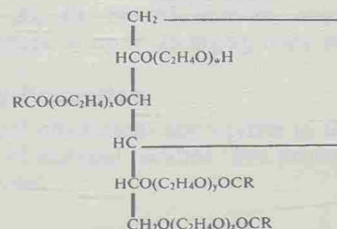
Table II: Empirical formula and molecular weight of selected polysorbates.

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)

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.

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 (%)	Saponification 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.

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

20. Specific References

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21. General References

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22. Authors

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