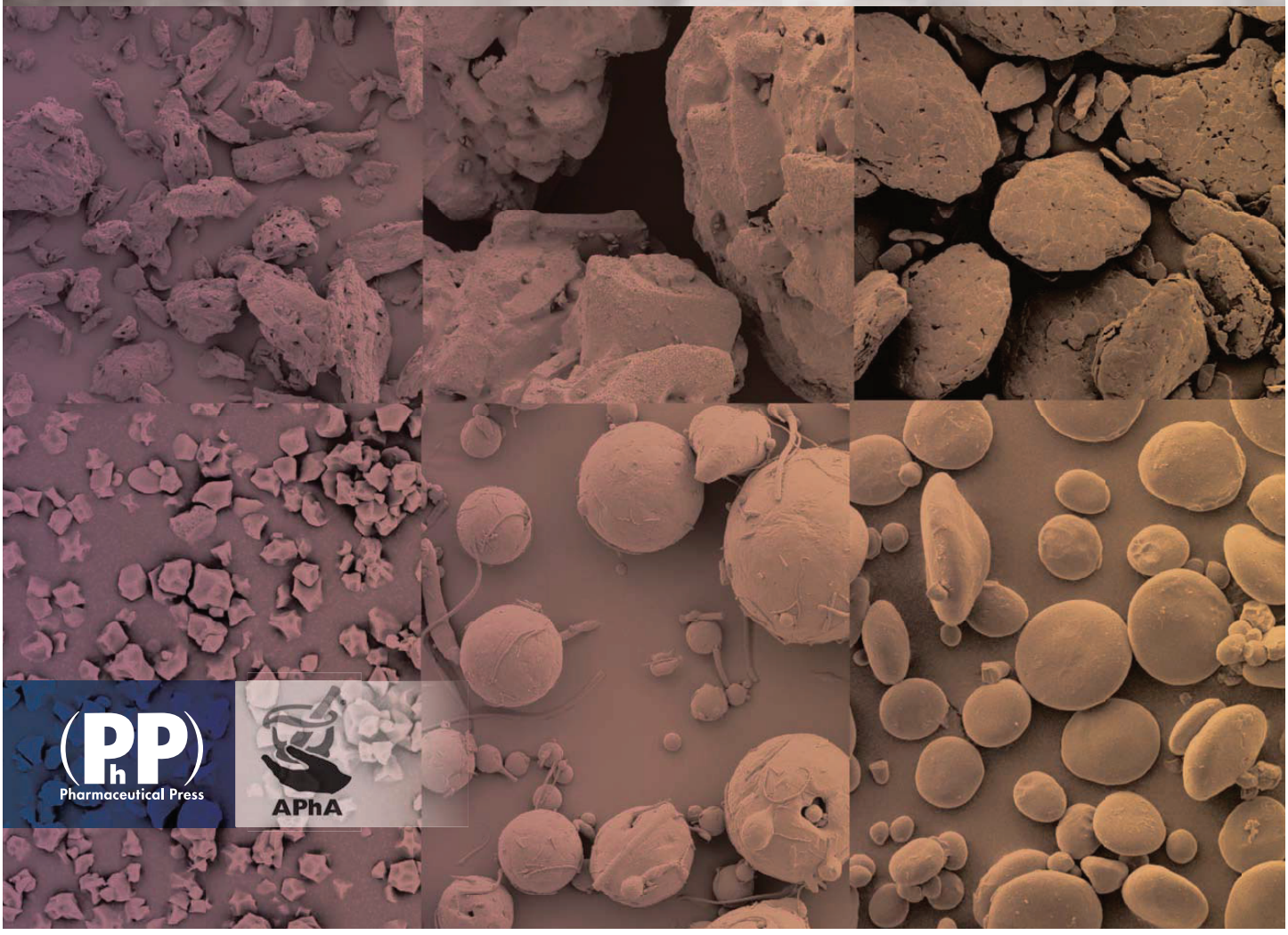
Handbook of Pharmaceutical Excipients

Sixth edition

Edited by
Raymond C Rowe, Paul J Sheskey and Marian E Quinn



Pharmaceutical Press
APhA

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Benzalkonium Chloride

B

1 Nonproprietary Names

BP: Benzalkonium Chloride

JP: Benzalkonium Chloride

PhEur: Benzalkonium Chloride

USP-NF: Benzalkonium Chloride

2 Synonyms

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

3 Chemical Name and CAS Registry Number

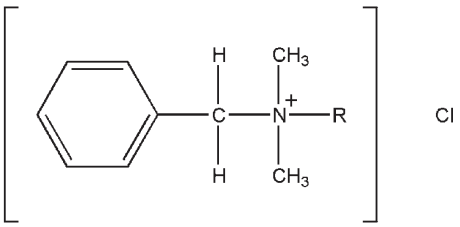
Alkyldimethyl(phenylmethyl)ammonium chloride [8001-54-5]

4 Empirical Formula and Molecular Weight

The USP32–NF27 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,[1] 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,[2] and otic formulations a concentration of 0.002–0.02% w/v 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 was also shown to enhance the topical penetration of lorazepam.[3]

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

See Table I.

Table I: Pharmacopeial specifications for benzalkonium chloride.

Test	JP XV	PhEur 6.4	USP32–NF27
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	–	+	+
Petroleum ether-soluble substances	⩽1.0%	–	–
Benzyl alcohol	–	⩽0.5%	–
Benzaldehyde	–	⩽0.15%	–
Chloromethylbenzene	–	⩽0.05%	–
Assay (dried basis)			
of *n*-$C_{12}H_{25}$	–	–	⩾40.0%
of *n*-$C_{14}H_{29}$	–	–	⩾20.0%
of *n*-$C_{12}H_{25}$ and *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, *see* Table II. The antimicrobial activity of benzalkonium chloride is significantly dependent upon the alkyl composition of the homolog mixture.[4] 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.[5] Antimicrobial activity may also be enhanced by the addition of phenylmercuric acetate, phenylmercuric borate, chlorhexidine, cetrimide, or *m*-cresol.[6,7] 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.[8] Inhibitory activity

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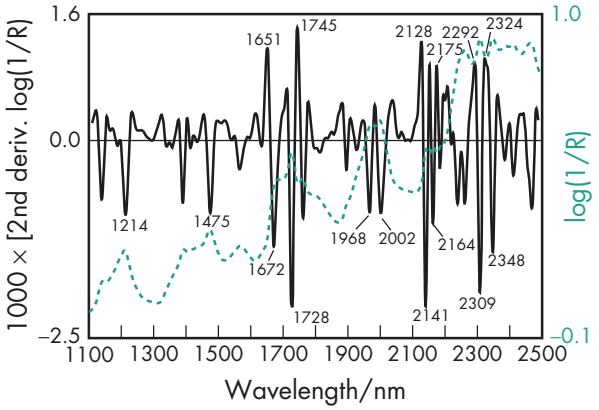


Figure 1: Near-infrared spectrum of benzalkonium chloride measured by reflectance.

increases with pH, although antimicrobial activity occurs at pH 4–10.

Table II: 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
NIR spectra *see* Figure 1.
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, hypromellose,[9] 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.[10]

13 Method of Manufacture

Benzalkonium chloride is formed by the reaction of a solution of *N*-alkyl-*N*-methylbenzamine 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 is 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.[11]

Ototoxicity can occur when benzalkonium chloride is applied to the ear[12] 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.[13–17]

Toxicity experiments with rabbits have shown benzalkonium chloride to be harmful to the eye in concentrations higher than that normally used as a preservative. 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.[18] 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} (mouse, oral): 150 mg/kg[19]
LD_{50} (rat, IP): 14.5 mg/kg
LD_{50} (rat, IV): 13.9 mg/kg
LD_{50} (rat, oral): 300 mg/kg
LD_{50} (rat, skin): 1.42 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 Database (inhalations, IM injections, nasal, ophthalmic, otic, and topical preparations).

Included in nonparenteral medicines licensed in the UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzethonium chloride; cetrimide.

18 Comments

Benzalkonium chloride has been used in antiseptic wipes and has been shown to produce significantly less stinging or burning than isopropyl alcohol and hydrogen peroxide.[20]

The EINECS numbers for benzalkonium chloride are 264-151-6; 260-080-8; 269-919-4; 270-325-2; 287-089-1. The PubChem Compound ID (CID) for benzalkonium chloride is 3014024

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21 Author

AH Kibbe.

22 Date of Revision

15 January 2009.

Benzethonium Chloride

1 Nonproprietary Names

BP: Benzethonium Chloride
JP: Benzethonium Chloride
PhEur: Benzethonium Chloride
USP: Benzethonium Chloride

2 Synonyms

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

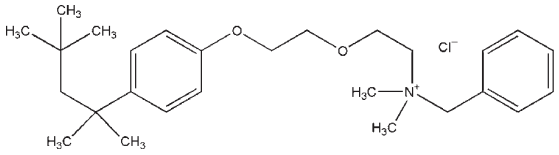
3 Chemical Name and CAS Registry Number

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

4 Empirical Formula and Molecular Weight

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

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Benzethonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative. Typically, it is used for this purpose in injections, ophthalmic and otic preparations at concentrations 0.01–0.02% w/v. Benzethonium chloride may also be used as a wetting and solubilizing agent, and as a topical disinfectant.[1,2]

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

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

8 Description

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

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzethonium chloride.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	—
Acidity or alkalinity	—	+	—
Melting range	158–164°C	158–164°C	158–163°C
Loss on drying	⩽5.0%	⩽5.0%	⩽5.0%
Residue on ignition	⩽0.1%	—	⩽0.1%
Sulfated ash	—	⩽0.1%	—
Ammonium compounds	+	⩽50 ppm	+
Assay (dried basis)	⩾97.0%	97.0–103.0%	97.0–103.0%

10 Typical Properties

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

Antimicrobial activity Optimum antimicrobial activity occurs between pH 4–10. Preservative efficacy is enhanced by ethanol and reduced by soaps and other anionic surfactants. For typical minimum inhibitory concentrations (MICs) *see* Table II.[3]

Table II: Minimum inhibitory concentration (MIC) for benzethonium chloride.

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

NIR spectra *see* Figure 1.

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

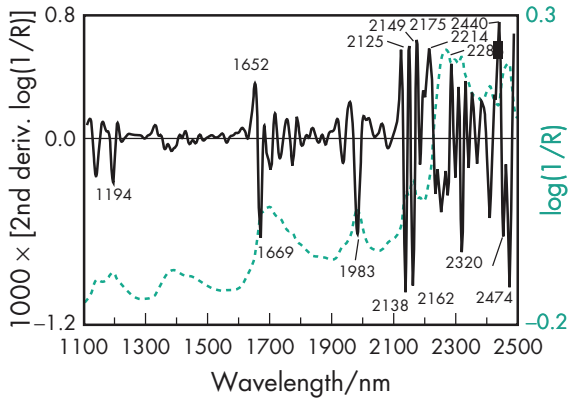


Figure 1: Near-infrared spectrum of benzethonium chloride measured by reflectance.

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11 Stability and Storage Conditions

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

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

12 Incompatibilities

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

13 Method of Manufacture

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

14 Safety

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

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

See also Benzalkonium Chloride.

LD_{50} (mouse, IP): 15.5 mg/kg[6]
LD_{50} (mouse, IV): 30 mg/kg
LD_{50} (mouse, oral): 338 mg/kg
LD_{50} (rat, IP): 16.5 mg/kg
LD_{50} (rat, IV): 19 mg/kg
LD_{50} (rat, oral): 368 mg/kg
LD_{50} (rat, SC): 119 mg/kg

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (IM and IV injections; nasal, ophthalmic and otic preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzalkonium chloride; cetrimide.

18 Comments

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

The EINECS number for benzethonium chloride is 204-479-9. The PubChem Compound ID (CID) for benethonium chloride includes 8478 and 547429.

19 Specific References

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21 Author

ME Quinn.

22 Date of Revision

27 January 2009.

Benzyl Alcohol

B

1 Nonproprietary Names

BP: Benzyl Alcohol
JP: Benzyl Alcohol
PhEur: Benzyl Alcohol
USP-NF: Benzyl Alcohol

2 Synonyms

Alcohol benzylicus; benzenemethanol; α-hydroxytoluene; phenylcarbinol; phenylmethanol; α-toluenol.

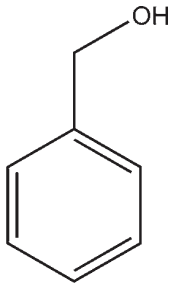
3 Chemical Name and CAS Registry Number

Benzenemethanol [100-51-6]

4 Empirical Formula and Molecular Weight

C_7H_8O 108.14

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations,[1–4] including oral and parenteral preparations, at concentrations up to 2.0% v/v. The typical concentration used is 1% v/v, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006.[5] In cosmetics, concentrations up to 3.0% v/v may be used as a preservative. Concentrations of 5% v/v or more are employed as a solubilizer, while a 10% v/v solution is used as a disinfectant.

Benzyl alcohol 10% v/v solutions also have some local anesthetic properties, which are exploited in some parenterals, cough products, ophthalmic solutions, ointments, and dermatological aerosol sprays.

Although widely used as an antimicrobial preservative, benzyl alcohol has been associated with some fatal adverse reactions when administered to neonates. It is now recommended that parenteral products preserved with benzyl alcohol, or other antimicrobial preservatives, should not be used in newborn infants if at all possible; *see* Section 14.

8 Description

A clear, colorless, oily liquid with a faint aromatic odor and a sharp, burning taste.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

Table I: Pharmacopeial specifications for benzyl alcohol.

Test	JP XV	PhEur 6.5	USP32–NF27
Identification	+	+	+
Characters	+	+	—
Solubility	+	+	—
Acidity	+	+	+
Clarity and color of solution	+	+	+
Specific gravity	1.043–1.049	1.043–1.049	—
Refractive index	1.538–1.541	1.538–1.541	1.538–1.541
Residue on evaporation	⩽0.05%	⩽0.05%	⩽0.05%
Related substances	+	+	+
Benzaldehyde	+	+	0.05–0.15
Peroxide value	⩽5	⩽5	⩽5
Assay	98.0–100.5%	98.0–100.5%	98.0–100.5%

10 Typical Properties

Acidity/alkalinity Aqueous solutions are neutral to litmus.

Antimicrobial activity Benzyl alcohol is bacteriostatic and is used as an antimicrobial preservative against Gram-positive bacteria, molds, fungi, and yeasts, although it possesses only modest bactericidal properties. Optimum activity occurs at pH below 5; little activity is shown above pH 8. Antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80. However, the reduction in activity is less than is the case with either hydroxybenzoate esters or quaternary ammonium compounds. The activity of benzyl alcohol may also be reduced by incompatibilities with some packaging materials, particularly polyethylene; *see* Section 12.

See Table II for reported minimum inhibitory concentrations (MICs).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.[4]

Microorganism	MIC (μg/mL)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

Bacteria Benzyl alcohol is moderately active against most Gram-positive organisms (typical MICs are 3–5 mg/mL), although some Gram-positive bacteria are very sensitive (MICs 0.025–0.05 mg/mL). In general, benzyl alcohol is less active against Gram-negative organisms.

Fungi Benzyl alcohol is effective against molds and yeasts; typical MICs are 3–5 mg/mL.

Spores Benzyl alcohol is inactive against spores, but activity may be enhanced by heating. Benzyl alcohol 1% v/v, at pH 5–6, has been claimed to be as effective as phenylmercuric nitrate 0.002% w/v against *Bacillus stearothermophilus* at 100°C for 30 min.

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Autoignition temperature 436.5°C
Boiling point 204.7°C
Flammability Flammable. Limits in air 1.7–15.0% v/v.
Flash point
100.6°C (closed cup);
104.5°C (open cup).
Freezing point −15°C
Partition coefficients
Liquid paraffin : water = 0.2;
Octanol : water = 1.10;
Peanut oil : water = 1.3.
Solubility *see* Table III.

Table III: Solubility of benzyl alcohol.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Miscible in all proportions
Ethanol	Miscible in all proportions
Ethanol (50%)	1 in 1.5
Ether	Miscible in all proportions
Fixed and volatile oils	Miscible in all proportions
Water	1 in 25 at 25°C 1 in 14 at 90°C

Surface tension 38.8 mN/m (38.8 dynes/cm)
Vapor density (relative) 3.72 (air = 1)
Vapor pressure
13.3 Pa (0.1 mmHg) at 30°C;
1.769 kPa (13.3 mmHg) at 100°C.
Viscosity (dynamic) 6 mPa s (6 cP) at 20°C

11 Stability and Storage Conditions

Benzyl alcohol oxidizes slowly in air to benzaldehyde and benzoic acid; it does not react with water. Aqueous solutions may be sterilized by filtration or autoclaving; some solutions may generate benzaldehyde during autoclaving.

Benzyl alcohol may be stored in metal or glass containers. Plastic containers should not be used; exceptions to this include polypropylene containers or vessels coated with inert fluorinated polymers such as Teflon; *see* Section 12.

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

12 Incompatibilities

Benzyl alcohol is incompatible with oxidizing agents and strong acids. It can also accelerate the autoxidation of fats.

Although antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80, the reduction is less than is the case with hydroxybenzoate esters or quaternary ammonium compounds.

Benzyl alcohol is incompatible with methylcellulose and is only slowly sorbed by closures composed of natural rubber, neoprene, and butyl rubber closures, the resistance of which can be enhanced by coating with fluorinated polymers.[6] However, a 2% v/v aqueous solution in a polyethylene container, stored at 20°C, may lose up to 15% of its benzyl alcohol content in 13 weeks.[7] Losses to polyvinyl chloride and polypropylene containers under similar conditions are usually negligible. Benzyl alcohol can damage polystyrene syringes by extracting some soluble components.[8]

13 Method of Manufacture

Benzyl alcohol is prepared commercially by the distillation of benzyl chloride with potassium or sodium carbonate. It may also be prepared by the Cannizzaro reaction of benzaldehyde and potassium hydroxide.

14 Safety

Benzyl alcohol is used in a wide variety of pharmaceutical formulations. It is metabolized to benzoic acid, which is further metabolized in the liver by conjugation with glycine to form hippuric acid, which is excreted in the urine.

Ingestion or inhalation of benzyl alcohol may cause headache, vertigo, nausea, vomiting, and diarrhea. Overexposure may result in CNS depression and respiratory failure. However, the concentrations of benzyl alcohol normally employed as a preservative are not associated with such adverse effects.

Reports of adverse reactions to benzyl alcohol[9,10] used as an excipient include toxicity following intravenous administration;[11–13] neurotoxicity in patients administered benzyl alcohol in intrathecal preparations;[14,15] hypersensitivity,[16–18] although relatively rare; and a fatal toxic syndrome in premature infants.[19–22]

The fatal toxic syndrome in low-birth-weight neonates, which includes symptoms of metabolic acidosis and respiratory depression, was attributed to the use of benzyl alcohol as a preservative in solutions used to flush umbilical catheters. As a result of this, the FDA has recommended that benzyl alcohol should not be used in such flushing solutions and has advised against the use of medicines containing preservatives in the newborn.[23,24]

The WHO has set the estimated acceptable daily intake of the benzyl/benzoic moiety at up to 5 mg/kg body-weight daily.[25]

LD_{50} (mouse, IV): 0.32 g/kg[26]
LD_{50} (mouse, oral): 1.36 g/kg
LD_{50} (rat, IP): 0.4 g/kg
LD_{50} (rat, IV): 0.05 g/kg
LD_{50} (rat, oral): 1.23 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzyl alcohol (liquid and vapor) is irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and protective clothing are recommended. Benzyl alcohol should be handled in a well-ventilated environment; a self-contained breathing apparatus is recommended in areas of poor ventilation. Benzyl alcohol is flammable.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (dental injections, oral capsules, solutions and tablets, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Benzyl alcohol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

The EINECS number for benzyl alcohol is 202-859-9. The PubChem Compound ID (CID) for benzyl alcohol is 244.

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21 Author

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22 Date of Revision

3 February 2009.

Benzyl Benzoate

1 Nonproprietary Names

BP: Benzyl Benzoate
JP: Benzyl Benzoate
PhEur: Benzyl Benzoate
USP: Benzyl Benzoate

2 Synonyms

Benzoic acid benzyl ester; benzylbenzenecarboxylate; benzylis benzoas; benzyl phenylformate; phenylmethyl benzoate.

3 Chemical Name and CAS Registry Number

Benzoic acid phenylmethyl ester [120-51-4]

4 Empirical Formula and Molecular Weight

$C_{14}H_{12}O_2$ 212.24

5 Structural Formula

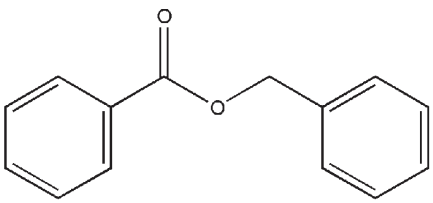


Table I: FCC specification for butylene glycol.[13]

Test	FCC 6
Distillation range	200–215°C
Lead	⩽2 mg/kg
Specific gravity	1.004–1.006 at 20°C
Assay	⩾99.0%

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21 Authors

ME Quinn, RC Rowe.

22 Date of Revision

27 February 2009.

Butylparaben

1 Nonproprietary Names

BP: Butyl Hydroxybenzoate
JP: Butyl Parahydroxybenzoate
PhEur: Butyl Parahydroxybenzoate
USP-NF: Butylparaben

2 Synonyms

Butylis parahydroxybenzoas; butyl *p*-hydroxybenzoate; *CoSept B*; 4-hydroxybenzoic acid butyl ester; *Lexgard B*; *Nipabutyl*; *Tegosept B*; *Trisept B*; *Uniphen P-23*; *Unisept B*.

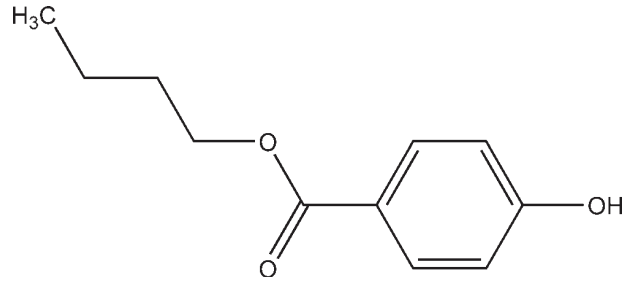
3 Chemical Name and CAS Registry Number

Butyl-4-hydroxybenzoate [94-26-8]

4 Empirical Formula and Molecular Weight

$C_{11}H_{14}O_3$ 194.23

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Butylparaben is widely used as an antimicrobial preservative in cosmetics and pharmaceutical formulations; *see* Table I.

It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics, it is the fourth most frequently used preservative.[1]

As a group, the parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

Owing to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used in formulations. However, this may raise the pH of poorly buffered formulations.

See Methylparaben for further information.

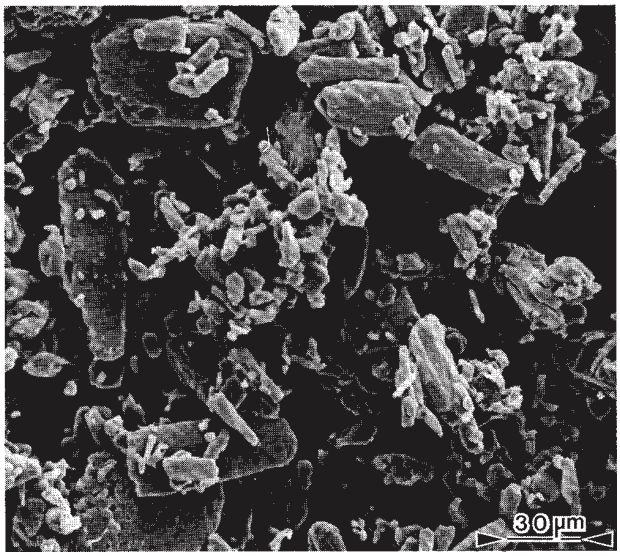
Table I: Uses of butylparaben.

Use	Concentration (%)
Oral suspensions	0.006–0.05
Topical preparations	0.02–0.4

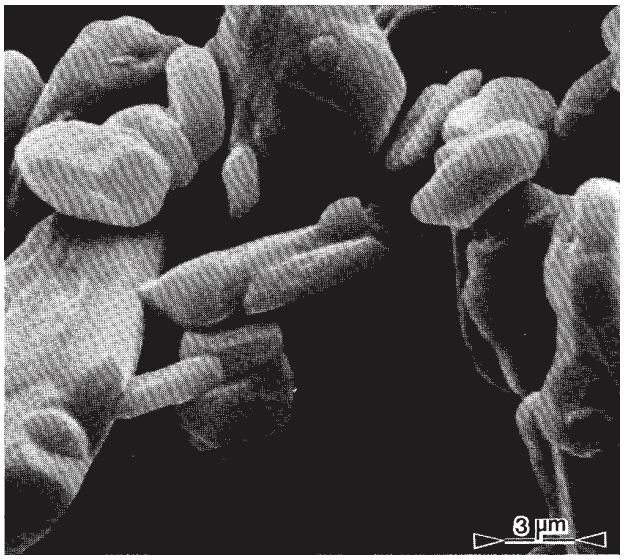
8 Description

Butylparaben occurs as colorless crystals or a white, crystalline, odorless or almost odorless, tasteless powder.

SEM 1: Excipient: butylparaben; magnification: 240×.



SEM 2: Excipient: butylparaben; magnification: 2400×.



9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for butylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	+
Melting range	68–71°C	68–71°C	68–71°C
Acidity	+	+	+
Residue on ignition	⩽0.1%	—	⩽0.1%
Sulfated ash	—	⩽0.1%	—
Related substances	+	+	+
Heavy metals	⩽20 ppm	—	—
Assay (dried basis)			
98.0–102.0%			
98.0–102.0%			
98.0–102.0%			

10 Typical Properties

Antimicrobial activity Butylparaben exhibits antimicrobial activity between pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria; *see* Table III.[2]

The activity of the parabens increases with increasing chain length of the alkyl moiety, but solubility decreases. Butylparaben is thus more active than methylparaben. Activity may be improved by using combinations of parabens since synergistic effects occur. Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben for further information.

Table III: Minimum inhibitory concentrations (MICs) for butylparaben in aqueous solution.[2]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	400
Aspergillus niger ATCC 9642	125
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	63
Bacillus subtilis ATCC 6633	250
Candida albicans ATCC 10231	125
Enterobacter cloacae ATCC 23355	250
Escherichia coli ATCC 8739	5000
Escherichia coli ATCC 9637	5000
Klebsiella pneumoniae ATCC 8308	250
Penicillium chrysogenum ATCC 9480	70
Penicillium digitatum ATCC 10030	32
Proteus vulgaris ATCC 13315	125
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	63
Saccharomyces cerevisiae ATCC 9763	35
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	125
Staphylococcus epidermidis ATCC 12228	250
Trichophyton mentagrophytes	35

Density (bulk) 0.731 g/cm^3
Density (tapped) 0.819 g/cm^3
Melting point 68–71°C
NIR spectra *see* Figure 1.
Partition coefficients Values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.[3]
Solubility *see* Table V.

Table IV: Partition coefficients for butylparaben between oils and water.[3]

Solvent	Partition coefficient oil : water
Mineral oil	3.0
Peanut oil	280
Soybean oil	280

11 Stability and Storage Conditions

Aqueous butylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.[4] At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).[5]

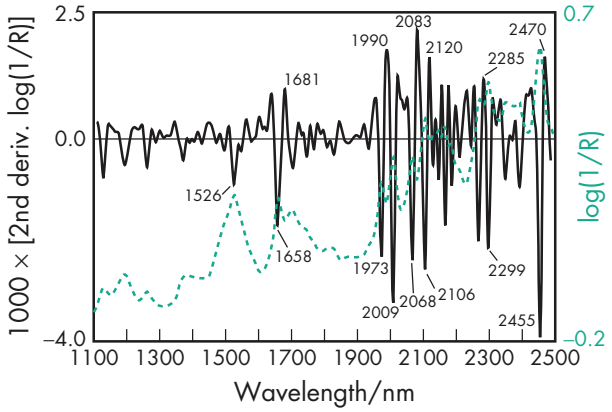


Figure 1: Near-infrared spectrum of butylparaben measured by reflectance.

Table V: Solubility of butylparaben.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 0.5
Ethanol (95%)	Freely soluble
Ether	Freely soluble
Glycerin	1 in 330
Methanol	1 in 0.5
Mineral oil	1 in 1000
Peanut oil	1 in 20
Propylene glycol	1 in 1
Water	1 in >5000 1 in 670 at 80°C

Butylparaben should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

The antimicrobial activity of butylparaben is considerably reduced in the presence of nonionic surfactants as a result of micellization.[6] Absorption of butylparaben by plastics has not been reported but appears probable given the behavior of other parabens. Some pigments, e.g. ultramarine blue and yellow iron oxide, absorb butylparaben and thus reduce its preservative properties.[7]

Butylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13 Method of Manufacture

Butylparaben is prepared by esterification of *p*-hydroxybenzoic acid with *n*-butanol.

14 Safety

Butylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions generally appearing as contact dematitis. Immediate reactions with urticaria and bronchospasm have occurred rarely. *See* Methylparaben for further information.

LD_{50} (mouse, IP): 0.23 g/kg[8]

LD_{50} (mouse, oral): 13.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (injections; oral capsules, solutions, suspensions, syrups and tablets; rectal, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben sodium; ethylparaben; methylparaben; propylparaben.

Butylparaben sodium

Empirical formula $C_{11}H_{13}NaO_3$
Molecular weight 216.23
CAS number [36457-20-2]
Synonyms Butyl-4-hydroxybenzoate sodium salt; sodium butyl hydroxybenzoate.
Appearance White, odorless or almost odorless, hygroscopic powder.
Acidity/alkalinity pH = 9.5–10.5 (0.1% w/v aqueous solution)
Solubility 1 in 10 of ethanol (95%); 1 in 1 of water.
Comments Butylparaben sodium may be used instead of butylparaben because of its greater aqueous solubility. In unbuffered formulations, pH adjustment may be required.

18 Comments

Butylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

See Methylparaben for further information and references.

The EINECS number for butylparaben is 202-318-7. The PubChem Compound ID (CID) for butylparaben is 7184.

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See also Methylparaben.

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See also Methylparaben.

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S Gold.

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20 General References

Armstrong NA. Tablet manufacture. Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, 2nd edn, vol. **3**: New York: Marcel Dekker, 2002; 2713–2732.
Bolhuis GK, Armstrong NA. Excipients for direct compression – an update. *Pharm Dev Technol* 2006; **11**: 111–124.

21 Author

NA Armstrong.

22 Date of Revision

16 January 2009.

Dextrin

1 Nonproprietary Names

BP: Dextrin
JP: Dextrin
PhEur: Dextrin
USP-NF: Dextrin

2 Synonyms

Avedex; British gum; *Caloreen*; canary dextrin; *C*Pharm*; *Crystal Gum*; dextrinum; dextrinum album; *Primogran W*; starch gum; yellow dextrin; white dextrin.

3 Chemical Name and CAS Registry Number

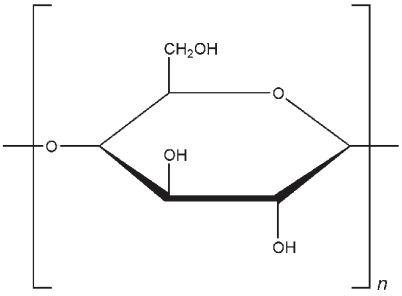
Dextrin [9004-53-9]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n{\cdot}xH_2O$ (162.14)*n*

The molecular weight of dextrin is typically 4500–85 000 and depends on the number of $(C_6H_{10}O_5)$ units in the polymer chain.

5 Structural Formula



6 Functional Category

Stiffening agent; suspending agent; tablet binder; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Dextrin is a dextrose polymer used as an adhesive and stiffening agent for surgical dressings. It is also used as a tablet and capsule diluent; as a binder for tablet granulation; as a sugar-coating ingredient that serves as a plasticizer and adhesive; and as a thickening agent for suspensions.

Additionally, dextrin has been used as a source of carbohydrate by people with special dietary requirements because it has a low electrolyte content and is free of lactose and sucrose.[1]

Dextrin is also used in cosmetics.

8 Description

Dextrin is partially hydrolyzed maize (corn), potato or cassava starch. It is a white, pale yellow or brown-colored powder with a slight characteristic odor.

9 Pharmacopeial Specifications

See Table I.

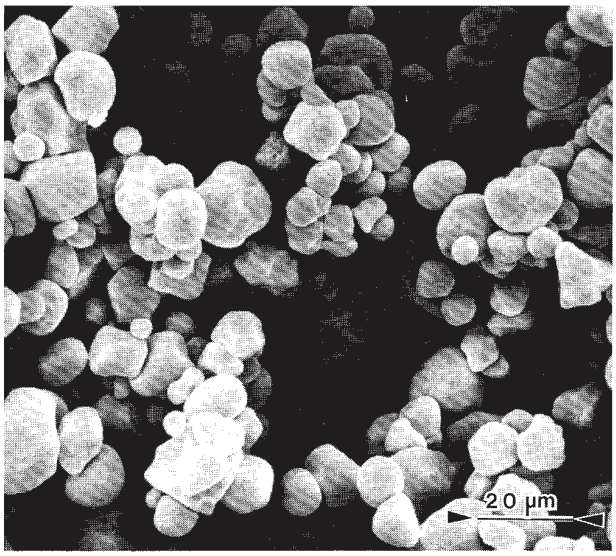
10 Typical Properties

Acidity/alkalinity pH = 2.8–8.0 for a 5% w/v aqueous solution.
Density (bulk) 0.80 g/cm^3
Density (tapped) 0.91 g/cm^3
Density (true) 1.495–1.589 g/cm^3
Melting point 178°C (with decomposition)
Moisture content 5% w/w
NIR spectra *see* Figure 1.
Particle size distribution *see* Figure 2.
Solubility Practically insoluble in chloroform, ethanol (95%), ether, and propan-2-ol; slowly soluble in cold water; very soluble in boiling water, forming a mucilaginous solution.
Specific surface area 0.14 m^2/g

11 Stability and Storage Conditions

Physical characteristics of dextrin may vary slightly depending on the method of manufacture and on the source material. In aqueous solutions, dextrin molecules tend to aggregate as density, tempera-

SEM 1: Excipient: dextrin; manufacturer: Matheson Colleman & Bell; magnification: 600×.



SEM 2: Excipient: dextrin; manufacturer: Matheson Colleman & Bell; magnification: 2400×.

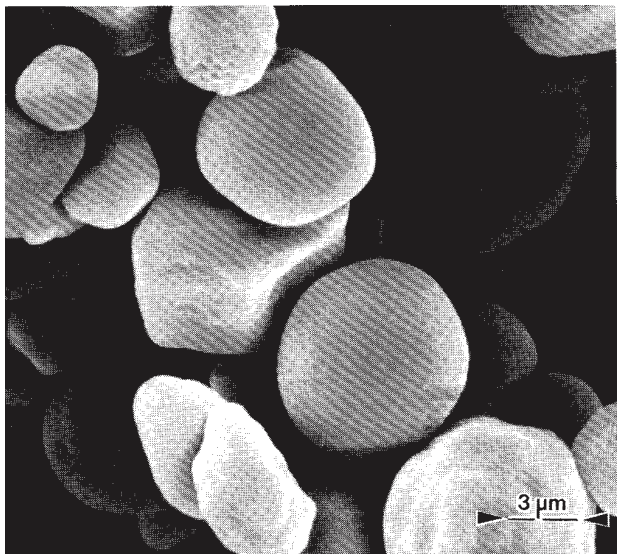


Table I: Pharmacopeial specifications for dextrin.

Test	JP XV	PhEur 6.4	USP32–NF27
Identification	+	+	+
Characters	–	+	–
Appearance of solution	+	–	–
Loss on drying	⩽10.0%	⩽13.0%	⩽13.0%
Acidity	+	–	+
pH	–	2.0–8.0	–
Residue on ignition	⩽0.5%	⩽0.5%	⩽0.5%
Chloride	⩽0.013%	⩽0.2%	⩽0.2%
Sulfate	⩽0.019%	–	–
Oxalate	+	–	–
Calcium	+	–	–
Heavy metals	⩽50 ppm	⩽20 ppm	⩽20 µg/g
Protein	–	–	⩽1.0%
Reducing sugars/ substances (calculated as $C_6H_{12}O_6$)	–	⩽10.0%	⩽10.0%

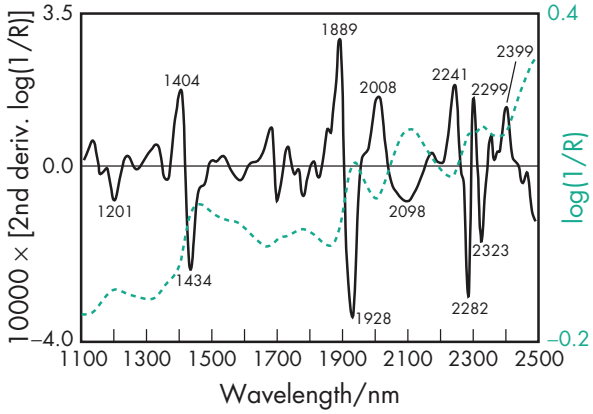


Figure 1: Near-infrared spectrum of dextrin measured by reflectance.

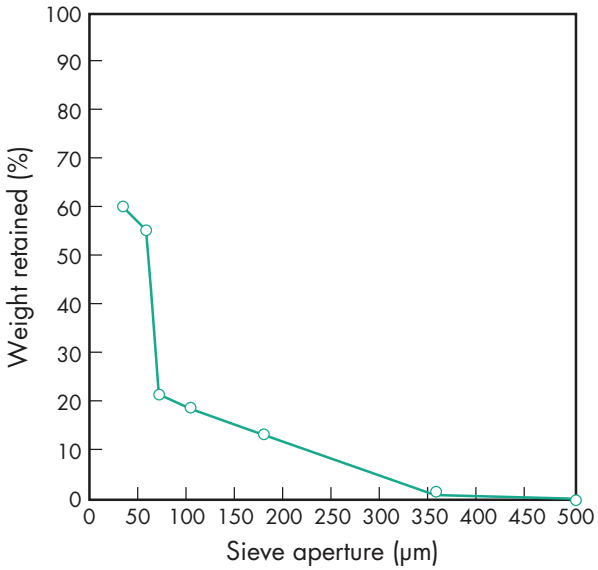


Figure 2: Particle size distribution of dextrin.

ture, pH, or other characteristics change. An increase in viscosity is caused by gelation or retrogradation as dextrin solutions age, and is particularly noticeable in the less-soluble maize starch dextrins. Dextrin solutions are thixotropic, becoming less viscous when sheared but changing to a soft paste or gel when allowed to stand. However, acids that are present in dextrin as residues from manufacturing can cause further hydrolysis, which results in a gradual thinning of solutions. Residual acid, often found in less-soluble dextrins such as pyrodextrin, will also cause a reduction in viscosity during dry storage. To eliminate these problems, dextrin manufacturers neutralize dextrins of low solubility with ammonia or sodium carbonate in the cooling vessel.

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

Dextrin is prepared by the incomplete hydrolysis of starch by heating in the dry state with or without the aid of suitable acids and buffers; moisture may be added during heating. The PhEur 6.4

specifies that dextrin is derived from maize (corn), potato or cassava starch. A specification for cassava is included in the USP32–NF27.

14 Safety

Dextrin is generally regarded as a nontoxic and nonirritant material at the levels employed as an excipient. Larger quantities are used as a dietary supplement without adverse effects, although ingestion of very large quantities may be harmful.

LD_{50} (mouse, IV): 0.35 g/kg[2]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dextrin may be irritant to the eyes. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (IV injections, oral tablets and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrates; dextrose; glucose liquid; maltodextrin.
See also Section 18.

18 Comments

Dextrin is available from suppliers in a number of modified forms and mixtures such as dextrimaltose, a mixture of maltose and dextrin obtained by the enzymatic action of barley malt on corn flour. It is a light, amorphous powder, readily soluble in milk or water.

Crystal Gum is a grade of dextrin containing carbohydrate not less than 98% of dry weight. *Caloreen* [1] is a water-soluble mixture of dextrins consisting predominantly of polysaccharides containing an average of 5 dextrose molecules, with a mean molecular weight of 840, that does not change after heating. A 22% w/v solution of *Caloreen* is isoosmotic with serum.

A specification for dextrin is contained in the Food Chemicals Codex (FCC).[3]

The EINECS number for dextrin is 232-675-4. The PubChem Compound ID (CID) for dextrin is 62698.

19 Specific References

1 Berlyne GM *et al*. A soluble glucose polymer for use in renal failure and calorie-deprivation states. *Lancet* 1969; **i**: 689–692.
2 Sweet DV, ed. *Registry of Toxic Effects of Chemical Substances*. Cincinnati: US Department of Health, 1987: 1859.
3 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 252.

20 General References

French D. Chemical and physical properties of starch. *J Animal Sci* 1973; **37**: 1048–1061.
Satterthwaite RW, Iwinski DJ. Starch dextrins. Whistler RL, Bemiller JN, eds. *Industrial Gums*. New York: Academic Press, 1973; 577–599.

21 Author

A Day.

22 Date of Revision

18 February 2009.

Dextrose

1 Nonproprietary Names

BP: Glucose
JP: Glucose
PhEur: Glucose Monohydrate
USP: Dextrose

2 Synonyms

Blood sugar; *Caridex*; corn sugar; C*PharmDex*; *Dextrofin*; D-(+)-glucopyranose monohydrate; glucosum monohydricum; grape sugar; *Lycadex PF*; *Roferose*; starch sugar; *Tabfine D-100*.

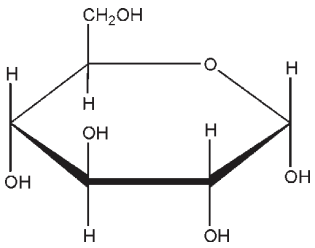
3 Chemical Name and CAS Registry Number

D-(+)-Glucose monohydrate [5996-10-1]
See also Section 17.

4 Empirical Formula and Molecular Weight

$C_6H_{12}O_6 \cdot H_2O$ 198.17 (for monohydrate)
See also Section 17.

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 wet granulation diluent and binder, and as a direct-compression tablet diluent and binder,

LD_{50} (mouse, IV): 3.02 g/kg
LD_{50} (mouse, SC): 9.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Dimethylacetamide can be absorbed into the bloodstream by inhalation and through the skin; it is irritating to the skin and eyes.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (IM injections, IV injections and infusions). Included in parenteral medicines licensed in the UK.

17 Related Substances

—

18 Comments

A specification for dimethylacetamide is included in the *Japanese Pharmaceutical Excipients* (JPE).[12]

The EINECS number for dimethylacetamide is 204-826-4. The PubChem Compound ID (CID) for dimethylacetamide is 31374.

19 Specific References

1 Strickley RG. Solubilizing excipients in oral and injectable formulations. *Pharm Res* 2004; **21**(2): 201–230.
2 Kawakami K *et al*. Solubilisation behavior of poorly soluble drugs with combined use of Gelucire 44/14 and cosolvent. *J Pharm Sci* 2004; **93**(6): 1471–1479.
3 Kawakami K *et al*. Solubilization behaviour of a poorly soluble drug under combined use of surfactants and cosolvents. *Eur J Pharm Sci* 2006; **28**(1–2): 7–14.
4 Taepaiboon P *et al*. Vitamin-loaded electrospun cellulose acetate nanofiber mats as transdermal and dermal therapeutic agents of vitamin A acid and vitamin E. *Eur J Pharm Biopharm* 2007; **67**(2): 387–397.
5 Larsen SW *et al*. Kinetics of degradation and oil solubility of ester prodrugs of a model dipeptide (Gly-Phe). *Eur J Pharm Sci* 2004; **22**: 399–408.
6 Jeon HJ *et al*. Effect of solvent on the preparation of surfactant-free poly (DL-lactide-*co*-glycolide) nanoparticles and norfloxacin release characteristics. *Int J Pharm* 2000; **207**(1–2): 99–108.
7 Horn HJ. Toxicology of dimethylacetamide. *Toxicol Appl Pharmacol* 1961; **3**: 12–24.
8 Anschel J. [Solvents and solubilization in injections.] *Pharm Ind* 1965; **27**: 781–787[in German].
9 Kennedy GL, Sherman H. Acute toxicity of dimethylformamide and dimethylacetamide following various routes of administration. *Drug Chem Toxicol* 1986; **9**: 147–170.
10 Kim SN. Preclinical toxicology and pharmacology of dimethylacetamide, with clinical notes. *Drug Metab Rev* 1988; **19**: 345–368.
11 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 1371.
12 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004; 244–245.

20 General References

Sinha VR, Kaur MP. Permeation enhancers for transdermal drug delivery. *Drug Dev Ind Pharm* 2000; **26**(11): 1131–1140.

21 Author

RT Guest.

22 Date of Revision

17 October 2008.

Disodium Edetate

1 Nonproprietary Names

BP: Disodium Edetate
JP: Disodium Edetate Hydrate
PhEur: Disodium Edetate
USP: Edetate Disodium

2 Synonyms

Dinatrii edetas; disodium EDTA; disodium ethylenediaminetetraacetate; edathamil disodium; edetate disodium; edetic acid, disodium salt.

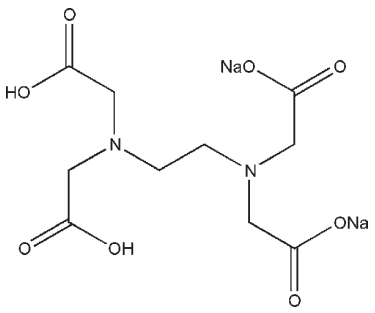
3 Chemical Name and CAS Registry Number

Ethylenediaminetetraacetic acid, disodium salt [139-33-3]
Disodium ethylenediaminetetraacetate dihydrate [6381-92-6]

4 Empirical Formula and Molecular Weight

$C_{10}H_{14}N_2Na_2O_8$ 336.2 (for anhydrous)
$C_{10}H_{18}N_2Na_2O_{10}$ 372.2 (for dihydrate)

5 Structural Formula



6 Functional Category

Chelating agent.

7 Applications in Pharmaceutical Formulation or Technology

Disodium edetate is used as a chelating agent in a wide range of pharmaceutical preparations, including mouthwashes, ophthalmic preparations, and topical preparations,[1–3] typically at concentrations between 0.005 and 0.1% w/v.

Disodium edetate forms 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, a process known as sequestering. The stability of the metal–edetate complex is dependent on the metal ion involved and the pH.

Disodium edetate is also used as a water softener as it will chelate calcium and magnesium ions present in hard water. It is also used therapeutically as an anticoagulant as 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.

See also Edetic acid.

8 Description

Disodium edetate occurs as a white crystalline, odorless powder with a slightly acidic taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for disodium edetate.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	4.3–4.7	4.0–5.5	4.0–6.0
Iron	—	⩽80 ppm	—
Calcium	—	—	+
Heavy metals	⩽10 ppm	⩽20 ppm	⩽0.005%
Cyanide	+	—	—
Arsenic	⩽2 ppm	—	—
Limit of nitrilotriacetic acid	—	⩽0.1%	⩽0.1%
Residue on ignition	37.0–39.0%	—	—
Loss on drying	—	—	8.7–11.4%
Assay	⩾99.0%	98.5–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity pH 4.3–4.7 (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.

NIR spectra *see* Figure 1.

Refractive index 1.33 (1% w/v aqueous solution)

Solubility Practically insoluble in chloroform and ether; slightly soluble in ethanol (95%); soluble 1 part in 11 parts water.

Specific gravity 1.004 (1% w/v aqueous solution)

Viscosity (kinematic) 1.03 mm^2/s (1.03 cSt) (1% w/v aqueous solution).

11 Stability and Storage Conditions

Edetate salts are more stable than edetic acid (*see also* Edetic acid). However, disodium edetate dihydrate loses water of crystallization when heated to 120°C. Aqueous solutions of disodium edetate may be sterilized by autoclaving, and should be stored in an alkali-free container.

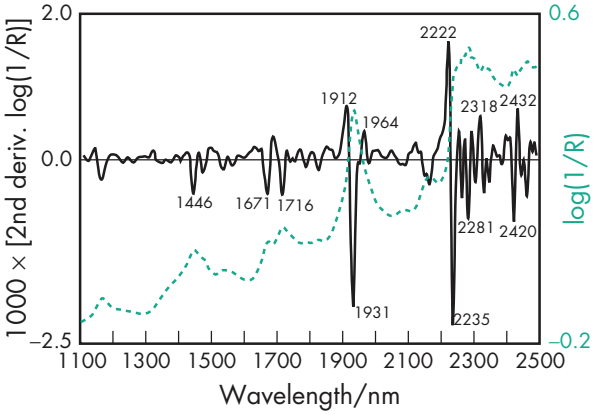


Figure 1: Near-infrared spectrum of disodium edetate dihydrate measured by reflectance.

Disodium edetate is hygroscopic and is unstable when exposed to moisture. It should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Disodium edetate behaves as a weak acid, displacing carbon dioxide from carbonates and reacting with metals to form hydrogen. It is incompatible with strong oxidizing agents, strong bases, metal ions, and metal alloys.

See also Edetic acid.

13 Method of Manufacture

Disodium edetate may be prepared by the reaction of edetic acid and sodium hydroxide.

14 Safety

Disodium edetate is used widely in topical, oral, and parenteral pharmaceutical formulations; it is used extensively in cosmetic and food products. Disodium edetate and edetate calcium disodium are used in a greater number and variety of pharmaceutical formulations than is edetic 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 of time, or if administered too rapidly by intravenous infusion. If used in preparations for the mouth, they can also leach calcium from the teeth. However, edetate calcium disodium does not chelate calcium.

Disodium edetate should be used with caution in patients with renal impairment, tuberculosis, and impaired cardiac function.

Although disodium edetate is generally considered safe, there have been reports of disodium edetate toxicity in patients receiving chelation therapy.[4]

Nasal formulations containing benzalkonium chloride and disodium edetate, both known to be local irritants, were shown to produce an inflammatory reaction, and microscopic examination showed an extended infiltration of the mucosa by eosinophils, and pronounced atrophy and disorganization of the epithelium, although these effects were subsequently shown to be reversible.[3]

The WHO has set an estimated acceptable daily intake for disodium EDTA in foodstuffs of up to 2.5 mg/kg body-weight.[5] *See also* Edetic acid.

LD_{50} (mouse, IP): 0.26 g/kg[6]

LD_{50} (mouse, IV): 0.056 g/kg

LD_{50} (mouse, OP): 2.05 g/kg
LD_{50} (rabbit, IV): 0.047 g/kg
LD_{50} (rabbit, OP): 2.3 g/kg
LD_{50} (rat, OP): 2.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Disodium edetate and its derivatives are mild irritants to the mucous membranes. Eye protection, gloves, and dust masks are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (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. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Edetic acid.

18 Comments

Disodium edetate has been used experimentally to investigate the stability and skin penetration capacity of captopril gel, in which disodium edetate was shown to exert a potent stabilizing effect, and may be used in the development of a transdermal drug delivery system.[7]

A chitosan–EDTA conjugate has been investigated as a novel polymer for use in topical gels. The conjugate was shown to be stable, colorless, and transparent, and it also demonstrated antimicrobial effects.[8]

The EINECS number for disodium edetate is 205-358-3. The PubChem Compound ID (CID) for disodium edetate includes 8759 and 636371.

19 Specific References

1 Ungphaiboon S, Maitani Y. *In vitro* permeation studies of triamcinolone acetonide mouthwashes. *Int J Pharm* 2001; **220**: 111–117.
2 Kaur IP *et al*. Formulation and evaluation of ophthalmic preparations of acetazolamide. *Int J Pharm* 2000; **199**: 119–127.
3 Bechgaard E *et al*. Reversibility and clinical relevance of morphological changes after nasal application of ephedrine nasal drops 1%. *Int J Pharm* 1997; **152**: 67–73.
4 Morgan BW *et al*. Adverse effects in 5 patients receiving EDTA at an outpatient chelation clinic. *Vet Hum Toxicol* 2002; **44**(5): 274–276.
5 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
6 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 1660.
7 Huang YB *et al*. Effect of antioxidants and anti-irritants on the stability, skin irritation and penetration capacity of captopril gel. *Int J Pharm* 2002; **241**: 345–351.
8 Valenta C *et al*. Chitosan–EDTA conjugate: novel polymer for topical gels. *J Pharm Pharmacol* 1998; **50**: 445–452.

20 General References

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21 Authors

S Shah, D Thassu.

22 Date of Revision

30 January 2009.

Docusate Sodium

1 Nonproprietary Names

BP: Docusate Sodium
PhEur: Docusate Sodium
USP: Docusate Sodium

2 Synonyms

Bis(2-ethylhexyl) sodium sulfosuccinate; dioctyl sodium sulfosuccinate; DSS; natrii docusas; sodium 1,4-bis(2-ethylhexyl) sulfosuccinate; sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate; sodium dioctyl sulfosuccinate; sulfo-butanedioic acid 1,4-bis(2-ethylhexyl) ester, sodium salt; sulfosuccinic acid 1,4-bis(2-ethylhexyl) ester *S*-sodium salt.

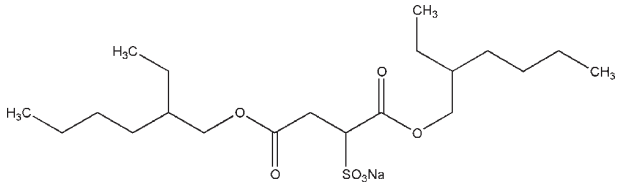
3 Chemical Name and CAS Registry Number

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

4 Empirical Formula and Molecular Weight

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

5 Structural Formula



6 Functional Category

Anionic surfactant; fecal softener; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Docusate sodium and docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Docusate sodium is mainly used in capsule and direct-compression tablet formulations to assist in wetting and dissolution.[1] Docusate salts are also used in oral formulations as laxatives and fecal softeners; *see* Table I.

Ethylparaben

E

1 Nonproprietary Names

BP: Ethyl Hydroxybenzoate
JP: Ethyl Parahydroxybenzoate
PhEur: Ethyl Parahydroxybenzoate
USP-NF: Ethylparaben

2 Synonyms

Aethylum hydrobenzoicum; *CoSept E*; E214; ethylis parahydroxybenzoas; ethyl *p*-hydroxybenzoate; *Ethyl parasept*; 4-hydroxybenzoic acid ethyl ester; *Nipagin A*; *Solbrol A*; *Tegosept E*; *Uniphen P-23*.

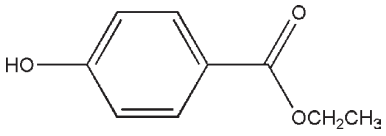
3 Chemical Name and CAS Registry Number

Ethyl-4-hydroxybenzoate [120-47-8]

4 Empirical Formula and Molecular Weight

$C_9H_{10}O_3$ 166.18

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Ethylparaben is widely used as an antimicrobial preservative in cosmetics,[1] food products, and pharmaceutical formulations.

It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics it is one of the most frequently used preservatives.

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

Owing to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used. However, this may cause the pH of poorly buffered formulations to become more alkaline.

See Methylparaben for further information.

8 Description

Ethylparaben occurs as a white, odorless or almost odorless, crystalline powder.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

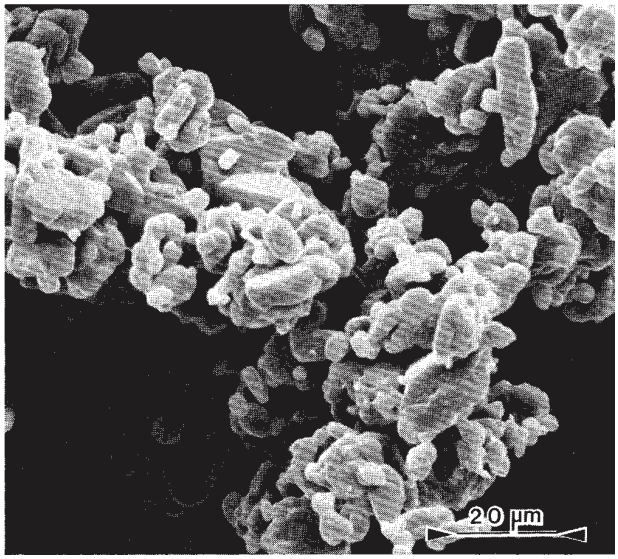
10 Typical Properties

Antimicrobial activity

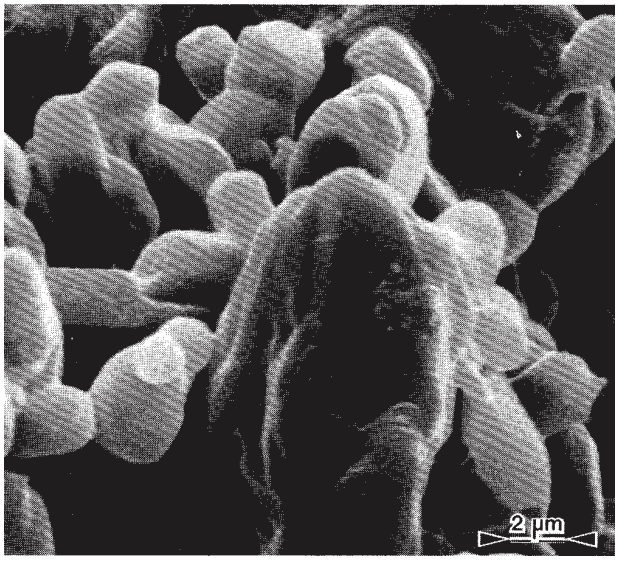
Ethylparaben exhibits antimicrobial activity from pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria.

The activity of the parabens increases with increasing chain length of the alkyl moiety, but solubility decreases. Activity may be improved by using combinations of parabens since synergistic effects occur. Ethylparaben is commonly used with methylparaben and propylparaben in oral and topical formulations (such mixtures are commercially available; for example, *Nipasept* (Nipa Laboratories Inc.). Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben for further information.

SEM 1: Excipient: ethylparaben; magnification: 600×.



SEM 2: Excipient: ethylparaben; magnification: 3000×.



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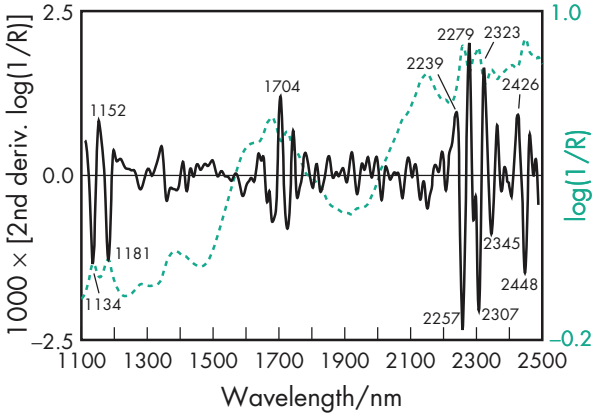


Figure 1: Near-infrared spectrum of ethylparaben measured by reflectance.

Table I: Pharmacopeial specifications for ethylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Appearance of solution	+	+	+
Characters	–	+	–
Heavy metals	⩽20 ppm	–	–
Acidity	+	+	+
Melting range	115–118°C	–	115–118°C
Related substances	+	+	+
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Assay (dried basis)	98.0–102.0%	98.0–102.0%	98.0–102.0%

See Table II for minimum inhibitory concentrations of ethylparaben.[2]

Boiling point 297–298°C with decomposition.

Melting point 115–118°C

NIR spectra *see* Figure 1.

Partition coefficient The values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table III.[3]

Solubility *see* Table IV.

11 Stability and Storage Conditions

Aqueous ethylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.[4] At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).[5]

Ethylparaben should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

The antimicrobial properties of ethylparaben are considerably reduced in the presence of nonionic surfactants as a result of micellization.[6] Absorption of ethylparaben by plastics has not been reported, although it appears probable given the behavior of other parabens. Ethylparaben is coabsorbed on silica in the presence of ethoxylated phenols.[7] Yellow iron oxide, ultramarine blue, and aluminum silicate extensively absorb ethylparaben in simple aqueous systems, thus reducing preservative efficacy.[8,9]

Ethylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

Table II: Minimum inhibitory concentrations (MICs) for ethylparaben in aqueous solution.[2]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1200
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	400
Bacillus cereus var. *mycoides* ATCC 6462	1000
Bacillus subtilis ATCC 6633	1000
Candida albicans ATCC 10231	500
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	250
Penicillium digitatum ATCC 10030	250
Proteus vulgaris ATCC 13315	500
Pseudomonas aeruginosa ATCC 9027	>2000
Pseudomonas aeruginosa ATCC 15442	>2000
Pseudomonas stutzeri	1000
Rhizopus nigricans ATCC 6227A	250
Saccharomyces cerevisiae ATCC 9763	500
Salmonella typhosa ATCC 6539	1000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	1000
Staphylococcus epidermidis ATCC 12228	1000
Trichophyton mentagrophytes	125

Table III: Partition coefficients for ethylparaben in vegetable oil and water.[3]

Solvent	Partition coefficient oil : water
Corn oil	14.0
Mineral oil	0.13
Peanut oil	16.1
Soybean oil	18.8

Table IV: Solubility of ethylparaben in various solvents.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 1.4
Ethanol (95%)	1 in 2
Ether	1 in 3.5
Glycerin	1 in 200
Methanol	1 in 0.9
Mineral oil	1 in 4000
Peanut oil	1 in 100
Propylene glycol	1 in 4
Water	1 in 1250 at 15°C 1 in 910 1 in 120 at 80°C

13 Method of Manufacture

Ethylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with ethanol (95%).

14 Safety

Ethylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics, food products, and oral and topical pharmaceutical formulations.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions. Parabens, *in vivo*, have also been reported to exhibit estrogenic responses in fish.[10] The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg body-weight.[11]

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LD_{50} (mouse, IP): 0.52 g/kg[12]
LD_{50} (mouse, oral): 3.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral, otic, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben potassium; ethylparaben sodium; methylparaben; propylparaben.

Ethylparaben potassium

Empirical formula $C_9H_9KO_3$
Molecular weight 204.28
CAS number [36547-19-9]
Synonyms Ethyl 4-hydroxybenzoate potassium salt; potassium ethyl hydroxybenzoate.

Ethylparaben sodium

Empirical formula $C_9H_9NaO_3$
Molecular weight 188.17
CAS number [35285-68-8]
Synonyms E215; ethyl 4-hydroxybenzoate sodium salt; sodium ethyl hydroxybenzoate.

18 Comments

Ethylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

See Methylparaben for further information.

The EINECS number for ethylparaben is 204-399-4. The PubChem Compound ID (CID) for ethylparaben is 8434.

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N Sandler.

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LV Allen Jr, PE Luner.

22 Date of Revision

3 February 2009.

Methylparaben

1 Nonproprietary Names

BP: Methyl Hydroxybenzoate
JP: Methyl Parahydroxybenzoate
PhEur: Methyl Parahydroxybenzoate
USP-NF: Methylparaben

2 Synonyms

Aseptoform M; *CoSept M*; E218; 4-hydroxybenzoic acid methyl ester; metagin; *Methyl Chemosept*; methylis parahydroxybenzoas; methyl *p*-hydroxybenzoate; *Methyl Parasept*; *Nipagin M*; *Solbrol M*; *Tegosept M*; *Uniphen P-23*.

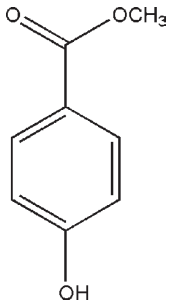
3 Chemical Name and CAS Registry Number

Methyl-4-hydroxybenzoate [99-76-3]

4 Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations; *see* Table I. It may be used either alone or in combination with other

parabens or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative.[1]

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2–5%), or by using parabens in combination with other antimicrobial agents such as imidurea; *see* Section 10.

Owing to the poor solubility of the parabens, paraben salts (particularly the sodium salt) are more frequently used in formulations. However, this raises the pH of poorly buffered formulations.

Methylparaben (0.18%) together with propylparaben (0.02%) has been used for the preservation of various parenteral pharmaceutical formulations; *see* Section 14.

Table I: Uses of methylparaben.

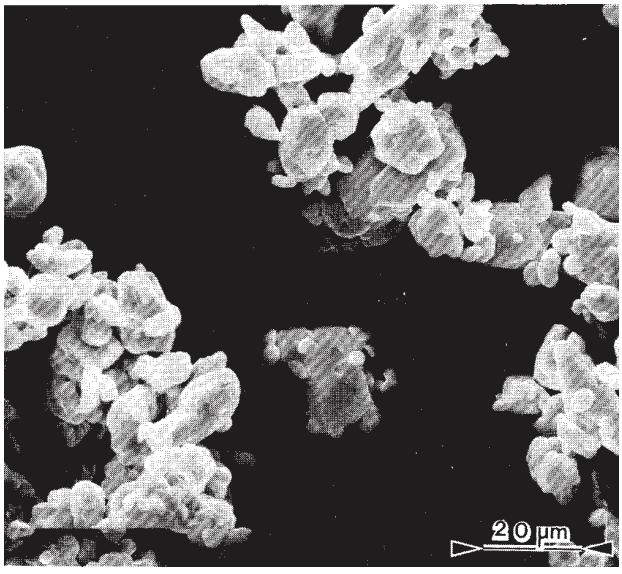
Use	Concentration (%)
IM, IV, SC injections[a]	0.065–0.25
Inhalation solutions	0.025–0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015–0.2
Oral solutions and suspensions	0.015–0.2
Rectal preparations	0.1–0.18
Topical preparations	0.02–0.3
Vaginal preparations	0.1–0.18

(a) *See* Section 14.

8 Description

Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

SEM 1: Excipient: methylparaben; supplier: Bate Chemical Co. Ltd; magnification: 600×.



9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for methylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	+
Acidity	+	+	+
Heavy metals	⩽20 ppm	—	—
Impurities	—	+	—
Melting range	—	—	125–128°C
Related substances	+	+	+
Sulfated ash	—	⩽0.1%	—
Residue on ignition	⩽0.1%	—	⩽0.1%
Assay (dried basis)	98.0–102.0%	98.0–102.0%	98.0–102.0%

10 Typical Properties

Antimicrobial activity *see* Table III. Methylparaben exhibits antimicrobial activity of pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive bacteria than against Gram-negative bacteria.

Methylparaben is the least active of the parabens; antimicrobial activity increases with increasing chain length of the alkyl moiety. Activity may be improved by using combinations of parabens as synergistic effects occur. Therefore, combinations of methyl-, ethyl-, propyl-, and butylparaben are often used together. Activity has also been reported to be enhanced by the addition of other excipients such as: propylene glycol (2–5%);[2] phenylethyl alcohol;[3] and edetic acid.[4] Activity may also be enhanced owing to synergistic effects by using combinations of parabens with other antimicrobial preservatives such as imidurea.[5]

The hydrolysis product *p*-hydroxybenzoic acid has practically no antimicrobial activity.

See also Section 12.

Table III: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[4]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	2000
Aspergillus oryzae	600
Aspergillus niger ATCC 9642	1000
Aspergillus niger ATCC 10254	1000
Bacillus cereus var. *mycoides* ATCC 6462	2000
Bacillus subtilis ATCC 6633	2000
Candida albicans ATCC 10231	2000
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	1000
Penicillium chrysogenum ATCC 9480	500
Penicillium digitatum ATCC 10030	500
Proteus vulgaris ATCC 8427	2000
Proteus vulgaris ATCC 13315	1000
Pseudomonas aeruginosa ATCC 9027	4000
Pseudomonas aeruginosa ATCC 15442	4000
Pseudomonas stutzeri	2000
Rhizopus nigricans ATCC 6227A	500
Saccharomyces cerevisiae ATCC 9763	1000
Salmonella typhosa ATCC 6539	1000
Sarcina lutea	4000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	2000
Staphylococcus epidermidis ATCC 12228	2000
Trichoderma lignorum ATCC 8678	250
Trichoderma mentagrophytes	250

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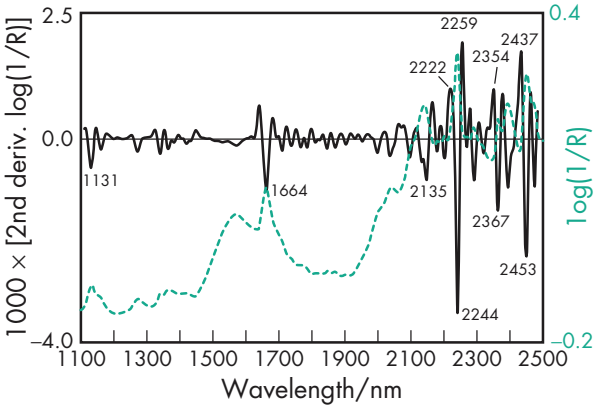


Figure 1: Near-infrared spectrum of methylparaben measured by reflectance.

Density (true) 1.352 g/cm^3
Dissociation constant pK_a = 8.4 at 22°C
Melting point 125–128°C
NIR spectra *see* Figure 1.
Partition coefficients Values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.
Solubility *see* Table V.

Table IV: Partition coefficients of methylparaben in vegetable oil and water.[6,7]

Solvent	Partition coefficient oil : water
Almond oil	7.5
Castor oil	6.0
Corn oil	4.1
Diethyl adipate	200
Isopropyl myristate	18.0
Lanolin	7.0
Mineral oil	0.1
Peanut oil	4.2
Soybean oil	6.1

Table V: Solubility of methylparaben in various solvents.[4]

Solvent	Solubility at 25°C unless otherwise stated
Ethanol	1 in 2
Ethanol (95%)	1 in 3
Ethanol (50%)	1 in 6
Ether	1 in 10
Glycerin	1 in 60
Mineral oil	Practically insoluble
Peanut oil	1 in 200
Propylene glycol	1 in 5
Water	1 in 400
	1 in 50 at 50°C
	1 in 30 at 80°C

11 Stability and Storage Conditions

Aqueous solutions of methylparaben at pH 3–6 may be sterilized by autoclaving at 120°C for 20 minutes, without decomposition.[8] Aqueous solutions at pH 3–6 are stable (less than 10% decomposition) for up to about 4 years at room temperature, while aqueous solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days storage at room temperature); *see* Tables VI and VII.[9]

Methylparaben should be stored in a well-closed container in a cool, dry place.

Table VI: Predicted rate constants and half-lives for methylparaben dissolved in dilute hydrochloric acid solution, at 25°C.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Half-life $t_{1/2} \pm \sigma^{(a)}$ (day)
1	$(1.086 \pm 0.005) \times 10^{-4}$	266 ± 13
2	$(1.16 \pm 0.12) \times 10^{-5}$	2 490 ± 260
3	$(6.1 \pm 1.5) \times 10^{-7}$	47 000 ± 12 000
4	$(3.27 \pm 0.64) \times 10^{-7}$	88 000 ± 17 000

(a) Indicates the standard error.

Table VII: Predicted remaining amount of methylparaben dissolved in dilute hydrochloric acid solution, after autoclaving.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Predicted residual amount after autoclaving (%)
1	$(4.96 \pm 0.16) \times 10^{-1}$	84.77 ± 0.46
2	$(4.49 \pm 0.37) \times 10^{-2}$	98.51 ± 0.12
3	$(2.79 \pm 0.57) \times 10^{-3}$	99.91 ± 0.02
4	$(1.49 \pm 0.22) \times 10^{-3}$	99.95 ± 0.01

(a) Indicates the standard error.

12 Incompatibilities

The antimicrobial activity of methylparaben and other parabens is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization.[10,11] However, propylene glycol (10%) has been shown to potentiate the antimicrobial activity of the parabens in the presence of nonionic surfactants and prevents the interaction between methylparaben and polysorbate 80.[12]

Incompatibilities with other substances, such as bentonite,[13] magnesium trisilicate,[14] talc, tragacanth,[15] sodium alginate,[16] essential oils,[17] sorbitol,[18] and atropine,[19] have been reported. It also reacts with various sugars and related sugar alcohols.[20]

Absorption of methylparaben by plastics has also been reported; the amount absorbed is dependent upon the type of plastic and the vehicle. It has been claimed that low-density and high-density polyethylene bottles do not absorb methylparaben.[21]

Methylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

13 Method of Manufacture

Methylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with methanol.

14 Safety

Methylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations. Although parabens have also been used as preservatives in injections and ophthalmic preparations, they are now generally regarded as being unsuitable for these types of formulations owing to the irritant potential of the parabens. These experiences may depend on immune responses to enzymatically formed metabolites of the parabens in the skin.

Parabens are nonmutagenic, nonteratogenic, and noncarcinogenic. Sensitization to the parabens is rare, and these compounds do not exhibit significant levels of photocontact sensitization or phototoxicity.

Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon; the classification of

parabens in some sources as high-rate sensitizers may be overstated.[22]

Immediate hypersensitivity reactions following injection of preparations containing parabens have also been reported.[23–25] Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration.[26–28]

Unexpectedly, preparations containing parabens may be used by patients who have reacted previously with contact dermatitis provided they are applied to another, unaffected, site. This has been termed the paraben paradox.[29]

Concern has been expressed over the use of methylparaben in infant parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates.[30]

The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg bodyweight.[31]

LD_{50} (dog, oral): 3.0 g/kg[32]

LD_{50} (mouse, IP): 0.96 g/kg

LD_{50} (mouse, SC): 1.20 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Methylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

M

16 Regulatory Status

Methylparaben and propylparaben are affirmed GRAS Direct Food Substances in the USA at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan. In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM, IV, and SC injections; inhalation preparations; ophthalmic preparations; oral capsules, tablets, solutions and suspensions; otic, rectal, topical, and vaginal preparations). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben; methylparaben potassium; methylparaben sodium; propylparaben.

Methylparaben potassium

Empirical formula $C_8H_7KO_3$
Molecular weight 190.25
CAS number [26112-07-2]
Synonyms Methyl 4-hydroxybenzoate potassium salt; potassium methyl hydroxybenzoate.
Comments Methylparaben potassium may be used instead of methylparaben because of its greater aqueous solubility.

Methylparaben sodium

Empirical formula $C_8H_7NaO_3$
Molecular weight 174.14
CAS number [5026-62-0]
Synonyms E219; methyl 4-hydroxybenzoate sodium salt; sodium methyl hydroxybenzoate; soluble methyl hydroxybenzoate.
Appearance A white, odorless or almost odorless, hygroscopic crystalline powder.
Acidity/alkalinity pH = 9.5–10.5 (0.1% w/v aqueous solution)
Solubility 1 in 50 of ethanol (95%); 1 in 2 of water; practically insoluble in fixed oils.
Comments Methylparaben sodium may be used instead of methylparaben because of its greater aqueous solubility. However, it may cause the pH of a formulation to become more alkaline.

18 Comments

Methylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

The BP 2009, Ph Eur 6.0 and USP32–NF27 also list Methylparaben Sodium as a separate monograph.

The EINECS number for methylparaben is 202-785-7. In addition to the most commonly used paraben esters, some other less-common esters have also been used; *see* Table VIII. A specification for methylparaben is contained in the Food Chemicals Codex (FCC).[33]

The PubChem Compound ID (CID) for methylparaben is 7456.

Table VIII: CAS numbers of less common paraben esters.

Name	CAS Number
Benzylparaben	94-18-8
Isobutylparaben	4247-02-3
Isopropylparaben	4191-73-5

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S Haley.

22 Date of Revision

3 February 2009.

M

Mineral Oil

1 Nonproprietary Names

BP: Liquid Paraffin
JP: Liquid Paraffin
PhEur: Paraffin, Liquid
USP: Mineral Oil

2 Synonyms

Avatech; *Drakeol*; heavy mineral oil; heavy liquid petrolatum; liquid petrolatum; paraffin oil; paraffinum liquidum; *Sirius*; white mineral oil.

3 Chemical Name and CAS Registry Number

Mineral oil [8012-95-1]

4 Empirical Formula and Molecular Weight

Mineral oil is a mixture of refined liquid saturated aliphatic (C_{14}–C_{18}) and cyclic hydrocarbons obtained from petroleum.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; lubricant; oleaginous vehicle; solvent; vaccine adjuvant.

7 Applications in Pharmaceutical Formulation or Technology

Mineral oil is used primarily as an excipient in topical pharmaceutical formulations, where its emollient properties are exploited as an ingredient in ointment bases; *see* Table I. It is additionally used in oil-in-water emulsions,[1–5] as a solvent, and as a lubricant in capsule and tablet formulations, and to a limited extent as a mold-

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21 Authors

RT Forbes, M Isreb.

22 Date of Revision

10 March 2009.

Polyethylene Glycol

1 Nonproprietary Names

BP: Macrogols

JP: Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000

PhEur: Macrogols

USP-NF: Polyethylene Glycol

2 Synonyms

Carbowax; *Carbowax Sentry*; *Lipoxol*; *Lutrol E*; macrogola; PEG; *Pluriol E*; polyoxyethylene glycol.

3 Chemical Name and CAS Registry Number

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

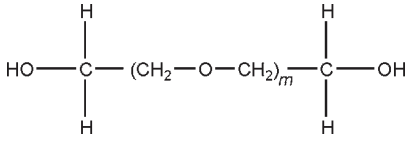
4 Empirical Formula and Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$ where *m* represents the average number of oxyethylene groups.

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

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

5 Structural Formula



6 Functional Category

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

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

Grade	*m*	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1 050
PEG 1450	32.5	1 300–1 600
PEG 1540	28.0–36.0	1 300–1 600
PEG 2000	40.0–50.0	1 800–2 200
PEG 3000	60.0–75.0	2 700–3 300
PEG 3350	75.7	3 000–3 700
PEG 4000	69.0–84.0	3 000–4 800
PEG 4600	104.1	4 400–4 800
PEG 8000	181.4	7 000–9 000

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.[1]

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; *see* Section 14. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.[2] Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases,[3] for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are

chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

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

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

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

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.[4] However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations,[5–7] a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes pastelike and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.[8] Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.[9] The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

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

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. Polyethylene glycol has also been used in insulin-loaded microparticles for the oral delivery of insulin;[10,11] it has been used in inhalation preparations to improve aerosolization;[12] polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine;[13] it has been used in self-assembled polymeric nanoparticles as a drug carrier;[14] and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.[15]

8 Description

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

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

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

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for polyethylene glycol.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	—
Characters	—	+	—
Acidity or alkalinity	+	+	—
Appearance of solution	+[a]	+	+
Density			
1.110–1.140[b]	*See* Table IV	—	
Freezing point	*See* Table III	*See* Table IV	—
Viscosity	—	*See* Table IV	*See* Table V
Average molecular weight	*See* Table III	—	*See* Table V
pH (5% w/v solution)	*See* Table III	—	4.5–7.5
Hydroxyl value	—	*See* Table IV	—
Reducing substances	—	+	—
Residue on ignition	*See* Table III	—	⩽0.1%
Sulfated ash	—	⩽0.2%	—
Limit of ethylene glycol and diethylene glycol	⩽0.25%	⩽0.4%	⩽0.25%
Ethylene oxide	—	⩽1 ppm	⩽10 µg/g
1,4-Dioxane	—	⩽10 ppm	⩽10 µg/g
Heavy metals	—	⩽20 ppm	⩽5 µg/g
Water	⩽1.0%	⩽2.0%	—
Formaldehyde	—	⩽30 ppm	—

(a) For PEG 1500, 4000, 6000, 20000.
(b) For PEG 400.

Table III: Specifications from JP XV.

Type of PEG	Average molecular weight	Freezing point (°C)	pH (5% w/v solution)	Residue on ignition
400	380–420	4–8	4.0–7.0	⩽0.1%
1500	—	37–41	4.0–7.0	⩽0.1%
4000				
2 600–3 800	53–57	4.0–7.5	⩽0.2%	
6000				
7 300–9 300	56–61	4.5–7.5	⩽0.2%	
20000				
15 000–25 000	56–64	4.5–7.5	⩽0.2%	

10 Typical Properties

Density

1.11–1.14 g/cm^3 at 25°C for liquid PEGs;
1.15–1.21 g/cm^3 at 25°C for solid PEGs.

Flash point

182°C for PEG 200;
213°C for PEG 300;
238°C for PEG 400;
250°C for PEG 600.

Freezing point

<−65°C PEG 200 sets to a glass;
−15 to −8°C for PEG 300;
4–8°C for PEG 400;
15–25°C for PEG 600.

Melting point

37–40°C for PEG 1000;
44–48°C for PEG 1500;

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Table IV: Specifications from PhEur 6.0.

Type of PEG	Density (g/cm^3)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPa s (cP)]	Viscosity (kinematic) [mm^2/s (cSt)]
300	1.120	—	340–394	80–105	71–94
400	1.120	—	264–300	105–130	94–116
600	1.080	15–25	178–197	15–20	13.9–18.5
1000	1.080	35–40	107–118	22–30	20.4–27.7
1500	1.080	42–48	70–80	34–50	31–46
3000	1.080	50–56	34–42	75–100	69–93
3350	1.080	53–57	30–38	83–120	76–110
4000	1.080	53–59	25–32	110–170	102–158
6000	1.080	55–61	16–22	200–270	185–250
8000	1.080	55–62	12–16	260–510	240–472
20000	1.080	⩾57	—	2 700–3 500	2 500–3 200
35000	1.080	⩾57	—	11 000–14 000	10 000–13 000

Table V: Specification for viscosity of polyethylene glycol of the given nominal molecular weight at 98.9°C ± 0.3°C from the USP32–NF27.

Type of PEG (nominal average molecular weight)	Viscosity (kinematic) [mm^2/s (cSt)]
200	3.9–4.8
300	5.4–6.4
400	6.8–8.0
500	8.3–9.6
600	9.9–11.3
700	11.5–13.0
800	12.5–14.5
900	15.0–17.0
1000	16.0–19.0
1100	18.0–22.0
1200	20.0–24.5
1300	22.0–27.5
1400	24–30
1450	25–32
1500	26–33
1600	28–36
1700	31–39
1800	33–42
1900	35–45
2000	38–49
2100	40–53
2200	43–56
2300	46–60
2400	49–65
2500	51–70
2600	54–74
2700	57–78
2800	60–83
2900	64–88
3000	67–93
3250	73–105
3350	76–110
3500	87–123
3750	99–140
4000	110–158
4250	123–177
4500	140–200
4750	155–228
5000	170–250
5500	206–315
6000	250–390
6500	295–480
7000	350–590
7500	405–735
8000	470–900

40–48°C for PEG 1540;
45–50°C for PEG 2000;
48–54°C for PEG 3000;
50–58°C for PEG 4000;
55–63°C for PEG 6000;
60–63°C for PEG 8000;
60–63°C for PEG 20000.

Moisture content Liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g. PEG 4000 and above, are not hygroscopic. *See* Figures 1, 2, and 3.

Particle size distribution *see* Figures 4 and 5.

Refractive index

n_D^{25} = 1.459 for PEG 200;
n_D^{25} = 1.463 for PEG 300;
n_D^{25} = 1.465 for PEG 400;
n_D^{25} = 1.467 for PEG 600.

Solubility All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension Approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic) *see* Tables IV, V, and VI.

Table VI: Viscosity of selected polyethylene glycols at 25°C and 99°C.

Type of PEG	Viscosity [mm^2/s (cSt)]	
	25°C	**99°C**
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	—
PEG 2000 solid	47	—
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20000 solid	6 900	—

11 Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.[16]

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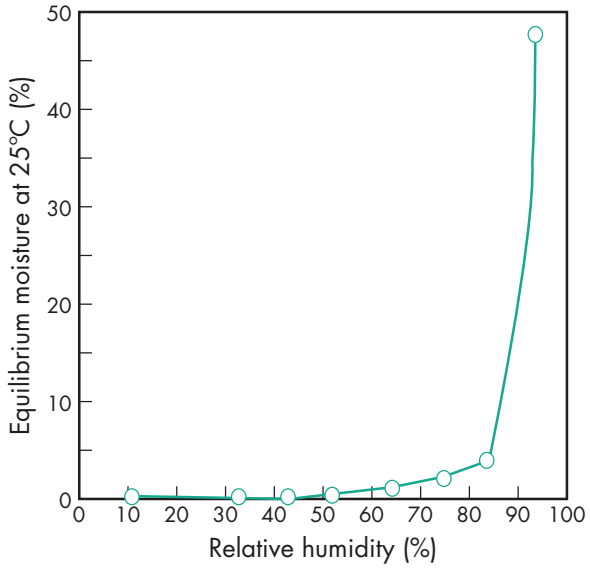


Figure 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot No. B192–8209) at 25°C.

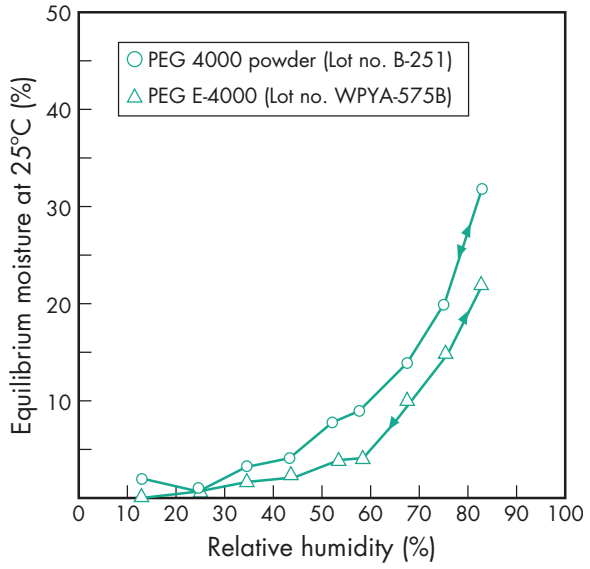


Figure 2: Equilibrium moisture content of PEG 4000 (Dow Chemical Company) and PEG E-4000 (BASF) at 25°C.

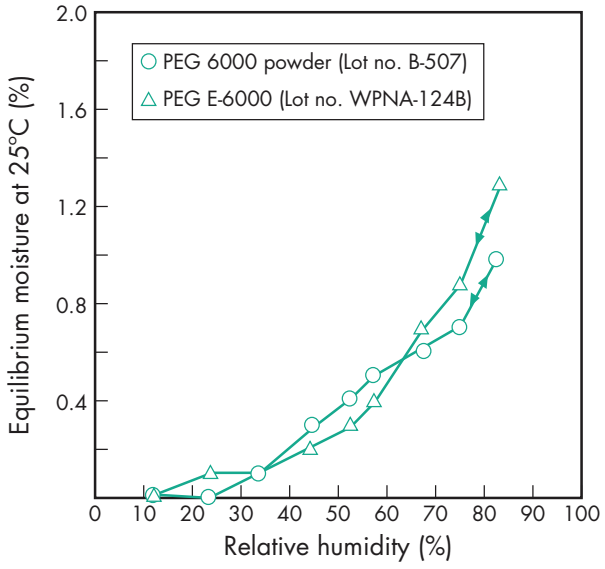


Figure 3: Equilibrium moisture content of PEG 6000 (Dow Chemical Company) and PEG E-6000 (BASF) at 25°C.

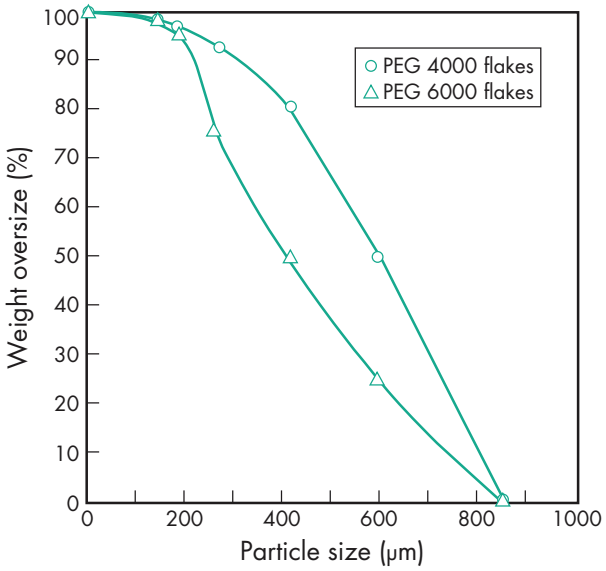


Figure 4: Particle size distribution of PEG 4000 and PEG 6000 flakes.

Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

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

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

12 Incompatibilities

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

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

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

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

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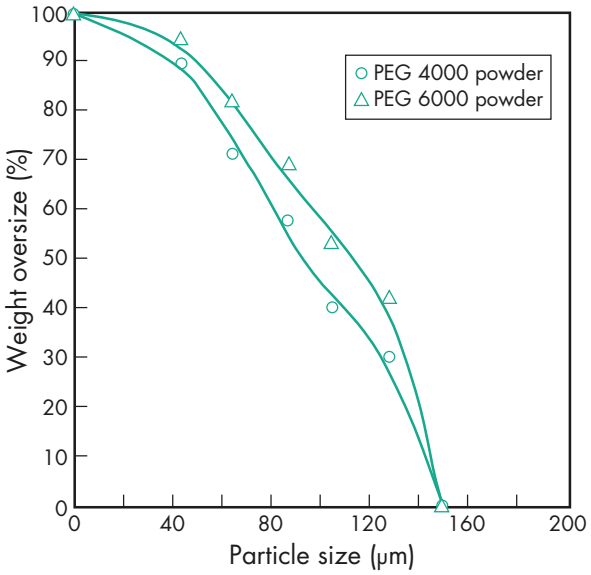


Figure 5: Particle size distribution of PEG 4000 and PEG 6000 powder.

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

13 Method of Manufacture

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

14 Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.[17–19]

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions.[20]

The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.[21] Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.[22]

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

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.[23]

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

For animal toxicity data, *see* Table VII.[24]

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyoxyethylene alkyl ethers; polyethylene oxide; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene stearates; suppository bases.

18 Comments

Polyethylene glycol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

A specification for polyethylene glycol is contained in the Food Chemicals Codex (FCC).[25]

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Table VII: Animal toxicity data (LD_{50}) for various grades of polyethylene glycol.[24]

PEG grade	LD_{50} (g/kg)								
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (IV)	Rat (IP)	Rat (IV)	Rat (oral)
PEG 200	—	7.5	—	34	19.9	—	—	—	28.0
PEG 300	19.6	—	—	—	17.3	—	—	—	27.5
PEG 400	15.7	10.0	8.6	28.9	26.8	—	9.7	7.3	—
PEG 600	—	—	—	47	—	—	—	—	38.1
PEG 1000	—	20	—	—	—	—	15.6	—	32
PEG 1500	28.9	—	—	—	28.9	8	17.7	—	44.2
PEG 4000	50.9	—	16	—	76	—	11.6	—	50
PEG 6000	50	—	—	—	—	—	6.8	—	—

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21 Author

D Wallick.

22 Date of Revision

3 February 2009.

Polyethylene Oxide

1 Nonproprietary Names

USP-NF: Polyethylene Oxide

2 Synonyms

Polyox; polyoxiante; polyoxirane; polyoxyethylene.

3 Chemical Name and CAS Registry Number

Polyethylene oxide [25322-68-3]

4 Empirical Formula and Molecular Weight

See Table I.

5 Structural Formula

The USP32–NF27 describes polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula $(CH_2CH_2O)_n$, where n represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide or suitable antioxidant.

6 Functional Category

Mucoadhesive; coating agent; tablet binder; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach;[1,2] *see* Table I. Polyethylene oxide has also been shown to facilitate coarse extrusion for tableting[3] as well as being an aid in hot-melt extrusion.[4,5]

The relationship between swelling capacity and molecular weight is a good guide when selecting products for use in immediate- or sustained-release matrix formulations; *see* Figure 1.

Propylparaben

1 Nonproprietary Names

BP: Propyl Hydroxybenzoate
JP: Propyl Parahydroxybenzoate
PhEur: Propyl Parahydroxybenzoate
USP-NF: Propylparaben

2 Synonyms

Aseptoform P; *CoSept P*; E216; 4-hydroxybenzoic acid propyl ester; *Nipagin P*; *Nipasol M*; propagin; *Propyl Aseptoform*; propyl butex; *Propyl Chemosept*; propylis parahydroxybenzoas; propyl *p*-hydroxybenzoate; *Propyl Parasept*; *Solbrol P*; *Tegosept P*; *Uniphen P-23*.

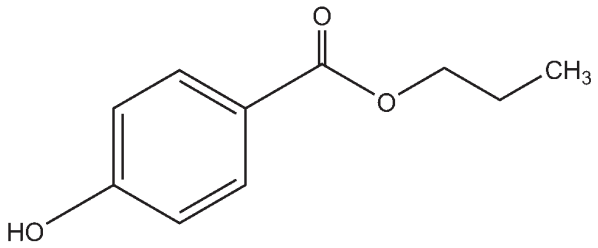
3 Chemical Name and CAS Registry Number

Propyl 4-hydroxybenzoate [94-13-3]

4 Empirical Formula and Molecular Weight

$C_{10}H_{12}O_3$ 180.20

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations; *see* Table I.

It may be used alone, in combination with other paraben esters, or with other antimicrobial agents. It is one of the most frequently used preservatives in cosmetics.[1]

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

Owing to the poor solubility of the parabens, the paraben salts, particularly the sodium salt, are frequently used in formulations. This may cause the pH of poorly buffered formulations to become more alkaline.

Propylparaben (0.02% w/v) together with methylparaben (0.18% w/v) has been used for the preservation of various parenteral pharmaceutical formulations; *see* Section 14.

See Methylparaben for further information.

Table I: Uses of propylparaben in pharmaceutical preparations.

Use	Concentration (%)
IM, IV, SC injections	0.005–0.2
Inhalation solutions	0.015
Intradermal injections	0.02–0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005–0.01
Oral solutions and suspensions	0.01–0.02
Rectal preparations	0.02–0.01
Topical preparations	0.01–0.6
Vaginal preparations	0.02–0.1

8 Description

Propylparaben occurs as a white, crystalline, odorless, and tasteless powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for propylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Melting range	96.0–99.0°C	—	96.0–99.0°C
Acidity	+	+	+
Loss on drying	—	—	⩽0.5%
Residue on ignition	⩽0.1%	—	⩽0.1%
Sulfated ash	—	⩽0.1%	—
Appearance of solution	+	+	+
Heavy metals	⩽20 ppm	—	—
Related substances	+	+	+
Assay	98.0–102.0%	98.0–102.0%	98.0–102.0%

10 Typical Properties

Antimicrobial activity

Propylparaben exhibits antimicrobial activity between pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria. The activity of the parabens increases with increasing chain length of the alkyl moiety; however, solubility decreases.

Activity may be improved by using combinations of parabens, as additive effects occur. Propylparaben has been used with methylparaben in parenteral preparations, and is used in combination with other parabens in topical and oral formulations. Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben.

Reported minimum inhibitory concentrations (MICs) for propylparaben are provided in Table III.[2]

Boiling point 295°C
Density (bulk) 0.426 g/cm^3
Density (tapped) 0.706 g/cm^3
Density(true) 1.288 g/cm^3
Dissociation constant pK_a = 8.4 at 22°C
Flash point 140°C

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Table III: Minimum inhibitory concentrations (MICs) for propylparaben in aqueous solution.[2]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1000
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	125
Bacillus subtilis ATCC 6633	500
Candida albicans ATCC 10231	250
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	500
Escherichia coli ATCC 9637	100
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	125
Penicillium digitatum ATCC 10030	63
Proteus vulgaris ATCC 13315	250
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	125
Saccharomyces cerevisiae ATCC 9763	125
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	500
Staphylococcus epidermidis ATCC 12228	500
Trichophyton mentagrophytes	65

NIR spectra *see* Figure 1.

Partition coefficients Values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.

Table IV: Partition coefficients for propylparaben in vegetable oil and water.[3]

Solvent	Partition coefficient oil : water
Corn oil	58.0
Mineral oil	0.5
Peanut oil	51.8
Soybean oil	65.9

Refractive index $n_D^{14} = 1.5049$

Solubility *see* Table V.

Table V: Solubility of propylparaben in various solvents.[2]

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol (95%)	1 in 1.1
Ethanol (50%)	1 in 5.6
Ether	Freely soluble
Glycerin	1 in 250
Mineral oil	1 in 3330
Peanut oil	1 in 70
Propylene glycol	1 in 3.9
Propylene glycol (50%)	1 in 110
Water	1 in 4350 at 15°C 1 in 2500 1 in 225 at 80°C

11 Stability and Storage Conditions

Aqueous propylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.[4] At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).[5]

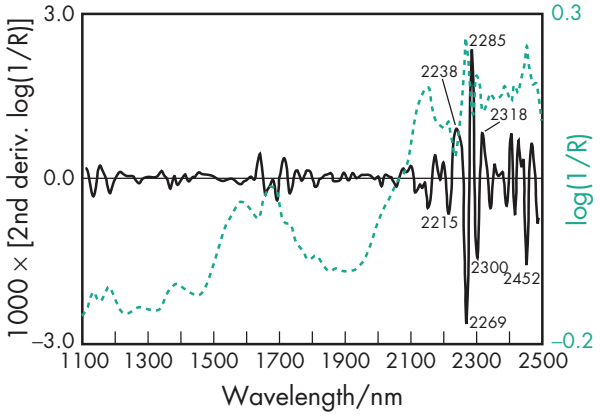


Figure 1: Near-infrared spectrum of propylparaben measured by reflectance.

See Table VI, for the predicted rate constants and half-lives at 25°C for propylparaben.[5]

Propylparaben should be stored in a well-closed container in a cool, dry place.

Table VI: Predicted rate constants and half-lives at 25°C for propylparaben dissolved in hydrochloric acid solution.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (h^{-1})	Half-life $t_{1/2} \pm \sigma^{(a)}$ (day)
1	$(1.255 \pm 0.042) \times 10^{-4}$	230 ± 7.6
2	$(1.083 \pm 0.081) \times 10^{-5}$	2670 ± 200
3	$(8.41 \pm 0.96) \times 10^{-7}$	$34\,300 \pm 3900$
4	$(2.23 \pm 0.37) \times 10^{-7}$	$130\,000 \pm 22\,000$

(a) σ indicates the standard error.

The predicted amount of propylparaben remaining after autoclaving is given in Table VII.[5]

Table VII: Predicted amount of propylparaben dissolved in hydrochloric acid, after autoclaving.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (h^{-1})	Predicted residual amount after sterilization (%)
1	$(4.42 \pm 0.10) \times 10^{-1}$	86.30 ± 0.30
2	$(4.67 \pm 0.19) \times 10^{-2}$	98.46 ± 0.06
3	$(2.96 \pm 0.24) \times 10^{-3}$	99.90 ± 0.01
4	$(7.8 \pm 1.1) \times 10^{-4}$	99.97 ± 0.004

(a) σ indicates the standard error.

12 Incompatibilities

The antimicrobial activity of propylparaben is reduced considerably in the presence of nonionic surfactants as a result of micellization.[6] Absorption of propylparaben by plastics has been reported, with the amount absorbed dependent upon the type of plastic and the vehicle.[7] Magnesium aluminum silicate, magnesium trisilicate, yellow iron oxide, and ultramarine blue have also been reported to absorb propylparaben, thereby reducing preservative efficacy.[8,9]

Propylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13 Method of Manufacture

Propylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with *n*-propanol.

14 Safety

Propylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics, food products, and oral and topical pharmaceutical formulations.

Propylparaben and methylparaben have been used as preservatives in injections and ophthalmic preparations; however, they are now generally regarded as being unsuitable for these types of formulations owing to the irritant potential of the parabens.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions. The WHO has set an estimated acceptable total daily intake for methyl, ethyl, and propyl parabens at up to 10 mg/kg body-weight.[10]

LD_{50} (mouse, IP): 0.2 g/kg[11]

LD_{50} (mouse, oral): 6.33 g/kg

LD_{50} (mouse, SC): 1.65 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Propylparaben and methylparaben are affirmed GRAS direct food substances in the USA at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan.

In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM, IV, and SC injections; inhalations; ophthalmic preparations; oral capsules, solutions, suspensions, and tablets; otic, rectal, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben; methylparaben; propylparaben potassium; propylparaben sodium.

Propylparaben potassium
Empirical formula $C_{10}H_{11}KO_3$
Molecular weight 218.30
CAS number [84930-16-5]
Synonyms Potassium propyl hydroxybenzoate; propyl 4-hydroxybenzoate potassium salt.

18 Comments

Propylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

A specification for propylparaben is contained in the Food Chemicals Codex (FCC)[12].

The EINECS number for propylparaben is 202-307-7. The PubChem Compound ID (CID) for propylparaben is 7175.

See Methylparaben for further information and references.

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