HANDBOOK OF PHARMACEUTICAL EXCIPIENTS

THIRD EDITION

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EDITED BY

ARTHUR H. KIBBE

Handbook of
PHARMACEUTICAL EXCIPIENTS

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Third Edition

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dl-Alpha Tocopheryl Acetate
d-Alpha Tocopheryl Acid Succinate
dl-Alpha Tocopheryl Acid Succinate
Amylopectin
α-Amylose
Anhydrous Citric Acid
Anhydrous Sodium Citrate
Anhydrous Sodium Propionate
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Dextrose Anhydrous
Diazolidinyl Urea
Dibasic Sodium Phosphate
Dibutyl Phthalate
Dilute Alcohol
Dilute Hydrochloric Acid
Dimethyl-β-Cyclodextrin
Dimethyl Phthalate
Dipotassium Edetate
Disodium Edetate
Docusate Calcium
Docusate Potassium
Dodecyl Gallate
Dodecyltrimethylammonium Bromide
Edetate Calcium Disodium
Eglumine
Ethyl Gallate
Ethylparaben Potassium
Ethylparaben Sodium
Fructose Liquid
Fructose Milled
Fructose Pyrogen-Free
Gamma-Tocopherol
Glyceryl Behenate
Hard Water
Hexadecyltrimethylammonium Bromide
High Fructose Syrup
Hydrogenated Vegetable Oil, Type II
2-Hydroxyethyl-β-Cyclodextrin
2-Hydroxypropyl-β-Cyclodextrin
Indigo Carmine
Invert Sugar
Iron Oxides
Liquified Phenol
Magnesium Carbonate Anhydrous
Magnesium Carbonate Hydroxide
Magnesium Lauryl Sulfate
Magnesium Silicate
Magnesium Trisilicate Anhydrous
D-Malic Acid
L-Malic Acid
d-Menthol
l-Menthol
Methyl Methacrylate
Methyl Oleate
Methylparaben Potassium
Methylparaben Sodium
Microcrystalline Cellulose and Carboxymethylcellulose Sodium
Monobasic Potassium Phosphate
Montmorillonite
Normal Magnesium Carbonate
Octyl Gallate
Palmitic Acid
Pharmaceutical Glaze
Phenoxypropanol
Polacrilin
Poly (Methyl Methacrylate)
Potassium Alginate
Potassium Benzoate
Potassium Bicarbonate
Potassium Bisulfite
Potassium Citrate Anhydrous
Potassium Metabisulfite
Potassium Propionate
Powdered Fructose
Propan-1-ol
Propionic Acid
(*S*)-Propylene Carbonate
Propylparaben Potassium
Propylparaben Sodium
Purified Stearic Acid
Rapeseed Oil
Saccharin Ammonium
Saccharin Calcium
Saponite

Self-emulsifying Glyceryl Monostearate
Shellolic Acid
Sodium Bisulfite
Sodium Edetate
Sodium Sorbate
Sodium Sulfite
Soft Water
Sorbitol Solution 70%
Spermaceti Wax
Sterile Water for Inhalation
Sterile Water for Injection
Sterile Water for Irrigation
Sugartab
Sunset Yellow FCF
Synthetic Paraffin
D-(-)-Tartaric Acid
DL-(±)-Tartaric Acid
Tartrazine
Theobroma Oil
Tocopherols Excipients
Tribasic Sodium Phosphate
Tributyl Citrate
Trimethyl-β-Cyclodextrin
Trimethyltetradecylammonium Bromide
Trisodium Edetate
Water for Injection
White Petrolatum
Zinc Propionate

Benzalkonium Chloride

1. Nonproprietary Names

BP: Benzalkonium chloride
JP: Benzalkonium chloride
PhEur: Benzalkonii chloridum
USP: Benzalkonium chloride

2. Synonyms

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

3. Chemical Name and CAS Registry Number

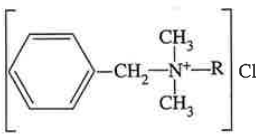
Alkyldimethyl(phenylmethyl)ammonium chloride [8001-54-5]

4. Empirical Formula Molecular Weight

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

The average molecular weight of benzalkonium chloride is 360.

5. Structural Formula



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

6. Functional Category

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

7. Applications in Pharmaceutical Formulation or Technology

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

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

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

Benzalkonium chloride is additionally used as a preservative in cosmetics.

8. Description

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

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	—	+	—
Acidity or alkalinity	—	+	—
Appearance of solution	+	+	—
Water	≤ 15.0%	≤ 10.0%	≤ 15.0%
Residue on ignition	≤ 0.2%	—	≤ 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	95.0-105.0%	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 (μg/mL)
Aerobacter aerogenes	64
Clostridium histolyticum	5
Clostridium oedematiens	5
Clostridium tetani	5
Clostridium welchii	5
Escherichia coli	16
Pneumococcus II	5
Proteus vulgaris	64
Pseudomonas aeruginosa	30
Salmonella enteritidis	30
Salmonella paratyphi	16
Salmonella typhosa	4
Shigella dysenteriae	2
Staphylococcus aureus	1.25
Streptococcus pyrogenes	1.25
Vibrio cholerae	2

Density: ≈ 0.98 g/cm^3 at 20°C

Melting point: ≈ 40°C

Partition coefficients: the octanol: water partition coefficient varies with the alkyl chain length of the homolog; 9.98 for C_{12}, 32.9 for C_{14}, and 82.5 for C_{16}.

Solubility: practically insoluble in ether; very soluble in acetone, ethanol (95%), methanol, propanol, and water. Aqueous solutions of benzalkonium chloride foam when shaken, have a low surface tension and possess detergent and emulsifying properties.

11. Stability and Storage Conditions

Benzalkonium chloride is hygroscopic and may be affected by light, air, and metals.

Solutions are stable over a wide pH and temperature range and may be sterilized by autoclaving without loss of effectiveness. Solutions may be stored for prolonged periods at room temperature. Dilute solutions stored in polyvinyl chloride or polyurethane foam containers may lose antimicrobial activity.

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

12. Incompatibilities

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

Benzalkonium chloride has been shown to be adsorbed to various filtering membranes especially those that are hydrophobic or anionic.[7]

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.[8]

Ototoxicity can occur when benzalkonium chloride is applied to the ear[9] 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.[10-14]

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.[15] Solutions stronger than 0.03% w/v concentration entering the eye require prompt medical attention.

Local irritation of the throat, esophagus, stomach, and intestine can occur following contact with strong solutions (> 0.1% w/v). The fatal oral dose of benzalkonium chloride in humans is estimated to be 1-3 g. Adverse effects following oral ingestion include vomiting, collapse, and coma. Toxic doses lead to paralysis of the respiratory muscles, dyspnea, and cyanosis.

LD_{50} (guinea pig, oral): 200 mg/kg[16]
LD_{50} (mouse, IP): 10 mg/kg
LD_{50} (mouse, IV): 10 mg/kg
LD_{50} (mouse, oral): 175 mg/kg
LD_{50} (mouse, SC): 64 mg/kg
LD_{50} (rat, IP): 14.5 mg/kg
LD_{50} (rat, IV): 13.9 mg/kg
LD_{50} (rat, oral): 240 mg/kg
LD_{50} (rat, SC): 400 mg/kg
LD_{50} (rat, skin): 1.56 g/kg

15. Handling Precautions

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

16. Regulatory Status

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

17. Pharmacopeias

Eur, Int, Jpn, Pol, and US.

18. Related Substances

Benzethonium chloride; cetrimide.

19. Comments

-

20. Specific References

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22. Authors

AH Kibbe.

Carboxymethylcellulose Sodium

1. Nonproprietary Names

BP: Carmellose sodium
JP: Carmellose sodium
PhEur: Carboxymethylcellulosum natricum
USP: Carboxymethylcellulose sodium

2. Synonyms

Akucell; *Aquasorb*; *Blanose*; *Cekol*; cellulose gum; CMC sodium; E466; *Finnfix; Nymcel*; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; *Tylose CB*.

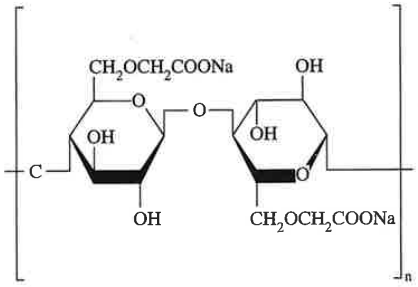
3. Chemical Name and CAS Registry Number

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

4. Empirical Formula Molecular Weight

The USP 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; water absorbing 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 3-6%, of the medium viscosity grade is used to produce gels which can be used as the base for applications and pastes; glycols are 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] incontinence, personal hygiene, and food products.

Use	Concentration (%)
Emulsifying agent	0.25-1.0
Gel-forming agent	3.0-6.0
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

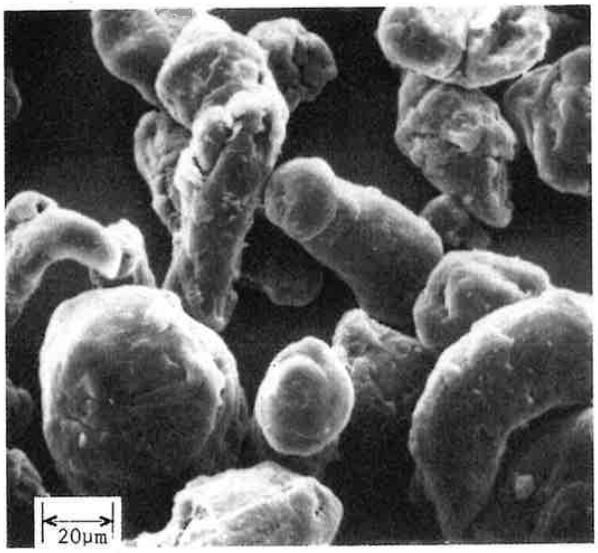
Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
pH (1% w/v solution)	6.0-8.0	6.0-8.0	6.5-8.5
Degree of substitution	—	—	1.15-1.45
Appearance of solution	+	+	—
Viscosity	+	+	+
Loss on drying	≤ 10.0%	≤ 10.0%	≤ 10.0%
Heavy metals	≤ 20 ppm	≤ 20 ppm	≤ 20 ppm
Chloride	≤ 0.640%	≤ 0.25%	—
Arsenic	≤ 10 ppm	—	—
Sulfate	≤ 0.960%	—	—
Silicate	≤ 0.5%	—	—
Sodium glycolate	—	≤ 0.4%	≤ 0.5%
Starch	+	—	—
Sulfated ash	—	20.0-33.3%	—
Organic volatile impurities	—	—	+
Assay (of sodium)	6.5-8.5%	6.5-10.8%	10.5-12.0%

10. Typical Properties

Compaction data: *See* Fig. 1.[a]
Density (*bulk*): 0.520 g/cm^3
Density (*tapped*): 0.783 g/cm^3
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* Section 11. *See also* Fig. 2.[a]
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.

SEM: 1
Excipient: Carboxymethylcellulose sodium
Manufacturer: Buckeye Cellulose Corp
Lot No: 9247 AP
Magnification: 120×
Voltage: 10 kV

SEM: 2
Excipient: Carboxymethylcellulose sodium
Manufacturer: Hercules Ltd
Lot No: 21 A-1 (44390)
Magnifiction: 600×
Voltage: kV



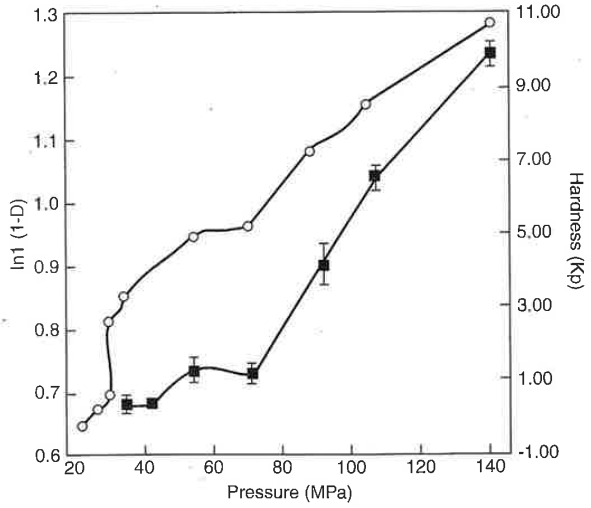


Fig. 1: Heckel plot carboxymethylcellulose sodium.
○: In1/(1-D)
■ : Hardness

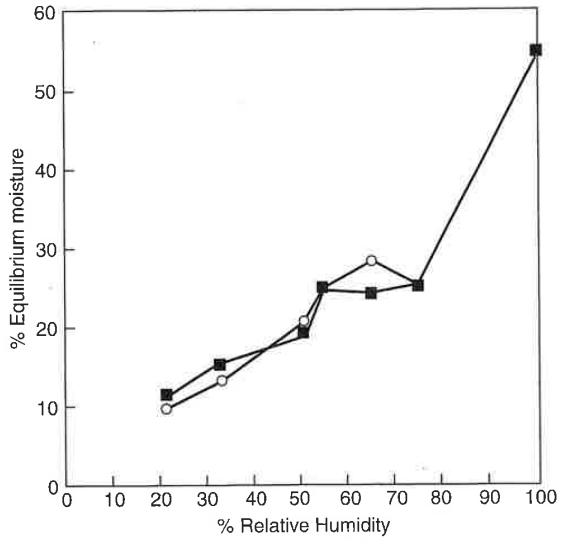


Fig. 2: Sorption-desorption isotherm of carboxymethylcellulose sodium.
○: Sorption
■ : Desorption

Viscosity: various grades of carboxymethylcellulose sodium are commercially available which have differing aqueous viscosities; aqueous 1% w/v solutions with viscosities of 5-13 000 mPa s (5-13 000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity.[6] Prolonged heating at high temperatures will depolymerize the gum and permanently decrease the viscosity. The viscosity of sodium carboxymethylcellulose solutions is fairly stable over a pH range of 4 to 10. The optimum pH range is neutral. Viscosities of three grades of sodium carboxymethylcellulose are shown in Table 1. *See also* Section 11.

[a] Results of laboratory project for third edition.

Table I: Viscosity of aqueous carboxymethylcellulose sodium solutions[a] (Measurements taken with a Brookfield LVT viscometer at 25°C).

	Grade	Concen. (% w/v)	Viscosity (mPa s)	Spindle	Speed
Low viscosity	*Akucell AF 0305*	1%	10-15	#1	60 rpm
Medium viscosity	*Akucell AF 2785*	1%	1500-2500	#3	30 rpm
High viscosity	*Akucell AF 3085*	1%	8000-1200	#4	30 rpm

[a] Ashland Chemical Company technical literature.

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. 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 fibers 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] It is listed as a substance that may be added to all foodstuffs in the European Council Directive No 95/2/EC.[10]

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.[11]

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.[12,13]

LD_{50} (guinea pig, oral): 16 g/kg[14]
LD_{50} (mouse, oral): > 27 g/kg
LD_{50} (rabbit, oral): > 27 g/kg
LD_{50} (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, intralesional, 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

Eur, Int, Jpn, Pol, and US.

18. Related Substances

Carboxymethylcellulose calcium; carboxymethylcellulose sodium 12; croscarmellose sodium.

Carboxymethylcellulose sodium 12

Pharmacopeias: US.

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,with a degree of substitution (DS) in the range of 0.7 to 1.2. 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. Thermal crosslinking reduces solubility while retaining water absorption therefore producing materials suitable for water absorption.

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.[15]

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22. Authors

D Parsons.

Cellulose, Microcrystalline

1. Nonproprietary Names

BP: Microcrystalline cellulose
JP: Microcrystalline cellulose
PhEur: Cellulosum microcrystallinum
USP: Microcrystalline cellulose

2. Synonyms

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

3. Chemical Name and CAS Registry Number

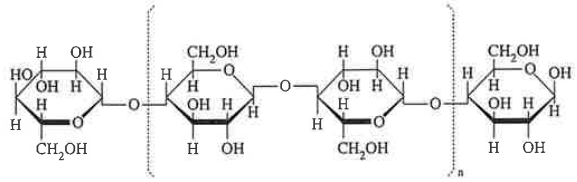
Cellulose [9004-34-6]

4. Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈ 36 000

Where n ≈ 220.

5. Structural Formula



6. Functional Category

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

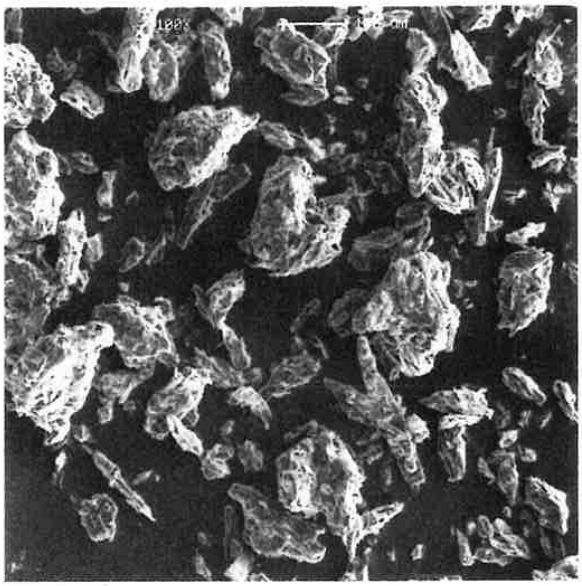
7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/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 binder/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 binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

SEM: 1
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals
Lot: 98662
Magnification: 100×



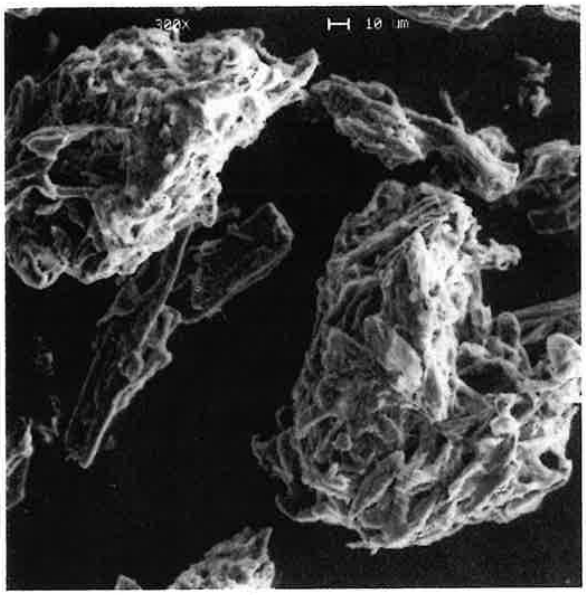
8. Description

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

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	+	—
pH	5.0-7.0	5.0-7.5	5.0-7.0
Bulk density	+	–	+
Solubility	–	+	—
Loss on drying	≤ 7.0%	≤ 6.0%	≤ 7.0%
Residue on ignition	≤ 0.05%	–	≤ 0.05%
Conductivity	+	–	+
Sulfated ash	–	≤ 0.1%	—
Ether-soluble substances	≤ 0.05%	≤ 0.05%	≤ 0.05%
Water-soluble substances	≤ 0.24%	≤ 0.25%	≤ 0.24%
Heavy metals	≤ 10 ppm	≤ 10 ppm	≤ 0.001%
Starch	—	+	—
Organic volatile impurities	—	—	+
Microbial limits	+	+	+
Assay	—	—	97.0-102.0%

SEM: 2
Excipient: Microcrystalline cellulose
Manufacturer: Penwest Pharmaceuticals
Lot: 98662
Magnification: 300×



10. Typical Properties

Angle of repose: 34.4° for *Emcocel 90M*.[9]
Density (*bulk*):
0.337 g/cm^3;[a]
0.32 g/cm^3 for Avicel PH-101;[10]
0.29 g/cm^3 for Emcocel 90M.[9]
Density (*tapped*):
0.478 g/cm^3;[a]
0.45 g/cm^3 for *Avicel PH-101*;[10]
0.35 g/cm^3 for *Emcocel 90M*.[9]
Density (*true*): 1.512-1.668 g/cm^3[a]
Compressibility: *See* Figs. 1, 2, and 3.[a]

Mechanical properties[a]

Compression pressure:	9.84 kN/cm^2
Tensile strength:	0.8711 kN/cm^2
Permanent deformation pressure:	15.3
Brittle fracture index:	0.0821
Bonding index:	0.0571
Reduced modulus of elasticity:	1472

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* Fig. 4[a] and Table I.
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:
1.06-1.12 m^2/g for *Avicel PH-101*.[a]
1.21-1.30 m^2/g for *Avicel PH-102*.[a]
0.78-1.18 m^2/g for *Avicel PH-200*.[a]

[a] Results of laboratory project for third edition.

SEM: 3
Excipient: Microcrystalline cellulose
Manufacturer: FMC Corp
Magnification: 100×

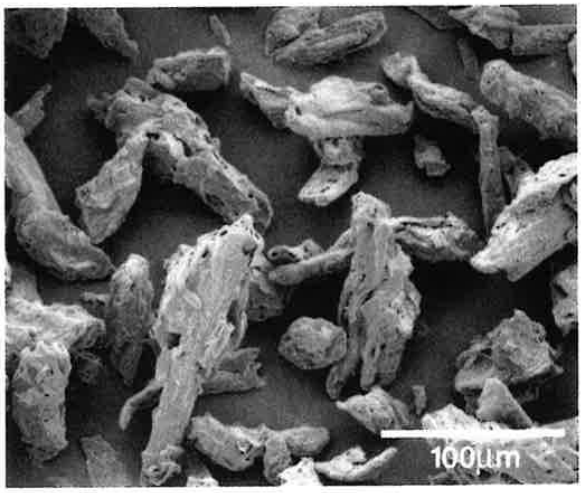


Table I: Properties of some commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (µm)	Particle Size Analysis: Mesh size	Particle Size Analysis: Amount retained (%)	Moisture content (%)
Avicel PH-101[a]	50	60	≤ 1.0	≤ 5.0
		200	≤ 30.0	
Avicel PH-102[a]	100	60	≤ 8.0	≤ 5.0
		200	≥ 45.0	
Avicel PH-103[a]	50	60	≤ 1.0	≤ 3.0
		200	≤ 30.0	
Avicel PH-105[a]	20	400	≤ 1.0	≤ 5.0
Avicel PH-112[a]	100	60	≤ 8.0	≤ 1.5
Avicel PH-113[a]	50	60	≤ 1.0	≤ 1.5
		200	≤ 30.0	
Avicel PH-200[a]	180	60	≥ 10.0	≤ 5.0
		100	≥ 50.0	
Avicel PH-301[a]	50	60	≤ 1.0	≤ 5.0
		200	≤ 30.0	
Avicel PH-302[a]	100	60	≤ 8.0	≤ 5.0
		200	≥ 45.0	
Emcocel 50M[b]	51	60	≤ 0.25	≤ 5.0
		200	≤ 30.0	
Emcocel 90M[b]	91	60	≤ 8.0	≤ 5.0
		200	≥ 45.0	
Vivacel 101[c]	50	50	≥ 35.0	≤ 5.0
		150	≤ 10.0	
Vivacel 102[c]	100	50	≥ 50.0	≤ 5.0
		150	≤ 30.0	
Vivacel 12[c]	180	50	≥ 70.0	≤ 5.0
		500	≤ 1.0	
Vivacel 20[c]	20	50	≤ 2.0	≤ 5.0
		150	≤ 0.1	

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

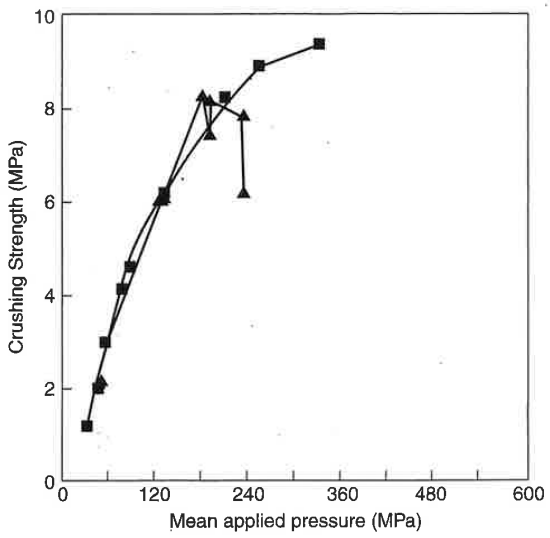


Fig. 1: Crushing strength.
(Reprinted with permission from Marcel Dekker, Inc., to be published in *Compaction of Pharmaceutical Excipients* by Metin Celik, in press, 1999.)
■ : Microcrystalline cellulose, *Emcocel 90M* (Lot # 1037X. Mendell) at V = 100 mm/s
▲ : Microcrystalline cellulose, *Emcocel 90M* (Lot # 1037X. Mendell) at V = 300 mm/s

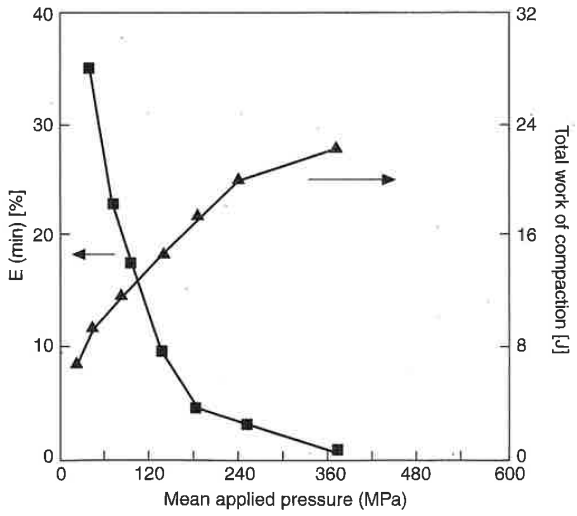


Fig. 2: Total work of compaction.
(Reprinted with permission from Marcel Dekker, Inc., to be published in *Compaction of Pharmaceutical Excipients* by Metin Celik, in press, 1999.)
■ : Percentage porosity (E) vs. pressure plot for microcrystalline cellulose, *Emcocel 90M* (Lot # 1037X. Mendell) at V = 100 mm/s
▲ : Total work of compaction (TWC) vs. pressure plot for microcrystalline cellulose, *Emcocel 90M* (Lot # 1037X, Mendell) at V = 100 mm/s

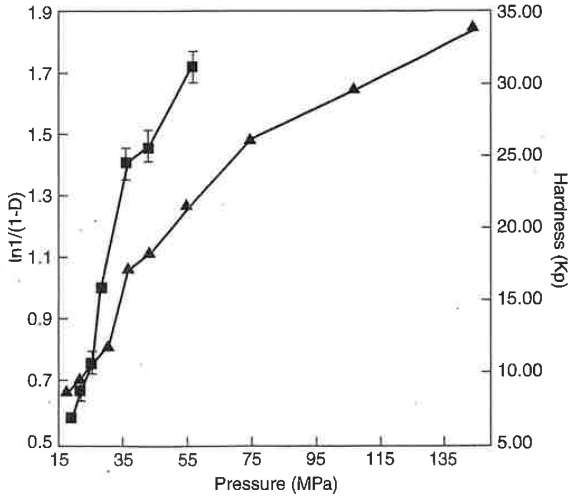


Fig. 3: Heckel plot for microcrystalline cellulose.
○: ln1/(1-D)
■ : Hardness

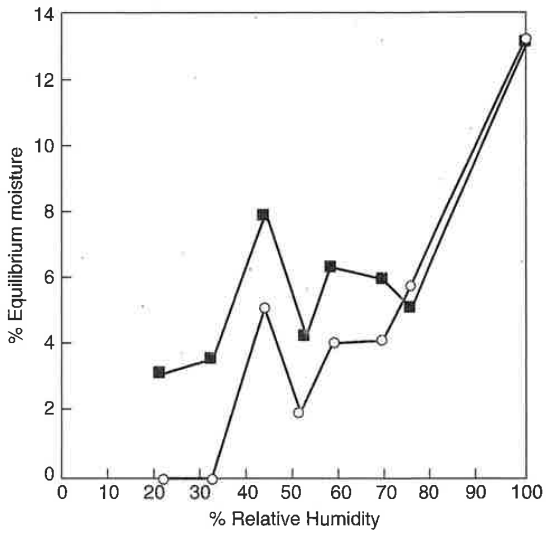


Fig. 4: Sorbtion-desorption isotherm for microcrystalline cellulose.
○: Sorption
■ : Desorption

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. 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 formulation 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 has been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 5 mg/m^3 for respirable dust; short-term limit for total inhalable dust has been set at 20 mg/m^3.[13]

16. Regulatory Status

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

17. Pharmacopeias

Eur, Int, Jpn, Pol, and US.

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 and US.

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 #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. Higher density grades improve flowability and weight uniformity.

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22. Authors

TA Wheatley.

Dextrose

1. Nonproprietary Names

BP: Glucose
JP: Glucose
PhEur: Dextrosum (glucosum) monohydricum
USP: Dextrose

2. Synonyms

Blood sugar; *Caridex*; corn sugar; D-(+)-glucopyranose monohydrate; grape sugar; starch sugar; *Tabfine D-100*.

3. Chemical Name and CAS Registry Number

D-(+)-Glucose monohydrate [5996-10-1]

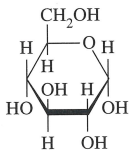
See also Section 18.

4. Empirical Formula — Molecular Weight

$C_6H_{12}O_6.H_2O$ — 198.17 (for monohydrate)

See also Section 18.

5. Structural Formula



Anhydrous material shown.

6. Functional Category

Tablet and capsule diluent; therapeutic agent; tonicity agent; sweetening agent.

7. Applications in Pharmaceutical Formulation or Technology

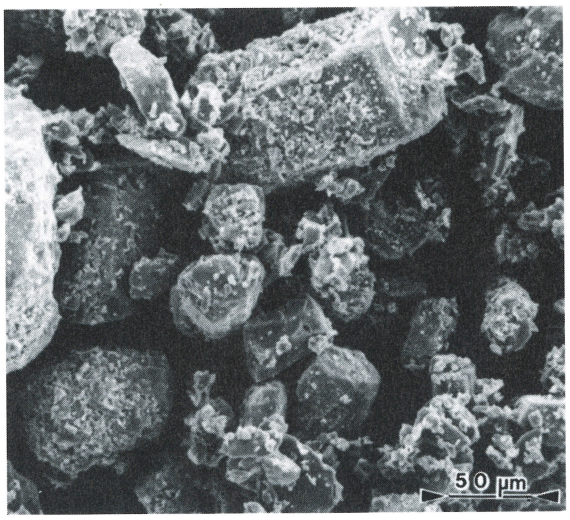
Dextrose is widely used in solutions to adjust tonicity and as a sweetening agent. Dextrose is also used as a direct-compression tablet diluent and binder, primarily in chewable tablets. Although comparable as a tablet diluent to lactose, tablets produced with dextrose monohydrate require more lubrication, are less friable, and have a tendency to harden.[1-3] The mildly reducing properties of dextrose may be used when tableting to improve the stability of active materials which are sensitive to oxidation.

Dextrose is also used therapeutically and is the preferred source of carbohydrate in parenteral nutrition regimens.

8. Description

Dextrose occurs as odorless, sweet-tasting, colorless crystals or as a white crystalline or granular powder.

SEM: 1.
Excipient: Dextrose anhydrous (granular)
Manufacturer: Mallinckrodt Speciality Chemicals Co
Lot No.: KLKZ
Magnification: 180×



9. Pharmacopeial Specifications

Test	PhEur	USP
Identification	+	+
Color of solution	+	+
Specific rotation	+52.5° to +53.3°	+52.5° to +53.5°
Acidity	+	+
Organic volatile	—	+
Water		
(for monohydrate)	7.0-9.5%	7.5-9.5%
(for anhydrous)	≤ 0.5%	≤ 1.0%
Residue on ignition	≤ 0.1%	≤ 0.1%
Chloride	≤ 125 ppm	≤ 0.018%
Sulfate	≤ 200 ppm	≤ 0.025%
Arsenic	≤ 1 ppm	≤ 1 ppm
Barium	≤ 1 ppm	—
Calcium	≤ 200 ppm	—
Heavy metals	—	≤ 5 ppm
Lead	≤ 0.5 ppm	—
Dextrin	+	+
Soluble starch, and sulfites	+	+

10. Typical Properties

Data for dextrose monohydrate shown, *see* Section 18 for dextrose anhydrous data.

Acidity/alkalinity:
pH = 3.5-5.5 (20% w/v aqueous solution)
Compressibility: *see* Fig. 1.[a]
Density (*bulk*): 0.826 g/cm^3[b]
Density (*tapped*): 1.020 g/cm^3[b]
Density(*true*): 1.54 g/cm^3
Flowability: 35 g/s[a]
Heat of solution: 105.4 J/g (25.2 cal/g)

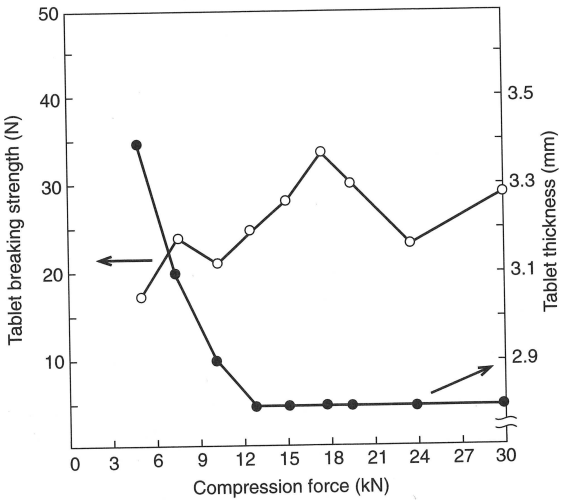


Fig. 1: Compression characteristics of dextrose monohydrate (*Staleydex*).[a]
Mean tablet weight: 502 mg
Minimum compressional force for compaction: 4.9 kN
Compressional force resulting in capping: 7.35 kN
Lubricant: 0.5% w/w magnesium stearate

Hygroscopicity: anhydrous dextrose absorbs significant amounts of moisture at 25°C and a relative humidity of about 85% to form the monohydrate. The monohydrate similarly only absorbs moisture at around 85% relative humidity and 25°C. *See* Fig. 2.[b]

Melting point: 83°C

Osmolarity: a 5.51% w/v aqueous solution is iso-osmotic with serum. However, it is not isotonic since dextrose can pass through the membrane of red cells and cause hemolysis.

Solubility:

Solvent	Solubility at 20°C
Chloroform	Practically insoluble
Ethanol (95%)	1 in 60
Ether	Practically insoluble
Glycerin	Soluble
Water	1 in 1

[a] *Handbook of Pharmaceutical Excipients,* First Edition.

[b] Results of laboratory project for third edition.

11. Stability and Storage Conditions

Dextrose has good stability under dry storage conditions. Aqueous solutions may be sterilized by autoclaving. However, excessive heating can cause a reduction in pH and caramelization of solutions.[4-7]

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

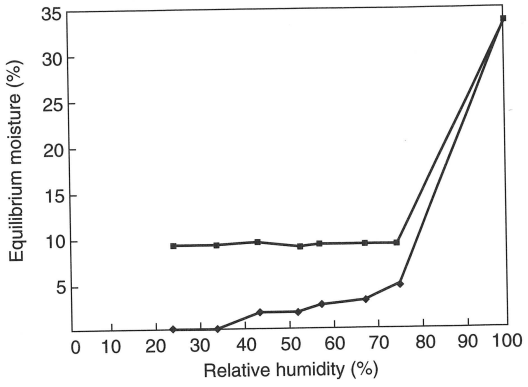


Fig. 2: Sorption-desorption isotherm for anhydrous dextrose granules.[b]
◆ : sorption
■ : desorption

12. Incompatibilities

Dextrose solutions are incompatible with a number of drugs such as: cyanocobalamin; kanamycin sulfate; novobiocin sodium, and warfarin sodium.[8] Erythromycin gluceptate is unstable in dextrose solutions at a pH less than 5.05.[9] Decomposition of B-complex vitamins may occur if they are warmed with dextrose.

In the aldehyde form, dextrose can react with amines, amides, amino acids, peptides, and proteins. Brown coloration and decomposition occurs with strong alkali.

Dextrose may cause browning of tablets containing amines.

13. Method of Manufacture

Dextrose, a monosaccharide sugar, occurs widely in plants and is manufactured on a large scale by the acid and enzymatic hydrolysis of starch, usually maize (corn) starch. Below 50°C α-D-dextrose monohydrate is the stable crystalline form produced, above 50°C the anhydrous form is obtained and at still higher temperatures β-D-dextrose is formed which has a melting point of 148-155°C.

14. Safety

Dextrose is rapidly absorbed from the gastrointestinal tract. It is metabolized to carbon dioxide and water with the release of energy.

Concentrated dextrose solutions given by mouth may cause nausea and vomiting. Dextrose solutions greater than 5% w/v concentration are hyperosmotic and are liable to cause local vein irritation following intravenous administration. Thrombophlebitis has been observed following the intravenous infusion of iso-osmotic dextrose solution with low pH, probably due to the presence of degradation products formed by overheating during sterilization. The incidence of phlebitis may be reduced by adding sufficient sodium bicarbonate to raise the pH of the infusion above pH 7.

LD_{50} (mouse, IP): 18 g/kg[10]
LD_{50} (mouse, IV): 9 g/kg
LD_{50} (rat, oral): 25.8 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Dust generation should be minimized to reduce the risk of explosion.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (capsules, inhalations, IM, IV and SC injections, tablets, oral solutions, and syrups). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

China, Eur, Int, and US.

Some pharmacopeias include separate monographs for dextrose anhydrous and/or dextrose monohydrate while others permit the anhydrous and/or monohydrate under a single monograph. The JP, for example, only includes anhydrous dextrose. The USP also includes a monograph for dextrose excipient; this material is dextrose monohydrate not intended for parenteral use, and with a specific optical rotation of +52.5° to +53.5°.

18. Related Substances

Dextrates; dextrin; dextrose anhydrous; fructose; glucose liquid; sucrose.

Dextrose anhydrous: $C_6H_{12}O_6$

Molecular weight: 180.16

CAS number: [50-99-7]

Synonyms: anhydrous D-(+)-glucopyranose; anhydrous glucose; anhydrous dextrose; dextrosum anhydricum.

Appearance: white, odorless, crystalline powder with a sweet taste.

Pharmacopeias: Eur, Int, Jpn, Pol, and US.

Acidity/alkalinity: pH = 5.9 (10% w/v aqueous solution)

Density (bulk): 1.3-1.4 g/cm^3

Density (tapped): 1.1-1.2 g/cm^3

Hygroscopicity: *see* Section 10.

Melting point: 146°C

Osmolarity: a 5.05% w/v aqueous solution is iso-osmotic with serum. *See also* Section 10.

Refractive index: n_D^{20} = 1.3479 (10% w/v aqueous solution)

Solubility:

Solvent	Solubility at 20°C Unless otherwise stated
Ethanol (95%)	Sparingly soluble
Ether	Sparingly soluble
Methanol	1 in 120
Water	1 in 1.1 at 25°C 1 in 0.8 at 30°C 1 in 0.41 at 50°C 1 in 0.28 at 70°C 1 in 0.18 at 90°C

Specific gravity:

Concentration of aqueous dextrose solution (% w/v)	Specific gravity at 17.5°C
5	1.019
10	1.038
20	1.076
30	1.113
40	1.149

Specific surface area: 0.22-0.29 m^2/g.[a]

[a] Results of laboratory project for third edition.

19. Comments

The way in which the strengths of dextrose solutions are expressed varies from country to country. The USP requires strengths to be expressed in terms of dextrose monohydrate while the BP requires strengths to be expressed in terms of anhydrous dextrose. Approximately 1.1 g of dextrose monohydrate is equivalent to 1 g of anhydrous dextrose.

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21. General References

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22. Authors

A Day.

Edetic Acid

1. Nonproprietary Names

BP: Edetic acid
USP: Edetic acid

2. Synonyms

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

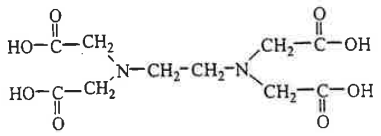
3. Chemical Name and CAS Registry Number

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

4. Empirical Formula Molecular Weight

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

5. Structural Formula



6. Functional Category

Chelating 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	BP	USP
Identification	+	+
Appearance of solution	+	—
Residue on ignition	—	≤ 0.2%
Sulfated ash	≤ 0.2%	—
Heavy metals	≤ 20 ppm	≤ 0.003%
Nitrilotriacetic acid	≤ 200 ppm	≤ 0.3%
Iron	≤ 80 ppm	≤ 0.005%
Chloride	≤ 200 ppm	—
Loss on drying	≤ 0.1%	—
Assay	98.0-101.0%	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 10 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 bodyweight.[6]

See also Section 19.

LD_{50} (mouse, IP): 0.25 g/kg[7]
LD_{50} (mouse, oral): 0.03 g/kg
LD_{50} (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

Br, Ger, and US.

18. Related Substances

Dipotassium edetate: $C_{10}H_{14}K_2N_2O_8$
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: $C_{10}H_{14}N_2Na_2O_8$
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: Eur, Int, Jpn, Pol, and US.

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 mm^2/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.
LD_{50} (mouse, IP): 0.26 g/kg[7]
LD_{50} (mouse, IV): 0.056 g/kg
LD_{50} (mouse, oral): 2.05 g/kg
LD_{50} (rabbit, IV): 0.047 g/kg
LD_{50} (rabbit, oral): 2.3 g/kg
LD_{50} (rat, oral): 2 g/kg
LD_{50} (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: $C_{10}H_{12}CaN_2Na_2O_8$
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)glycinato]](4-)-*N*,*N*′,*O*,*O*′,O^N,-O^N′]calciate(2-)disodium; EDTA calcium; ethylenediaminetetraacetic acid calcium disodium chelate; [(ethylenedinitrilo)tetraacetato]calciate(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: Eur, Pol, and US. Some pharmacopeias specify that edetate calcium disodium is the dihydrate, others that it is the anhydrous material. The USP 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/cm^3
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.
LD_{50} (dog, oral): 12 g/kg[7]
LD_{50} (mouse, IP): 4.5 g/kg
LD_{50} (mouse, oral): 10 g/kg
LD_{50} (rabbit, IP): 6 g/kg
LD_{50} (rabbit, oral): 7 g/kg
LD_{50} (rat, IP): 3.85 g/kg
LD_{50} (rat, IV): 3.0 g/kg
LD_{50} (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: $C_{10}H_{12}N_2Na_4O_8$
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.
LD_{50} (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: $C_{10}H_{13}N_2Na_3O_8$
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.
LD_{50} (mouse, IP): 0.3 g/kg[7]
LD_{50} (mouse, oral): 2.15 g/kg
LD_{50} (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, ferric 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.

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22. Authors

PJ Weller.

Glycerin

1. Nonproprietary Names

BP: Glycerol
JP: Concentrated Glycerin
PhEur: Glycerolum
USP: Glycerin

2. Synonyms

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

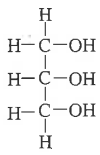
3. Chemical Name and CAS Registry Number

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] In oral solutions glycerin is used as a solvent, 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	JP	PhEur	USP
Identification	+	+	+
Characters	+	—	+
Specific gravity	1.221-1.230	—	≥ 1.249
Color	+	—	+
Appearance of solution	—	+	—
Acidity or alkalinity	+	—	+
Refractive index	1.449-1.454	1.470-1.475	—
Residue on ignition	≤ 0.01%	—	≤ 0.01%
Sulfated ash	—	≤ 0.01%	—
Chloride	≤ 0.001%	≤ 10 ppm	≤ 0.001%
Ammonium	+	—	—
Calcium	+	—	—
Sulfate	≤ 0.002%	—	≤ 0.002%
Arsenic	≤ 2 ppm	—	≤ 1.5 ppm
Heavy metals	≤ 5 ppm	≤ 5 ppm	≤ 5 ppm
Chlorinated compounds (as Cl)	—	+	≤ 0.003%
Organic volatile impurities	—	—	+
Aldehydes	—	+	—
Acrolein, glucose and other reducing substances	+	+	—
Fatty acids and esters	+	+	+
Readily carbonizable substances	+	—	—
Sugars	—	+	—
Water	—	≤ 2.0%	≤ 5.0%
Assay	84%-87%	98-101%	99-101%

10. Typical Properties

Boiling point: 290°C (with decomposition)
Density:
1.2656 g/cm^3 at 15°C;
1.2636 g/cm^3 at 20°C;
1.2620 g/cm^3 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%)	Soluble
Ether	1 in 500
Ethyl acetate	1 in 11
Methanol	Soluble
Oils	Practically insoluble
Water	Soluble

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):

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

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.

LD_{50} (guinea pig, oral): 7.75 g/kg[4]
LD_{50} (mouse, IP): 8.98 g/kg
LD_{50} (mouse, IV): 6.2 g/kg
LD_{50} (mouse, oral): 4.1 g/kg
LD_{50} (mouse, SC): 0.09 g/kg
LD_{50} (rat, IP): 8.3 g/kg
LD_{50} (rat, IV): 5.6 g/kg
LD_{50} (rat, oral): 12.6 g/kg
LD_{50} (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/m^3.[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

China, Eur, Int, Jpn, and US.

Eur and Int also include glycerin (85%); Pol includes glycerin (86%).

18. Related Substances

–

19. Comments

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20. Specific References

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22. Authors

JC Price.

Hydroxypropyl Methylcellulose

1. Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Methylhydroxypropylcellulosum
USP: Hydroxypropyl methylcellulose

2. Synonyms

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

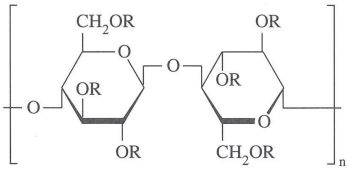
3. Chemical Name and CAS Registry Number

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

4. Empirical Formula Molecular Weight

The PhEur 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 specifies the substitution type by appending a four digit number to the nonproprietary name, e.g., hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CHOHCH_3$), calculated on a dried basis. Molecular weight is approximately 10 000-1 500 000.

5. Structural Formula



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

6. Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; 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 drugs from a matrix at levels 10-80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations between 2-20% 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 fibers 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 in the manufacture of capsules, as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

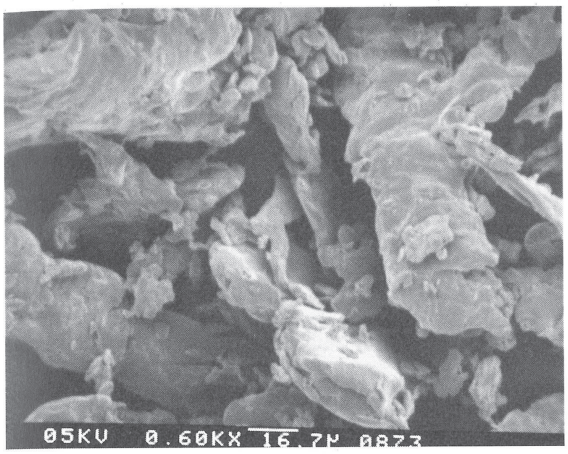
8. Description

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

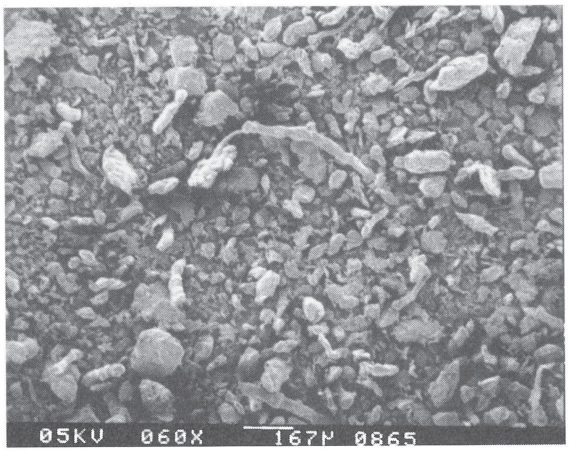
9. Pharmacopeial Specifications

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

SEM: 1
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Dow Chemical Co
Lot No.: ME20012N11
Magnification: 600×
Voltage: 5kV



SEM: 2
Excipient: Hydroxypropyl methylcellulose
Manufacturer: Dow Chemical Co
Lot No.: ME20012N11
Magnification: 60×
Voltage: 5kV



10. Typical Properties

Acidity/alkalinity:
pH = 5.5-8.0 for a 1% w/w aqueous solution.
Ash: 1.5-3.0%, depending upon the grade.
Autoignition temperature: 360°C
Density (bulk): 0.341 g/cm^3
Density (tapped): 0.557 g/cm^3
Density (true): 1.326 g/cm^3
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* Fig. 1.
Particle size distribution: *See* Table I.
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, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. 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 II.

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: Typical particle size distribution for hydroxypropyl methylcellulose.

	Average particle size (µm)	Cumulative frequency oversize (%)	Weight retained (%)
Lot LC15012N11	250	5.6	5.60
	200	18.8	13.20
	137	26.6	7.8
	115	35.4	8.8
	90	54.4	19.0
	64	85.8	31.4
	pan	100	14.0
Lot LA29012N02	250	2.8	2.8
	200	15.6	12.8
	137	20.6	5.0
	115	26.4	5.8
	90	42.8	16.4
	64	68	25.2
	pan	100	33

Note: Using an ATM Sonic Softener.

11. Stability and Storage Conditions

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

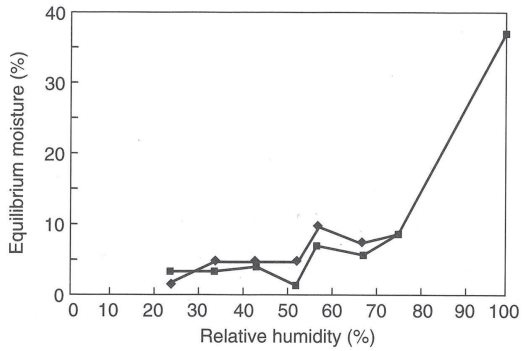


Fig. 1: Absorption desorption isotherm for hydroxypropyl methylcellulose.
◆ : sorption
■ : desorption

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.) Viscosities measured at 20°C.

Methocel grade	Nominal	Viscosity (mPa s)
K100LVP[a]	100	80-120
K4MP[a]	4000	3000-5600
K15MP[a]	15 000	12 000-21 000
K100MP[a]	100 000	80 000-120 000
E4MP[a]	4000	3500-5600
E10MP CR[a]	10 000	8000-13 000
E3 PREM.LV		2.4-3.6
E5 PREM.LV		4-6
E6 PREM.LV		5-7
E15 PREM.LV		12-18
E50 PREM.LV		40-60
K3 PREM.LV		2.4-3.6

[a] Dow Chemical Company.

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 and concentration 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 or ionic organics to form insoluble precipitates.

13. Method of Manufacture

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

14. Safety

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

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

LD_{50} (mouse, IP): 5 g/kg[16]
LD_{50} (rat, IP): 5.2 g/kg

15. Handling Precautions

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

16. Regulatory Status

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

17. Pharmacopeias

China, Eur, Int, Jpn, Pol, and US.

18. Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropyl methylcellulose phthalate; methylcellulose.

19. Comments

Powdered or granular, surface-treated grades of hydroxypropyl methylcellulose are also available which are dispersible in cold water. These are not recommended for oral use.

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22. Authors

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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.

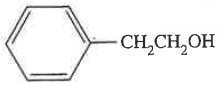
3. Chemical Name and CAS Registry Number

2-Phenylethanol [60-12-8]

4. Empirical Formula and Molecular Weight

$C_8H_{10}O$ 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 nasal, ophthalmic, and otic formulations at 0.25-0.5% v/v concentration; it is generally used in combination with other preservatives.[1-3] 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.[4] 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
Identification	+
Specific gravity	1.017-1.020
Refractive index	1.531-1.534
Residue on ignition	≤ 0.005%
Chlorinated compounds	+
Aldehyde	+
Organic volatile impurities	+

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.[5] 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.[6-10] 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.[11] *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.[12] 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.[13]

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 has been used as an antimicrobial preservative in parenteral, topical, otic, nasal, 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.[14]

LD_{50} (mouse, IP): 0.2 g/kg[15]
LD_{50} (mouse, oral): 0.8 g/kg
LD_{50} (rabbit, skin): 0.79 g/kg
LD_{50} (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, and otic preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Pol and US.

18. Related Substances

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19. Comments

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20. Specific References

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22. Authors

PJ Weller.

Polyoxyethylene Sorbitan Fatty Acid Esters

1. Nonproprietary Names

BP: Polysorbates 20, 60, and 80
JP: Polysorbate 80
PhEur: Polysorbatum 20, 60, and 80
USP: 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*; *Drewmulse; POE-SML; Durfax 20;* E432; *Glycosperse L-20*; *Hodag PSML-20*; *Lamesorb SML-20; Liposorb L-20*; *Liposorb L-20K*; *Montanox 20; Nissan Nonion LT-221; Norfox Sorbo T-20; Sorbax PML-20; Sorgen TW-20;* sorbitan monododecanoate; *T-Maz 20 T-Maz 20K;* 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*; *Lamesorb SMP-20; Liposorb P-20*; *Lonzest SMP-20; Montanox 40*; *Protasorb P-20*; sorbitan monohexadecanoate; poly(oxy-1,2-ethanediyl) derivatives; *Sorbax PMP-20; Tween 40.*
Polysorbate 60	*Atlas 70K; Atlas Armotan PMS 20*; *Capmul POE-S*; *Crillet 3*; *Drewpone 60K; Durfax 60; Durfax 60K; Emrite 6125; E435; Glycosperse S-20*; *Glycosperse S-20FG; Glycosperse S-20FKG; Hodag PSMS-20*; *Hodag SVS-18; Lamsorb SMS-20; Liposorb S-20*; *Liposorb S-20K*; *Lonzest SMS-20; Nikkol TS-10; Norfox SorboT-60 Montanox 60*; *Polycon T 60 K*; polyoxyethylene 20 stearate; sorbitan monooctadecanoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb S-20*; *Sorbax PMS-20; T-Maz 60; T-Max 60KHS; Tween 60; Tween 60K; Tween 60 VS.*
Polysorbate 61	*Crillet 31*; *Hodag PSMS-4*; *Protasorb S-4*; *Tween 61.*
Polysorbate 65	*Alkamuls PSTS-20; Crillet 35*; E436; *Glycosperse TS-20*; *Glycosperse TS-20 FG; Glycosperse TS-20 KFG:Hodag PSTS-20*; *Lamesorb STS-20; Liposorb TS-20*; *Liposorb TS-20K*; *Lanzet STS-20; Montanox 65*; sorbitan trioctadecanoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb STS-20*; *Sorbax PTS-20; T-Maz 65K; Tween 65; Tween 65K; Tween 65VS.*
Polysorbate 80	*Atlas E; Armotan PMO 20*; *Capmul POE-O*; *Crillet 4*; *Crillet 50*; *Drewmulse POE-SMO; Drewpone 80K; Durfax 80; Durfax 80K; Emrite 6120;* 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*; *Hetsorb O-5; Hodag PSMO-5*; sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb O-5*; *Sorbax PMO-5; T-Maz 81; Tween 81.*
Polysorbate 85	*AlkamulsPSTO-20; Crillet 45*; *Glycosperse TO-20; Hodag PSTO-20*; *Lonzest STO-20; Liposorb TO-20*; *Montanox 85*; sorbitan tri-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; *Protasorb TO-20*; *Sorbax PTO-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]

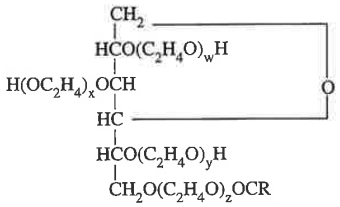
4. Empirical Formula Molecular Weight

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

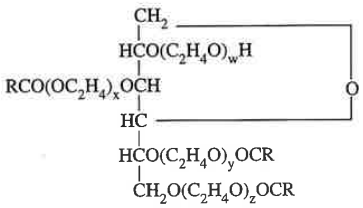
Table II: Empirical formula and molecular weight of selected polysorbates.

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)

R = fatty acid

6. Functional Category

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/suspending agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5, or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The resulting product is therefore a mixture of molecules of varying sizes rather than a uniform mixture of a single chemical.

Polysorbates containing 20 units of oxyethylene are hydrophilic nonionic surfactants which are 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. Recently they have been found to be useful in improving the oral bioavailability of drug molecules that are substrates for *p*-glycoprotein.[1]

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, although it should be noted that the absolute intensity of the products may vary from batch to batch and manufacturer to manufacturer.

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	JP	PhEur	USP
Identification			
Polysorbate 20	—	+	+
Polysorbate 40[a]	—	—	+
Polysorbate 60	—	+	+
Polysorbate 80	+	+	+
Saponification value			
Polysorbate 20	—	40-50	40-50
Polysorbate 40[a]	—	—	41-52
Polysorbate 60	—	45-55	45-55
Polysorbate 80	45-55	45-55	45-55
Hydroxyl value			
Polysorbate 20	—	95-108	96-108
Polysorbate 40[a]	—	—	89-105
Polysorbate 60	—	81-96	81-96
Polysorbate 80	—	65-80	65-80

(Continued)

Test	JP	PhEur	USP
Water			
Polysorbate 20	—	≤ 3.0%	≤ 3.0%
Polysorbate 40[a]	—	—	≤ 5.0%
Polysorbate 60	—	≤ 3.0%	≤ 3.0%
Polysorbate 80	—	≤ 3.0%	≤ 3.0%
Residue on ignition			
Polysorbate 20	—	—	≤ 0.25%
Polysorbate 40[a]	—	—	≤ 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	—	—	≤ 1ppm
Polysorbate 40[a]	—	—	≤ 1 ppm
Polysorbate 60	—	—	≤ 1 ppm
Polysorbate 80	—	—	≤ 1 ppm
Heavy metals			
Polysorbate 20	—	≤ 10 ppm	≤ 0.001%
Polysorbate 40[a]	—	—	≤ 0.001%
Polysorbate 60	—	≤ 10 ppm	≤ 0.001%
Polysorbate 80	≤ 20 ppm	≤ 10 ppm	≤ 0.001%
Acid value			
Polysorbate 20	—	≤ 2.0	≤ 2.2
Polysorbate 40[a]	—	—	≤ 2.2
Polysorbate 60	—	≤ 2.0	≤ 2.2
Polysorbate 80	≤ 2.0	≤ 2.0	≤ 2.2
Iodine value			
Polysorbate 20	—	≤ 5.0	—
Polysorbate 40	—		
Polysorbate 60	—	≤ 5.0	—
Polysorbate 80	19-24	18-24	—
Reducing substances			
Polysorbate 20	—	+	—
Polysorbate 60	—	+	—
Polysorbate 80	—	+	—
Specific gravity			
Polysorbate 20	—	1.10	—
Polysorbate 60	—	1.10	—
Polysorbate 80	1.005-1.095	1.08	1.06-1.09
Viscosity at 25°C			
Polysorbate 80	345-445 mm^2/s	—	300-500 mm^2/s

[a] Note that the PhEur contains monographs for polysorbate 20, 60, and 80; while the USP 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 VII.
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.

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 .

Table VII. Surface tension of related polysorbates.

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

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 are hygroscopic and should be examined for water content prior to use and dried if necessary. Also in common with other polyoxyethylene surfactants prolonged storage can lead to the formation of peroxides.

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.[2] *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.[3,4] When heated to decomposition the polysorbates emit acrid smoke and irritating fumes.

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.[5]

Polysorbate 20: LD_{50} (rat, oral): 37 g/kg. Moderate toxicity by intraperitoneal, and IV routes. Midley toxic by ingestion. Human skin irritant.

Polysorbate 21: Moderately toxic by IV.

Polysorbate 40: Moderately toxic by IV.

Polysorbate 60: LD_{50} (rat, IV): 1.22 g/kg. Moderate toxicity by IV route. Experimental tumorigen, reproductive effects.

Polysorbate 61: Moderately toxic by IV.

Polysorbate 80: LD_{50} (mouse, oral): 25 g/kg. Moderate toxicity by IV route. Mildly toxic by ingestion. Eye irriation. Experimental tumorigen, reproductive effects. Mutogenic data.

Polysorbate 85: Skin irritant.

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	Eur, Int, and US.
Polysorbate 40	US.
Polysorbate 60	Eur, Int, Pol, and US.
Polysorbate 80	China, Eur, Int, Jpn, Pol, and US.

18. Related Substances

Sorbitan esters (sorbitan fatty acide esters).

19. Comments

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Sodium Chloride

1. Nonproprietary Names

BP: Sodium chloride
JP: Sodium chloride
PhEur: Natrii chloridum
USP: Sodium chloride

2. Synonyms

Chlorure de sodium; cloreto de sódio; common salt; natural halite; rock salt; salt; sea salt; table salt.

3. Chemical Name and CAS Registry Number

Sodium chloride [7647-14-5]

4. Empirical Formula Molecular Weight

NaCl 58.44

5. Structural Formula

NaCl

6. Functional Category

Tablet and capsule diluent; tonicity agent.

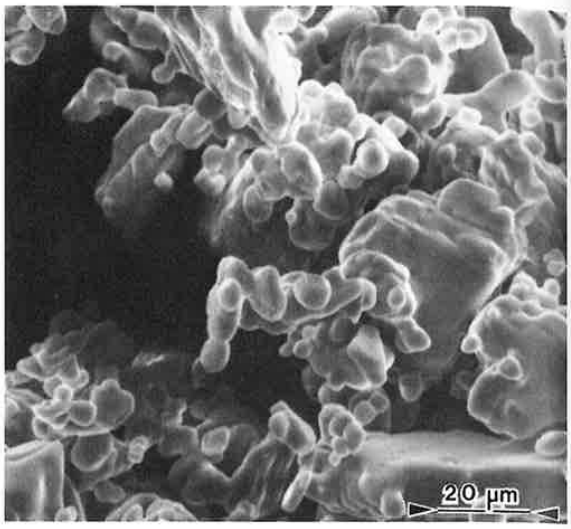
7. Applications in Pharmaceutical Formulation or Technology

Sodium chloride is widely used in a variety of parenteral and nonparenteral pharmaceutical formulations. Its primary use, in parenteral and ophthalmic preparations, is to produce isotonic solutions.

Sodium chloride has been used as a lubricant and diluent in capsules and direct-compression tablet formulations in the past.[1-5] This practice is no longer common. Sodium chloride has also been used as a channeling agent[6,7] and osmotic agent[8,9] in the cores of controlled-release tablets, as a porosity modifier in tablet coatings[10] and to control-drug release from microcapsules.[11,12] The addition of sodium chloride to aqueous spray-coating solutions containing hydroxypropyl cellulose or hypromellose suppressed the agglomeration of crystalline-cellulose particles;[13] it can also be used to modify drug-release from gels[14] and from multiple emulsions.[15] It may also be used to control micelle size,[16-18] and to adjust the viscosity of polymer dispersions by altering the ionic character of a formulation.[19,20]

Use	Concentration (%)
Capsule diluent	10-80
Controlled flocculation of suspensions	Up to 1
Direct compression tablet diluent	10-80
To produce isotonic solutions in intravenous or ophthalmic preparations	Up to 0.9
Water-soluble tablet lubricant	5 - 20

SEM: 1
Excipient: Sodium chloride, powder
Manufacturer: Mallinckrodt Speciality Chemicals Co
Magnification: 600×



8. Description

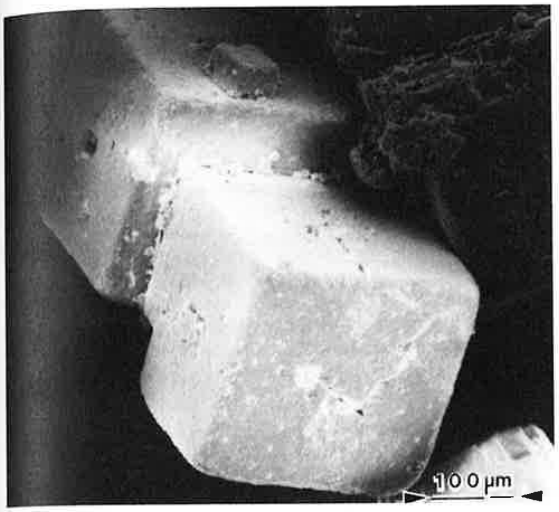
Sodium chloride occurs as a white crystalline powder or colorless crystals; it has a saline taste. The crystal lattice is a face-centered cubic structure. Solid sodium chloride contains no water of crystallization although, below 0°C, salt may crystallize as a dihydrate.

9. Pharmacopeial Specifications

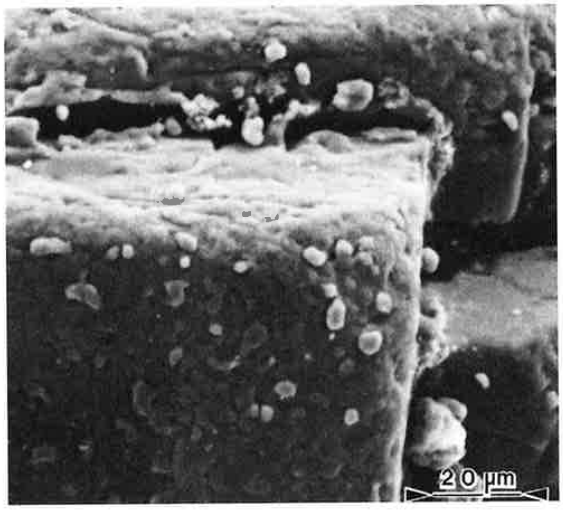
Test	JP	PhEur	USP
Identification	+	+	+
Appearance of solution	+	+	+
Acidity or alkalinity	pH 4.5-7.0	+	+
Loss on drying	≤ 0.5%	≤ 0.5%	0.05%
Arsenic	≤ 2 ppm	≤ 1 ppm	1 µg/g
Bromides	+	≤ 50 ppm	≤ 0.01%
Barium	+	+	+
Nitrites	—	+	+
Aluminum	0.2 ppm[a]	≤ 0.2 µg/g[a]	
Magnesium and alkaline earth metals	+	≤ 100 ppm	≤ 0.01%
Iodide	+	+	+
Iron	—	≤ 2 ppm	≤ 2 ppm
Sulfate	—	≤ 200 ppm	≤ 0.02%
Ferrocyanides	—	+	+
Heavy metals	≤ 3 ppm	≤ 5 ppm	≤ 5 ppm
Phosphate	—	≤ 25 ppm	≤ 0.0025%
Potassium	—	≤ 500 ppm[a][b]	≤ 0.05%[a][b]
Organic volatile impurities	—	—	+
Bacterial endotoxins	—	≤ 5 IU/g[b]	—
Assay (dried basis)	99.0-100.5%	99.0-100.5%	≤ 99.5-≥100.5%

[a] If for use in peritoneal dialysis, hemodialysis or hemofiltration solutions.
[b] If for parenteral use.

SEM: 2
Excipient: Sodium chloride, granular
Manufacturer: Van Waters & Rogers Inc
Magnification: 120×



SEM: 3
Excipient: Sodium chloride, granular
Manufacturer: Van Waters & Rogers Inc
Magnification: 600×



10. Typical Properties

Acidity/alkalinity:
pH = 6.7-7.3 (saturated aqueous solution)
Angle of repose: 38° for cubic crystals
Boiling point: 1439°C
Compressibility: with sodium chloride powder of less than 30 µm particle size, tablets are formed by plastic deformation. Above this size both plastic deformation and fracture occur.[1,3,4] *See also* Fig. 1.
Density:
2.17 g/cm^3;
1.20 g/cm^3 for saturated aqueous solution.
Density (bulk): 0.93 g/cm^3
Density (tapped): 1.09 g/cm^3
Freezing point depression:

Aqueous sodium chloride solution (% w/v)	Freezing point depression (°C)
11.69	6.90
17.53	10.82
23.38	15.14
30.39	21.12

Hardness (Mohs): 2-2.5
Hygroscopicity: hygroscopic above 75% RH.
Melting point: 801°C
Osmolarity: a 0.9% w/v aqueous solution is iso-osmotic with serum.
Refractive index:
n_D^{20} = 1.343 for a 1 M aqueous solution.
Solubility:

Solvent	Solubility at 25°C Unless otherwise stated
Ethanol	Slightly soluble
Ethanol (95%)	1 in 250
Glycerin	1 in 10
Water	1 in 2.8
	1 in 2.6 at 100°C

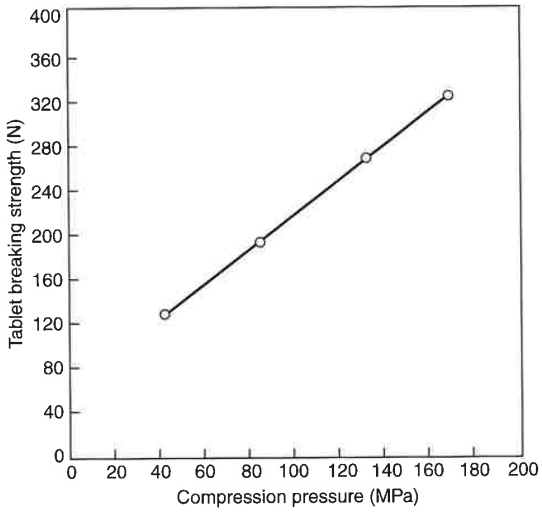


Fig. 1: Compression characteristics of sodium chloride (cubic crystals).[3]
Tablet diameter = 12 mm.

Vapor pressure:
133.3 Pa at 865°C for solid;
1759.6 Pa at 20°C for a saturated aqueous solution (equivalent to 75.3% RH).
Viscosity:
a 10% w/v solution has a viscosity of 1.19 mPa s (1.19 cP).

11. Stability and Storage Conditions

Aqueous sodium chloride solutions are stable but may cause the separation of glass particles from certain types of glass

containers. Aqueous solutions may be sterilized by autoclaving or filtration. The solid material is stable and should be stored in a well-closed container, in a cool, dry, place.

It has been shown that the compaction characteristics and the mechanical properties of tablets are influenced by the relative humidity of the storage conditions under which sodium chloride was stored.[21,22]

12. Incompatibilities

Aqueous sodium chloride solutions are corrosive to iron; they also react to form precipitates with silver, lead, and mercury salts. Strong oxidizing agents liberate chlorine from acidified solutions of sodium chloride. The solubility of the antimicrobial preservative methylparaben is decreased in aqueous sodium chloride solutions[23] and the viscosity of carbomer gels and solutions of hydroxyethyl cellulose or hydroxypropyl cellulose is reduced by the addition of sodium chloride.

13. Method of Manufacture

Sodium chloride occurs naturally as the mineral halite. Commercially, it is obtained by the solar evaporation of sea water, by mining or by the evaporation of brine from underground salt deposits.

14. Safety

Sodium chloride is the most important salt in the body for maintaining the osmotic tension of blood and tissues. About 5-12 g of sodium chloride is consumed daily, in the normal adult diet, and a corresponding amount excreted in the urine. As an excipient, sodium chloride may be regarded as an essentially nontoxic and nonirritant material. However, toxic effects following the oral ingestion of 0.5-1.0 g/kg body-weight in adults may occur. The oral ingestion of larger quantities of sodium chloride, e.g., 1000 g in 600 mL of water,[24] is harmful and can induce irritation of the gastrointestinal tract, vomiting, hypernatremia, respiratory distress, convulsions, or death.

In rats, the minimum lethal intravenous dose is 2.5 g/kg body-weight.

LD_{50} (mouse, IP): 6.61 g/kg[25]
LD_{50} (mouse, IV): 0.65 g/kg
LD_{50} (mouse, oral): 4.0 g/kg
LD_{50} (mouse, SC): 3.0 g/kg
LD_{50} (rat, oral): 3.0 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium chloride evolves a vapor irritating to the eyes if heated to high temperatures.

16. Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (injections, inhalations, nasal, ophthalmic, oral, otic, rectal, and topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

China, Eur, Int, Jpn, Pol, and US.

18. Related Substances

Potassium chloride.

19. Comments

Domestic table salt may contain sodium iodide (as a prophylactic substance against goiter) and agents such as magnesium carbonate, calcium phosphate, or starch, which reduce the hygroscopic characteristics of the salt and maintain the powder in a free-flowing state.

Food-grade dendritic salt, which is porous, can be used as an absorbent for liquid medications, and as a tablet diluent in specific formulations.

Each gram of sodium chloride represents approximately 17.1 mmol of sodium and 17.1 mmol of chloride; 2.54 g of sodium chloride is approximately equivalent to 1 g of sodium.

A saturated solution of sodium chloride can be used as a constant humidity solution; at 25°C, a relative humidity of 75% is produced.

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21. General References

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22. Authors

CG Cable.

Water

1. Nonproprietary Names

BP: Purified water
JP: Purified water
PhEur: Aqua purificata
USP: Purified water

See also Sections 8 and 18.

2. Synonyms

Aqua; hydrogen oxide.

3. Chemical Name and CAS Registry Number

Water [7732-18-5]

4. Empirical Formula and Molecular Weight

H_2O 18.02

5. Structural Formula

H_2O

6. Functional Category

Solvent.

7. Applications in Pharmaceutical Formulation or Technology

Water is the most widely used excipient in pharmaceutical production operations. Specific grades of water are used for particular applications in concentrations up to 100%, *see* Table I. Purified water and water for injection are also used for cleaning operations during production of pharmaceutical products.

8. Description

The term 'water' is used to describe potable water freshly drawn direct from the public supply and suitable for drinking. The chemical composition of potable water is variable and the nature and concentration of the impurities in it depends upon the source from which it is drawn. Although potable water must be both palatable and safe to drink, for most pharmaceutical applications potable water is purified by distillation, ion exchange treatment, reverse osmosis, or some other suitable process to produce 'purified water'. For certain applications, water with pharmacopeial specifications differing from purified water should be used, e.g., water for injection, *see* Sections 9 and 20.

Water is a clear, colorless, odorless, and tasteless liquid.

9. Pharmacopeial Specifications

See Table II.

Significant changes to the USP testing of Purified Water and Water for Injection were introduced in the 5th supplement to the USP23. These changes were not intended to tighten specifications but to allow the application of modern rapid analytical techniques and to replace the old semiquantitative methods. The changes involve the introduction of a conductivity test for inorganic contamination to replace the various chemical tests and the introduction of a Total Organic Carbon test (TOC) to replace the oxidizable substances test. A TOC limit of 500 ppb was selected based on the JP and this was found to be acceptable when applied to pharmaceutical companies throughout the US. The conductivity test is multistaged to allow for CO_2 absorption and temperature effects. Meeting the limits at the first stage precludes the need to test stages 2 and 3; if the results are higher than the limit at stage 1 the sample does not fail if shown to be satisfactory at stage 2 or 3. It is preferable to test TOC on line rather than laboratory testing.

The PhEur has issued a monograph which is comparable to the chemical testing requirements of the USP. Work is currently ongoing to produce a document which harmonizes the quality requirements of purified water in the PhEur, the JP, and the USP.

Table I: Typical applications of specific grades of water.

Type	Use
Bacteriostatic water for injection	Diluent for ophthalmic and multiple-dose injections.
Potable water	Public supply suitable for drinking, the purity of which is unlikely to be suitable for use in the manufacture of pharmaceuticals.
Purified water	Vehicle and solvent for the manufacture of drug products and pharmaceutical preparations; not suitable for use in the manufacture of parenteral products.
Sterile water for inhalation	Diluent for inhalation therapy products.
Sterile water for injection	Diluent for injections.
Sterile water for irrigation	Diluent for internal irrigation therapy products.
Water for injections in bulk	Water for the bulk preparation of medicines for parenteral administration.

10. Typical Properties

Boiling point: 100°C
Critical pressure: 22.1 MPa (218.3 atm)
Critical temperature: 374.2°C
Dielectric constant: $D^{25} = 78.54$
Dipole moment:
1.76 in benzene at 25°C;
1.86 in dioxane at 25°C.
Ionization constant: 1.008×10^{-14} at 25°C
Latent heat of fusion: 6 kJ/mole (1.436 kcal/mole)
Latent heat of vaporization:
40.7 kJ/mole (9.717 kcal/mole)
Melting point: 0°C
Refractive index: $n_D^{20} = 1.3330$
Solubility: miscible with most polar solvents.
Specific gravity: 0.9971 at 25°C.
Specific heat (liquid):
4.184 J/g/°C (1.00 cal/g/°C) at 14°C
Surface tension:
71.97 mN/m (71.97 dynes/cm) at 25°C.
Vapor pressure: 3.17 kPa (23.76 mmHg) at 25°C.
Viscosity (dynamic): 0.89 mPa s (0.89 cP) at 25°C.

Table II: Pharmacopeial specifications of water for different pharmaceutical applications.

Test	Purified Water in bulk JP	Purified Water in bulk PhEur	Purified Water in bulk USP	Purified Water in containers PhEur	Water for injection JP	Water for injection PhEur	Water for injection USP	Sterile water for injection PhEur	Sterile water for injection USP	Sterile bacteriostatic water for injection USP	Sterile water for inhalation USP	Sterile water for irrigation JP	Sterile water for irrigation USP	Sterile purified water USP
Identification	—	—	+	+	—	—	+	+	+	+	+	—	+	—
pH	—	—	—	—	—	—	—	—	5-7	4.5-7.0	4.5-7.5	—	5.0-7.0	5.0-7.0
Acid or alkali	+	—	—	+	+	—	—	+	—	—	—	+	—	—
Chloride	+	—	—	+	+	—	—	+[a]	+	+	+	+	+	+
Sulfate	+	—	—	+	+	—	—	—	+	+	+	+	+	+
Ammonium	+	—	—	+	+	—	—	—	+	+	+	≤ 0.05 mg/L	+	+
Calcium	—	—	—	+	—	—	—	—	+	+	+	—	+	+
Magnesium	—	—	—	+	—	—	—	—	—	—	—	—	—	—
Nitrate	+	+	—	+	+	+	—	+	—	—	—	—	—	—
Carbon dioxide	—	—	—	—	—	—	—	—	+	+	+	—	+	+
Heavy metals	+	+	—	+	+	+	—	+	—	—	—	+	—	—
Oxidizable substances	+	+	—	+	+	+	—	+	+	—	+	+	+	+
TOC	—	≤ 500 ppb	≤ 500 ppb	≤ 500 ppb	—	≤ 500 ppb	≤ 500 ppb	+	—	—	—	—	—	—
Conductivity	—	≤ 4.3 µs/cm	1.25 µs/cm	≤ 4.3 µs/cm	—	≤ 1.1 µs/cm	1.25 µs/cm	+[b]	—	—	—	—	—	—
Antimicrobial agents	—	—	—	—	—	—	—	—	—	+	—	—	—	—
Sterility	—	—	—	—	—	—	—	+	+	+	+	+	+	+
Particulate matter	+	—	—	—	+	—	+	+	—	+	—	+	—	—
Microbial contamination	+	≤ 100 cfu/mL	—	≤ 100 cfu/mL	+	≤ 10 cfu/mL	—	+	+	+	+	+	+	+
Bacterial endotoxins	—	+	—	—	≤ 0.25 EU/mL	≤ 0.25 IU/mL	≤ 0.25 EU/mL	≤ 0.25 IU/mL	≤ 0.25 EU/mL	≤ 0.5 EU/mL	≤ 0.5 EU/mL	—	≤ 0.25 EU/mL	—

Note: + = tested for; - = not tested for.

[a] If volume 100 mL or less.

[b] Containers with nominal volume at 10 mL or less, ≤ 25 µs/cm. If the nominal volume is greater than 10 mL, ≤ 5 µs/cm.

Table III: Storage requirements for different grades of water.

Type	Storage requirements[a]
Bacteriostatic water for injection	Preserve in single-dose and multiple-dose containers, preferably of Type I or Type II glass, not larger than 30 mL in size.
Potable water	Preserve in tightly sealed containers.
Purified water	Preserve in tightly sealed containers. If stored in bulk, the conditions of storage should be designed to limit the growth of microorganisms and avoid any other contamination.
Sterile water for inhalation	Preserve in single-dose containers, preferably of Type I or Type II glass.
Sterile water for injection	Preserve in single-dose containers, preferably of Type I or Type II glass, not more than 1000 mL in size.
Water for injection	Preserve in tightly sealed containers.
Water for injections in bulk	Collected and stored in conditions designed to prevent growth of microorganisms and avoid any other contamination.

[a] To prevent evaporation and to maintain quality.

11. Stability and Storage Conditions

Water is chemically stable in all physical states (ice, liquid, and steam). Water for specific purposes should be stored in an appropriate container, *see* Table III.

12. Incompatibilities

In pharmaceutical formulations, water can react with drugs and other excipients that are susceptible to hydrolysis (decomposition in the presence of water or moisture) at ambient and elevated temperatures.

Water can react violently with alkali metals and rapidly with alkaline metals and their oxides, such as calcium oxide and magnesium oxide. Water also reacts with anhydrous salts to form hydrates of various compositions, and with certain organic materials and calcium carbide.

13. Method of Manufacture

Unlike other excipients water is not purchased from outside suppliers but is manufactured in-house by pharmaceutical companies. The selection of the most appropriate system and the overall design of the system are crucial factors to ensure that water of the correct quality is produced.[1,14]

To produce potable or drinking water, insoluble matter is first removed from a water supply by coagulation, settling, and filtering processes. Pathogenic microorganisms present are then destroyed by aeration, chlorination, or some other means. Water may also be rendered free of viable pathogenic microorganisms by active boiling for 15-20 minutes. Finally, the palatability of the water is then improved by aeration and charcoal filtration.

The quality attributes of water for injection (WFI) are stricter than for purified water. Consequently the preparation methods typically vary in the last stage to ensure good control of quality of WFI. Methods for the production of WFI are the subject of current debate. The PhEur believes only distillation would give assurance of consistent supply of the right quality. The USP and the JP however permit the use of reverse osmosis (RO) in addition to distillation and ultrafiltration, agreement is therefore required before a harmonized document can be issued.

Purified water suitable for use in pharmaceutical formulations is usually prepared by purifying potable water by one of several processes, such as: distillation; de-ionization; or reverse osmosis.[1-7]

Distillation: a wide variety of stills are available to produce purified or distilled water. A typical design consists of an evaporator, vapor separator, and compressor. The distill and (raw feed water) is heated in the evaporator to boiling and the vapor produced separated from entrained distill and in the separator. The vapor then enters a compressor where the temperature of the vapors is raised to 107°C. Superheated vapors are then condensed on the outer surface of the tubes of the evaporator containing cool distill and circulating within.

Vapor compression stills of various sizes are commercially available and can be used to produce water of high purity when properly constructed. A high-quality distillate, such as water for injection, can be obtained if the water is first deionized. The best stills are constructed of types 304 or 316 stainless steel and coated with pure tin, or are made from chemical-resistant glass.

De-ionization: cationic and anionic ion-exchange resins are used to purify potable water by removing any dissolved ions. Dissolved gases are also removed, while chlorine, in the concentrations generally found in potable water, is destroyed by the resin itself. Some organics and colloidal particles are removed by adsorption and filtration. Resin beds may however foster microbial life and produce pyrogenic effluent unless adequate precautions are taken to prevent contamination. Mixed bed units produce purer water (decreased conductivity) than stills. However, the organic matter content is usually higher. Ion-exchange units are normally used today to treat raw feed water prior to distillation or reverse osmosis processing.

Reverse osmosis: water is forced through a semipermeable membrane in the opposite direction to normal osmotic diffusion. A very small proportion of inorganic salts passes through, but undissolved materials (bacteria and large molecules, such as viruses, pyrogens, and high molecular weight organics) are removed.

Ultra filtration: a permeable membrane is used for mechanical separation. Impurities including endotoxins are removed by the membrane.

14. Safety

Water is the base for many biological life forms, and its safety in pharmaceutical formulations is unquestioned provided it meets standards of quality for potability[8] and microbial content, *see* Sections 9 and 19. Plain water is considered slightly more toxic upon injection to laboratory animals than physiological salt solutions such as normal saline or Ringer's solution.

Ingestion of excessive quantities of water can lead to water intoxication with disturbances of the electrolyte balance.

Water for injection should be free from pyrogens.

15. Handling Precautions

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

16. Regulatory Status

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

17. Pharmacopeias

China, Eur, Int, Jpn, Pol, and US.

18. Related Substances

–

Bacteriostatic water for injection

Pharmacopeias: US.

Comments: the USP describes bacteriostatic water for injection as sterile water for injection which contains one or more suitable antimicrobial agents.

Carbon dioxide-free water

Comments: purified water that has been boiled vigorously for 5 minutes and allowed to cool while protecting it from absorption of atmospheric carbon dioxide.

De-aerated water

Comments: purified water that has been boiled vigorously for 5 minutes and cooled to reduce the air (oxygen) content.

Hard water

Comments: water containing the equivalent to not less than 120 mg/L and not more than 180 mg/L of calcium carbonate.

Soft water

Comments: water containing the equivalent to not more than 60 mg/L of calcium carbonate.

Sterile water for inhalation

Pharmacopeias: US.

Comments: the USP describes sterile water for inhalation as water purified by distillation or by reverse osmosis and rendered sterile. It contains no antimicrobial agents or other added substances, except where used in humidifiers or other similar devices, and where liable to contamination over a period of time.

Sterile water for injection

Pharmacopeias: US.

Comments: the USP describes sterile water for injection as water for injection sterilized and suitably packaged. It contains no antimicrobial agents or other substances.

Sterile water for irrigation

Pharmacopeias: Br and US.

Comments: the USP describes sterile water for irrigation as water for injection sterilized and suitably packaged. It contains no antimicrobial agents or other substances.

Water for injection

Pharmacopeias: China, Eur, Int, Jpn, Pol, and US.

Comments: the USP describes water for injection as water purified by distillation or reverse osmosis. It contains no added substances. The PhEur title is 'water for injections' and comprises two parts, 'water for injections in bulk' and 'sterilized water for injection'. The PhEur states that water for injections is produced by distillation.

19. Comments

In most pharmacopeias, the term 'water' now refers to purified or distilled water.

Without further purification, 'water' may be unsuitable for certain pharmaceutical applications, e.g., the presence of calcium in water affects the viscosity and gel strength of algins and pectin dispersions, while the use of potable water affects the clarity and quality of cough mixtures, and the stability of antibiotic liquid preparations.

Water commonly contains salts of aluminum, calcium, iron, magnesium, potassium, sodium, and zinc. Toxic substances such as arsenic, barium, cadmium, chromium, cyanide, lead, mercury, and selenium may constitute a danger to health if present in excessive amounts. Ingestion of water containing high amounts of calcium and nitrate is also contra-indicated. National standards generally specify the maximum limits for these inorganic substances in potable water. Limits have also been placed on microorganisms, detergents, phenolics, chlorinated phenolics, and other organic substances. The WHO,[9] and other national bodies, have issued guidelines for water quality although many countries have their own standards for water quality embodied in specific legislation.[10] *See* Table IV.

Table IV: Limits for inorganic substances in potable water (mg/L).

Contaminant	UK (mg/L)	WHO (mg/L)
Aluminum	0.2	0.2
Ammonium	0.5	—
Antimony	0.01	—
Arsenic	0.05	0.05
Barium	1.0	No limit
Beryllium	—	No limit
Boron	2.0	—
Cadmium	0.005	0.005
Calcium	250	—
Chloride	400	250
Chromium	0.05	0.05
Copper	3.0	1.0
Cyanide	0.05	0.1
Fluoride	1.5	1.5
Iron	0.2	0.3
Lead	0.05	0.05
Magnesium	50	—
Manganese	0.05	0.1
Mercury	0.001	0.001
Nickel	0.05	No limit
Nitrate (as N)	—	10
Nitrate (as NO_3)	50	—
Nitrite (as NO_2)	0.1	—
Phosphorus	2.2	—
Potassium	12	—
Selenium	0.01	0.01
Silver	0.01	No limit
Sodium	150	200
Sulfate	250	400
Zinc	5.0	5.0

Control of microbiological contamination is critical for waters used in preparation of pharmaceuticals as proliferation of microorganisms can potentially occur during all stages of manufacture, storage, or distribution. Suitable control is achieved by ensuring that the water system is well designed and well maintained. Purified water which is produced, stored, and circulated at ambient temperatures is susceptible to the establishment of biofilms; therefore, frequent monitoring, high usage, correct flow rate, and appropriate sanitization are all factors which require consideration to ensure that water is satisfactory.[12]

In order to demonstrate correct microbiological quality is achieved monitoring of the whole system is essential. For WFI the recommended methodology is membrane filtration (0.45 μm) as a large sample size (100-300 mL) is required. For purified water, membrane filtration or plate count methods are typically used depending on the quality requirements of the system. It is important to set appropriate target, alert, and action limits to serve as an indication of action required to bring the quality of water back under control. It is recognized that limits are not intended as pass/fail criteria for water or product batches; however, an investigation regarding the implications should be conducted.[13]

Validation is conducted to provide a high level of assurance that the water production and distribution system will consistently produce water conforming to a defined quality specification. The validation process serves to qualify the design (DQ), installation (IQ), operation (OQ), and performance (PQ) of the system. The extent of monitoring data required should be defined with consideration given to whether validation to FDA guidelines is required.[13] It is also important to have an ongoing control program with respect to maintenance and periodic reviews of the performance of the water system.

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