Bentonite

1 Nonproprietary Names

BP: Bentonite

JP: Bentonite

PhEur: Bentonite

USP-NF: Bentonite

2 Synonyms

Albagel; bentonitum; E558; mineral soap; *Polargel*; soap clay; taylorite; *Veegum HS*; wilkinite.

3 Chemical Name and CAS Registry Number

Bentonite [1302-78-9]

4 Empirical Formula and Molecular Weight

$Al_2O_3{\cdot}4SiO_2{\cdot}H_2O$ 359.16

Bentonite is a native colloidal hydrated aluminum silicate consisting mainly of montmorillonite, $Al_2O_3{\cdot}4SiO_2{\cdot}H_2O$; it may also contain calcium, magnesium, and iron. The average chemical analysis is expressed as oxides, *see* Table I, in comparison with magnesium aluminum silicate.

Table I: Average chemical analysis of bentonite expressed as oxides in comparison with magnesium aluminum silicate.

	Bentonite	Magnesium aluminum silicate
Silicon dioxide	59.92%	61.1%
Aluminum oxide	19.78%	9.3%
Magnesium oxide	1.53%	13.7%
Ferric oxide	2.96%	0.9%
Calcium oxide	0.64%	2.7%
Sodium oxide	2.06%	2.9%
Potassium oxide	0.57%	0.3%

5 Structural Formula

The PhEur 6.4 describes bentonite as a natural clay containing a high proportion of montmorillonite, a native hydrated aluminum silicate in which some aluminum and silicon atoms may be replaced by other atoms such as magnesium and iron.

The USP32–NF27 describes bentonite, purified benonite, and bentonite magma in three separate monographs. Bentonite is described as a native, colloidal, hydrated aluminum silicate; and purified bentonite is described as a colloidal montmorillonite that has been processed to remove grit and nonswellable ore compounds.

See also Section 4.

6 Functional Category

Adsorbent; stabilizing agent; suspending agent; viscosity increasing agent

7 Applications in Pharmaceutical Formulation or Technology

Bentonite is a naturally occurring hydrated aluminum silicate used primarily in the formulation of suspensions, gels, and sols, for topical pharmaceutical applications. It is also used to suspend powders in aqueous preparations and to prepare cream bases containing oil-in-water emulsifying agents.

Bentonite may also be used in oral pharmaceutical preparations, cosmetics, and food products, *see* Section 18. In oral preparations, bentonite, and other similar silicate clays, can be used to adsorb cationic drugs and so retard their release.[1–3] Adsorbents are also used to mask the taste of certain drugs. *See* Table II.

Bentonite has been investigated as a diagnostic agent for magnetic resonance imaging.[4]

Therapeutically, bentonite has been investigated as an adsorbent for lithium poisoning.[5]

Table II: Uses of bentonite.

Use	Concentration (%)
Adsorbent (clarifying agent)	1.0–2.0
Emulsion stabilizer	1.0
Suspending agent	0.5–5.0

8 Description

Bentonite is a crystalline, claylike mineral, and is available as an odorless, pale buff, or cream to grayish-colored fine powder, which is free from grit. It consists of particles about 50–150 µm in size along with numerous particles about 1–2 µm. Microscopic examination of samples stained with alcoholic methylene blue solution reveals strongly stained blue particles. Bentonite may have a slight earthy taste.

9 Pharmacopeial Specifications

See Table III.

Table III: Pharmacopeial specifications for bentonite.

Test	JP XV	PhEur 6.4	USP32–NF27
Identification	+	+	+
Characters	+	+	–
Alkalinity	–	+	–
Microbial limit	–	$\leqslant 10^3$ cfu/g	+
Coarse particles	–	⩽0.5%	–
pH (2% w/v suspension)	9.0–10.5	–	9.5–10.5
Loss on drying	5.0–10.0%	⩽15%	5.0–8.0%
Arsenic	⩽2 ppm	–	⩽5 ppm
Lead	–	–	⩽0.004%
Heavy metals	⩽50 ppm	⩽50 ppm	–
Gel formation	+	–	+
Sedimentation volume	–	⩽2 mL	–
Swelling power	⩾20 mL	⩾22 mL	⩾24 mL
Fineness of powder	+	–	+

The USP32–NF27 also contains specifications for bentonite magma and purified bentonite. *See* Section 17.

10 Typical Properties

Acidity/alkalinity pH = 9.5–10.5 for a 2% w/v aqueous suspension.

Flowability No flow.

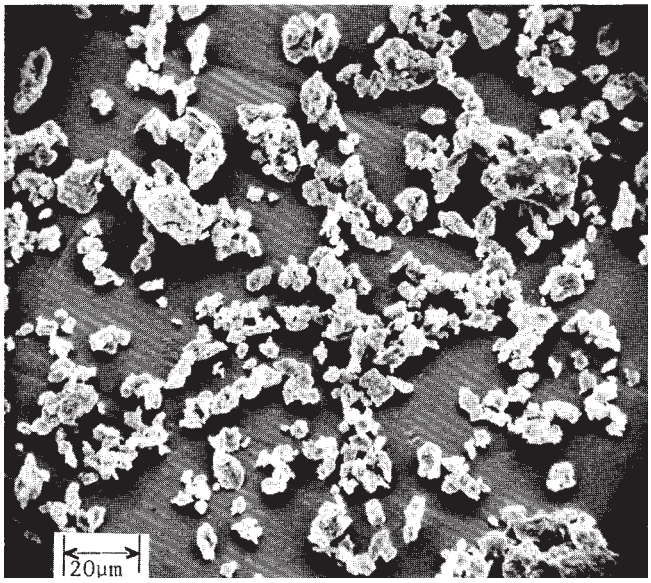
Hygroscopicity Bentonite is hygroscopic.[6] *See also* Figure 1.

Moisture content 5–12%.

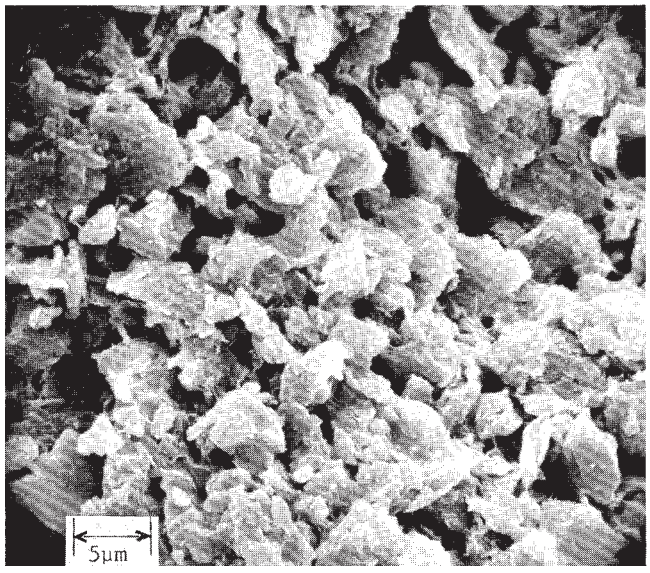
NIR spectra *see* Figure 2.

Solubility Practically insoluble in ethanol, fixed oils, glycerin, propan-2-ol, and water. Bentonite swells to about 12 times its original volume in water, to form viscous homogeneous suspensions, sols, or gels depending upon the concentration.

SEM 1: Excipient: bentonite; manufacturer: American Colloid Co.; lot no.: NMD 11780; magnification: 600×; voltage: 10 kV.



SEM 2: Excipient: bentonite; manufacturer: American Colloid Co.; lot no: NMD 11780; magnification: 2400×; voltage: 20 kV.



Bentonite does not swell in organic solvents. Sols and gels may be conveniently prepared by sprinkling the bentonite on the surface of hot water and allowing to stand for 24 hours, stirring occasionally when the bentonite has become thoroughly wetted. Water should not be added to bentonite alone, but bentonite may be satisfactorily dispersed in water if it is first triturated with glycerin or mixed with a powder such as zinc oxide. A 7% w/v aqueous suspension of bentonite is just pourable. *See also* Section 12.

Viscosity (dynamic) 75–225 mPa s (75–225 cP) for a 5.5% w/v aqueous suspension at 25°C. Viscosity increases with increasing concentration.

11 Stability and Storage Conditions

Bentonite is hygroscopic, and sorption of atmospheric water should be avoided.

Aqueous bentonite suspensions may be sterilized by autoclaving. The solid material may be sterilized by maintaining it at 170°C for 1 hour after drying at 100°C.

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

12 Incompatibilities

Aqueous bentonite suspensions retain their viscosity above pH 6, but are precipitated by acids. Acid-washed bentonite does not have suspending properties. The addition of alkaline materials, such as magnesium oxide, increases gel formation.

Addition of significant amounts of alcohol to aqueous preparations will precipitate bentonite, primarily by dehydration of the lattice structure; *see also* Section 18.

Bentonite particles are negatively charged and flocculation occurs when electrolytes or positively charged suspensions are added. Bentonite is thus said to be incompatible with strong electrolytes, although this effect is sometimes used beneficially to clarify turbid liquids.

The antimicrobial efficacy of cationic preservatives may be reduced in aqueous bentonite suspensions, but nonionic and anionic preservatives are unaffected.[7]

Bentonite is incompatible with acriflavine hydrochloride.

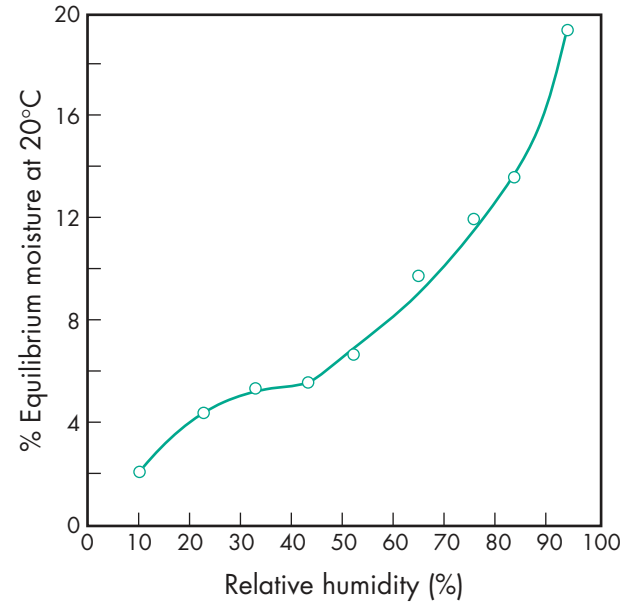


Figure 1: Equilibrium moisture content of bentonite USP–NF.

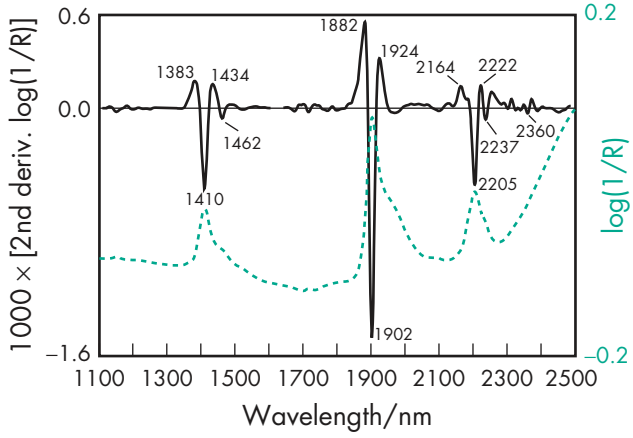


Figure 2: Near-infrared spectrum of bentonite measured by reflectance.

13 Method of Manufacture

Bentonite is a native, colloidal, hydrated aluminum silicate, found in regions of Canada and the USA. The mined ore is processed to remove grit and nonswelling materials so that it is suitable for pharmaceutical applications.

14 Safety

Bentonite is mainly used in topical pharmaceutical formulations but has also been used in oral pharmaceutical preparations, food products, and cosmetics.

Following oral administration, bentonite is not absorbed from the gastrointestinal tract. Bentonite is generally regarded as a nontoxic and nonirritant material.

LD_{50} (rat, IV): 0.035 g/kg[8]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. Bentonite should be handled in a well-ventilated environment and dust generation minimized.

16 Regulatory Status

Accepted in Europe as a food additive in certain applications. Included in the FDA Inactive Ingredients Database (oral capsules, tablets and suspensions, topical suspensions, controlled release transdermal films and vaginal suppositories). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Bentonite magma; kaolin; magnesium aluminum silicate; magnesium trisilicate; purified bentonite; talc.

Bentonite magma

Comments A 5% w/w suspension of bentonite in purified water appears in some pharmacopeias, such as the USP32–NF27.

Purified bentonite

Acidity/alkalinity pH = 9.0–10.0 for a 5% w/w aqueous suspension.

Viscosity (dynamic) 40–200 mPa s (40–200 cP) for a 5% w/w aqueous suspension.

Comments Specifications for purified bentonite occur in some pharmacopeias such as the USP32–NF27. Purified bentonite is bentonite that has been processed to remove grit and non-swellable ore components.

18 Comments

Bentonite may be used with concentrations of up to 30% ethanol or propan-2-ol; 50% glycerin; 30% propylene glycol; or high molecular weight polyethylene glycols. The EINECS number for bentonite is 215-108-5.

Bentonite is used in the food industry as a processing aid as a clarifying or filter agent. A specification for bentonite is contained in the Food Chemicals Codex (FCC).[9]

19 Specific References

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21 Author

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22 Date of Revision

15 January 2009.

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

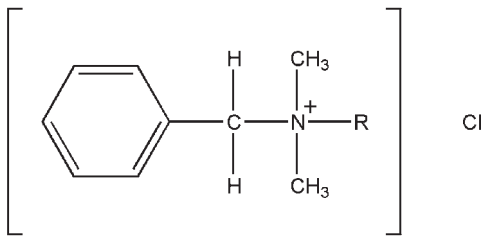
Alkyldimethyl(phenylmethyl)ammonium chloride [8001-54-5]

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

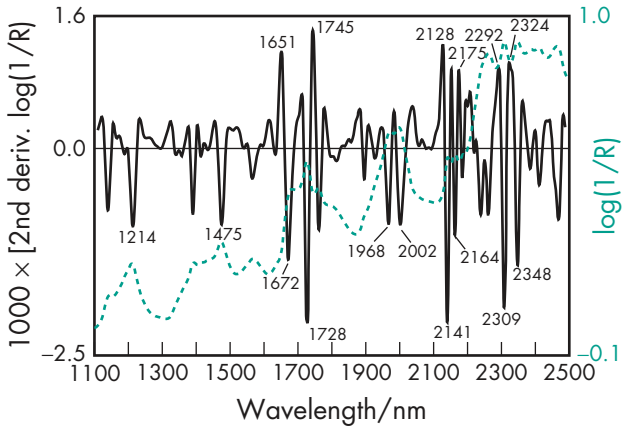


Figure 1: Near-infrared spectrum of benzalkonium chloride measured by reflectance.

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

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22 Date of Revision

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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*.

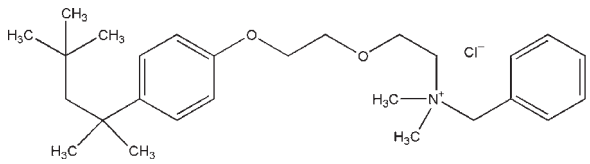
3 Chemical Name and CAS Registry Number

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.

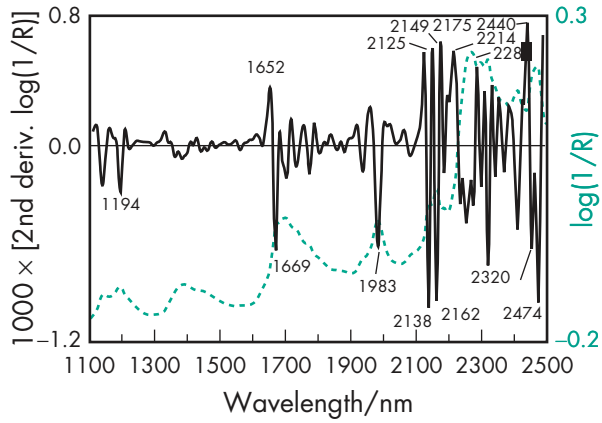


Figure 1: Near-infrared spectrum of benzethonium chloride measured by reflectance.

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.

Benzoic Acid

1 Nonproprietary Names

BP: Benzoic Acid
JP: Benzoic Acid
PhEur: Benzoic Acid
USP: Benzoic Acid

2 Synonyms

Acidum benzoicum; benzenecarboxylic acid; benzeneformic acid; carboxybenzene; dracylic acid; E210; phenylcarboxylic acid; phenylformic acid.

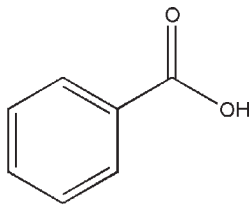
3 Chemical Name and CAS Registry Number

Benzoic acid [65-85-0]

4 Empirical Formula and Molecular Weight

$C_7H_6O_2$ 122.12

5 Structural Formula



6 Functional Category

Antimicrobial preservative; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzoic acid is widely used in cosmetics, foods, and pharmaceuticals (*see* Table I), as an antimicrobial preservative.[1–3] Greatest activity is seen at pH values between 2.5–4.5; *see* Section 10.

Benzoic acid also has a long history of use as an antifungal agent[4] in topical therapeutic preparations such as Whitfield's ointment (benzoic acid 6% and salicylic acid 3%).

Table I: Uses of benzoic acid.

Use	Concentration (%)
IM and IV injections	0.17
Oral solutions	0.01–0.1
Oral suspensions	0.1
Oral syrups	0.15
Topical preparations	0.1–0.2
Vaginal preparations	0.1–0.2

8 Description

Benzoic acid occurs as feathery, light, white or colorless crystals or powder. It is essentially tasteless and odorless or with a slight characteristic odor suggestive of benzoin.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for benzoic acid.

Test	JP XV	PhEur 6.4	USP 32
Identification	+	+	+
Characters	—	+	—
Melting point	121–124°C	121–124°C	121–123°C
Water	⩽0.5%	—	⩽0.7%
Residue on ignition	⩽0.05%	⩽0.1%	⩽0.05%
Readily carbonizable substances	+	+	+
Readily oxidizable substances	+	+	+
Heavy metals	⩽20 ppm	⩽10 ppm	⩽10 ppm
Halogenated compounds and halides	+	⩽300 ppm	—
Appearance of solution	—	+	—
Phthalic acid	+	—	—
Assay (anhydrous basis)	⩾99.5%	99.0–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity pH = 2.8 (saturated aqueous solution at 25°C)

Antimicrobial activity Only the undissociated acid shows antimicrobial properties; the activity therefore depends on the pH of the medium. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.[5] It has been reported that antimicrobial activity is enhanced by the addition of protamine, a basic protein.[6]

Bacteria Moderate bacteriostatic activity against most species of Gram-positive bacteria. Typical MIC is 100 µg/mL. Activity is less, in general, against Gram-negative bacteria. MIC for Gram-negative bacteria may be up to 1600 µg/mL.

Molds Moderate activity. Typical MICs are 400–1000 µg/mL at pH 3; 1000–2000 µg/mL at pH 5.

Spores Inactive against spores.

Yeasts Moderate activity. Typical MIC is 1200 µg/mL. The addition of propylene glycol may enhance the fungistatic activity of benzoic acid.

Autoignition temperature 570°C

Boiling point 249.2°C

Density

1.311 g/cm^3 for solid at 24°C;

1.075 g/cm^3 for liquid at 130°C.

Dissociation constant The dissociation of benzoic acid in mixed solvents is dictated by specific solute–solvent interactions as well as by relative solvent basicity. Increasing the organic solvent fraction favors the free acid form.[7]

pK_a = 4.19 at 25°C;

pK_a = 5.54 in methanol 60%.

Flash point 121–131°C

Melting point 122°C (begins to sublime at 100°C)

Moisture content 0.17–0.42% w/w

NIR spectra *see* Figure 1.

Partition coefficients

Benzene : water = 0.0044;[8]

Cyclohexane : water = 0.30;[9]

Octanol : water = 1.87.[10]

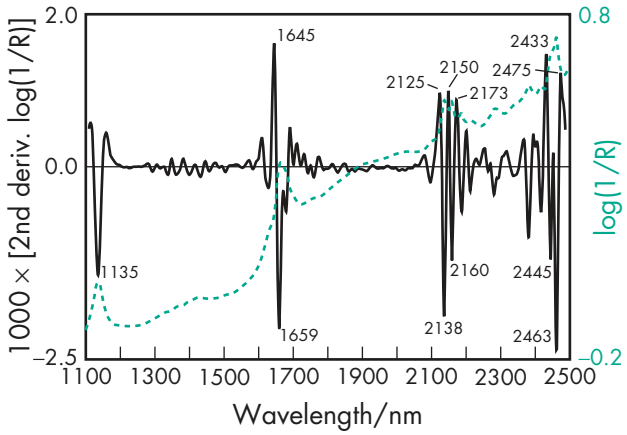


Figure 1: Near-infrared spectrum of benzoic acid measured by reflectance.

Refractive index

n_D^{15} = 1.5397 for solid;

n_D^{132} = 1.504 for liquid.

Solubility Apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution; *see* Table III.

Table III: Solubility of benzoic acid.

Solvent	Solubility at 25°C unless otherwise stated
Acetone	1 in 2.3
Benzene	1 in 9.4
Carbon disulfide	1 in 30
Carbon tetrachloride	1 in 15.2
Chloroform	1 in 4.5
Cyclohexane	1 in 14.6[9]
Ethanol	1 in 2.7 at 15°C 1 in 2.2
Ethanol (76%)	1 in 3.72[11]
Ethanol (54%)	1 in 6.27[11]
Ethanol (25%)	1 in 68[11]
Ether	1 in 3
Fixed oils	Freely soluble
Methanol	1 in 1.8
Toluene	1 in 11
Water	1 in 300

11 Stability and Storage Conditions

Aqueous solutions of benzoic acid may be sterilized by autoclaving or by filtration.

A 0.1% w/v aqueous solution of benzoic acid has been reported to be stable for at least 8 weeks when stored in polyvinyl chloride bottles, at room temperature.[12]

When added to a suspension, benzoic acid dissociates, with the benzoate anion adsorbing onto the suspended drug particles. This adsorption alters the charge at the surface of the particles, which may in turn affect the physical stability of the suspension.[13–15] The addition of sodium azide has been shown to increase the stability of benzoic acid in skin permeation experiments.[16]

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

12 Incompatibilities

Undergoes typical reactions of an organic acid, e.g. with alkalis or heavy metals. Preservative activity may be reduced by interaction with kaolin.[17]

13 Method of Manufacture

Although benzoic acid occurs naturally, it is produced commercially by several synthetic methods. One process involves the continuous liquid-phase oxidation of toluene in the presence of a cobalt catalyst at 150–200°C and 0.5–5.0 MPa (5.0–50.0 atm) pressure to give a yield of approximately 90% benzoic acid.

Benzoic acid can also be produced commercially from benzotrichloride or phthalic anhydride. Benzotrichloride, produced by chlorination of toluene, is reacted with 1 mole of benzoic acid to yield 2 moles of benzoyl chloride. The benzoyl chloride is then converted to 2 moles of benzoic acid by hydrolysis. Yield is 75–80%.

In another commercial process, phthalic anhydride is converted to benzoic acid, in about an 85% yield, by hydrolysis in the presence of heat and chromium and disodium phthalates.

Crude benzoic acid is purified by sublimation or recrystallization.

14 Safety

Ingested benzoic acid is conjugated with glycine in the liver to yield hippuric acid, which is then excreted in the urine;[18] care should be taken when administering benzoic acid to patients with chronic liver disease.[19] Benzoic acid is a gastric irritant, and a mild irritant to the skin.[20–23] It is also a mild irritant to the eyes and mucous membranes.[24] Allergic reactions to benzoic acid have been reported, although a controlled study indicated that the incidence of urticaria in patients given benzoic acid is no greater than in those given a lactose placebo.[25] It has been reported that asthmatics may become adversely affected by benzoic acid contained in some antiasthma drugs.[26]

The WHO acceptable daily intake of benzoic acid and other benzoates, calculated as benzoic acid, has been set at up to 5 mg/kg body-weight.[27,28] The minimum lethal human oral dose of benzoic acid is 500 mg/kg body-weight.[29,30]

LD_{50} (cat, oral): 2 g/kg[29]

LD_{50} (dog, oral): 2 g/kg

LD_{50} (mouse, IP): 1.46 g/kg

LD_{50} (mouse, oral): 1.94 g/kg

LD_{50} (rat, oral): 1.7 g/kg

See also Sodium benzoate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzoic acid may be harmful by inhalation, ingestion, or skin absorption and may be irritant to the eyes, skin, and mucous membranes. Benzoic acid should be handled in a well-ventilated environment; eye protection, gloves, and a dust mask or respirator are recommended. Benzoic acid is flammable.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM and IV injections, irrigation solutions, oral solutions, suspensions, 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

Potassium benzoate; sodium benzoate.

18 Comments

Benzoic acid is known to dimerize in many nonpolar solvents. This property, coupled with pH-dependent dissociation in aqueous media, comprises a classic textbook example of the effects of

dissociation and molecular association on apparent partitioning behavior. The principles involved may be practically applied in determination of the total concentration of benzoate necessary to provide a bacteriostatic level of benzoic acid in the aqueous phase of an oil-in-water emulsion.

A specification for benzoic acid is contained in the Food Chemicals Codex (FCC).[31]

The EINECS number for benzoic acid is 200-618-2. The PubChem Compound ID (CID) for benzoic acid is 243.

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21 Author

ME Quinn.

22 Date of Revision

12 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.

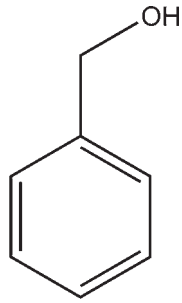
3 Chemical Name and CAS Registry Number

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.

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

RA Storey.

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.

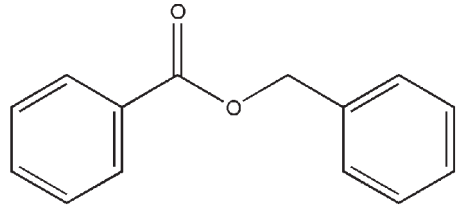
3 Chemical Name and CAS Registry Number

Benzoic acid phenylmethyl ester [120-51-4]

4 Empirical Formula and Molecular Weight

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

5 Structural Formula



6 Functional Category

Plasticizer; solubilizing agent; solvent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzyl benzoate is used as a solubilizing agent and nonaqueous solvent in intramuscular injections at concentrations of 0.01–46.0% v/v,[1] and as a solvent and plasticizer for cellulose and nitrocellulose. It is also used in the preparation of spray-dried powders using nanocapsules.[2]

However, the most widespread pharmaceutical use of benzyl benzoate is as a topical therapeutic agent in the treatment of scabies.[3] Benzyl benzoate is also used therapeutically as a parasiticide in veterinary medicine.[4]

Other applications of benzyl benzoate include its use as a pediculicide, and as a solvent and fixative for flavors and perfumes in cosmetics and food products.

8 Description

Benzyl benzoate is a clear, colorless, oily liquid with a slightly aromatic odor. It produces a sharp, burning sensation on the tongue. At temperatures below 17°C it exists as clear, colorless crystals.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzyl benzoate.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	+	+	—
Specific gravity	≈1.123	1.118–1.122	1.116–1.120
Congealing temperature	≈17°C	⩾17.0°C	⩾18.0°C
Boiling point	≈323°C	≈320°C	—
Refractive index	1.568–1.570	1.568–1.570	1.568–1.570
Aldehyde	—	—	⩽0.05%
Acidity	+	+	+
Sulfated ash	⩽0.05%	⩽0.1%	—
Assay	⩾99.0%	99.0–100.5%	99.0–100.5%

10 Typical Properties

Autoignition temperature 481°C
Boiling point 323–324°C
Flash point 148°C
Freezing point 17°C
Partition coefficient Octanol : water $\log k_{ow} = 3.97$
Refractive index $n_D^{21} = 1.5681$
Solubility Soluble in acetone and benzene; practically insoluble in glycerin and water; miscible with chloroform, ethanol (95%), ether, and with fatty acids and essential oils.
Specific gravity 1.12
Vapor density (relative) 7.3 (air = 1)

11 Stability and Storage Conditions

Benzyl benzoate is stable when stored in tight, well-filled, light-resistant containers. Exposure to excessive heat (above 40°C) should be avoided.

12 Incompatibilities

Benzyl benzoate is incompatible with alkalis and oxidizing agents.

13 Method of Manufacture

Benzyl benzoate is a constituent of Peru balsam and occurs naturally in certain plant species. Commercially, benzyl benzoate is produced synthetically by the dry esterification of sodium benzoate and benzoyl chloride in the presence of triethylamine or by the reaction of sodium benzylate with benzaldehyde.

14 Safety

Benzyl benzoate is metabolized by rapid hydrolysis to benzoic acid and benzyl alcohol. Benzyl alcohol is then further metabolized to hippuric acid, which is excreted in the urine.

Benzyl benzoate is widely used as a 25% v/v topical application in the treatment of scabies and as an excipient in intramuscular injections and oral products. Adverse reactions to benzyl benzoate include skin irritation and hypersensitivity reactions. Oral ingestion may cause harmful stimulation of the CNS and convulsions. Benzyl benzoate should be avoided by perople with perfume allergy.[5]

LD_{50} (cat, oral): 2.24 g/kg[6–9]
LD_{50} (dog, oral): 22.44 g/kg
LD_{50} (guinea pig, oral): 1.0 g/kg
LD_{50} (mouse, oral): 1.4 g/kg
LD_{50} (rabbit, oral): 1.68 g/kg
LD_{50} (rabbit, skin): 4.0 g/kg
LD_{50} (rat, oral): 0.5 g/kg
LD_{50} (rat, skin): 4.0 g/kg

15 Handling Precautions

Benzyl benzoate may be harmful if ingested, and is irritating to the skin, eyes, and mucous membranes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a respirator are recommended. It is recommended that benzyl benzoate is handled in a fume cupboard. Benzyl benzoate is flammable.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (IM injections and oral capsules). Included, as an active ingredient, in 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 benzoate has been shown to have an inhibitory effect on angiotensin II-induced hypertension.[10]

The EINECS number for benzyl benzoate is 204-402-9. The PubChem Compound ID (CID) for benzyl benzoate is 2345.

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21 Author

RA Storey.

22 Date of Revision

13 February 2009.

Boric Acid

1 Nonproprietary Names

BP: Boric Acid
JP: Boric Acid
PhEur: Boric Acid
USP-NF: Boric Acid

2 Synonyms

Acidum boricum; boracic acid; boraic acid; *Borofax*; boron trihydroxide; E284; orthoboric acid; trihydroxyborene.

3 Chemical Name and CAS Registry Number

Orthoboric acid [10043-35-3]
Metaboric acid [13460-50-9]

4 Empirical Formula and Molecular Weight

H_3BO_3 61.83 (for trihydrate)
HBO_2 43.82 (for monohydrate)

5 Structural Formula

See Section 4.

6 Functional Category

Antimicrobial preservative; buffering agent.

7 Applications in Pharmaceutical Formulation or Technology

Boric acid is used as an antimicrobial preservative[1] in eye drops, cosmetic products, ointments, and topical creams. It is also used as an antimicrobial preservative in foods.

Boric acid and borate have good buffering capacity and are used to control pH; they have been used for this purpose in external preparations such as eye drops.[2]

Boric acid has also been used therapeutically in the form of suppositories to treat yeast infections.[3,4] In dilute concentrations it is used as a mild antiseptic, with weak bacteriostatic and fungistatic properties, although it has generally been superseded by more effective and less toxic disinfectants.[5] *See* Section 14.

8 Description

Boric acid occurs as a hygroscopic, white crystalline powder, colorless shiny plates, or white crystals.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for boric acid.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Loss on drying	⩽0.50%	—	⩽0.50%
Sulfate	—	⩽450 ppm	—
Heavy metals	⩽10 ppm	⩽15 ppm	⩽0.002%
Organic matter	—	+	—
Arsenic	⩽5 ppm	—	—
pH	3.5–4.1	3.8–4.8	—
Solubility in ethanol (96%)	—	+	+
Completeness of solution	—	—	+
Assay	⩾99.5%	99.0–100.5%	99.5–100.5%

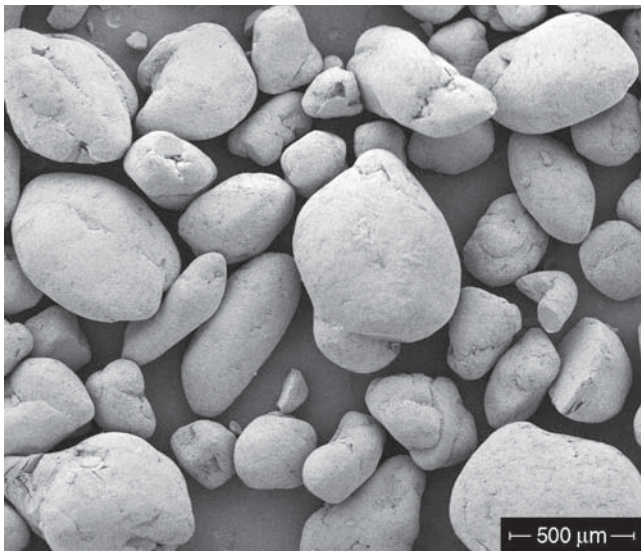
10 Typical Properties

Acidity/alkalinity pH = 3.5–4.1 (5% w/v aqueous solution)
Density 1.435
Melting point 170.9°C. When heated slowly to 181.0°C, boric acid loses water to form metaboric acid (HBO_2); tetraboric acid ($H_2B_4O_7$) and boron trioxide (B_2O_3) are formed at higher temperatures.[6]
Solubility Soluble in ethanol, ether, glycerin, water, and other fixed and volatile oils. Solubility in water is increased by addition of hydrochloric, citric, or tartaric acids.
Specific gravity 1.517

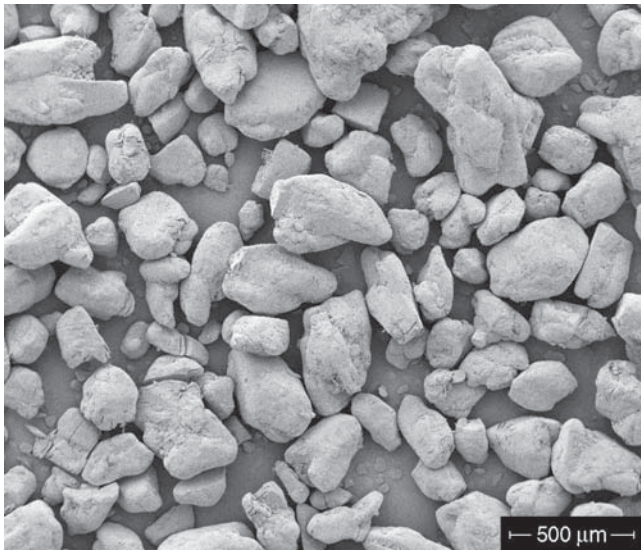
11 Stability and Storage Conditions

Boric acid is hygroscopic and should therefore be stored in an air-tight, sealed container. The container must be labeled 'Not for Internal Use'.

SEM 1: Excipient: boric acid; manufacturer: Alfa Aesar; lot no.: 23672; magnification: 100×; voltage: 5 kV.



SEM 2: Excipient: boric acid; manufacturer: Aldrich Chemical Company Inc.; lot no.: 01559BU; magnification: 100×; voltage: 5 kV.



12 Incompatibilities

Boric acid is incompatible with water, strong bases and alkali metals. It reacts violently with potassium and acid anhydrides. It also forms a complex with glycerin, which is a stronger acid than boric acid.

13 Method of Manufacture

Boric acid occurs naturally as the mineral sassolite. However, the majority of boric acid is produced by reacting inorganic borates with sulfuric acid in an aqueous medium. Sodium borate and partially refined calcium borate (colemanite) are the principal raw materials. When boric acid is made from colemanite, the fine-ground ore is vigorously stirred with mother liquor and sulfuric acid at about 90°C. The by-product calcium sulfate is removed by filtration, and the boric acid is crystallized by cooling the filtrate.

14 Safety

Boric acid is a weak bacteriostatic and antimicrobial agent, and has been used in topical preparations such as eye lotions, mouthwashes and gargles. It has also been used in US- and Japanese-approved intravenous products. Solutions of boric acid were formerly used to wash out body cavities, and as applications to wounds and ulcers, although the use of boric acid for these purposes is now regarded as inadvisable owing to the possibility of absorption.[5] Boric acid is not used internally owing to its toxicity. It is poisonous by ingestion and moderately toxic by skin contact. Experimentally it has proved to be toxic by inhalation and subcutaneous routes, and moderately toxic by intraperitoneal and intravenous routes.

Boric acid is absorbed from the gastrointestinal tract and from damaged skin, wounds, and mucous membranes, although it does not readily permeate intact skin. The main symptoms of boric acid poisoning are abdominal pain, diarrhea, erythematous rash involving both skin and mucous membrane, and vomiting. These symptoms may be followed by desquamation, and stimulation or depression of the central nervous system. Convulsions, hyperpyrexia, and renal tubular damage have been known to occur.[7]

Death has occurred from ingestion of less than 5 g in young children, and of 5–20 g in adults. Fatalities have occurred most frequently in young children after the accidental ingestion of solutions of boric acid, or after the application of boric acid powder to abraded skin.

The permissible exposure limit (PEL) of boric acid is 15 mg/m^3 total dust, and 5 mg/m^3 respirable fraction for nuisance dusts.[8]

Ld_{Lo} (man, oral): 429 mg/kg[9]
Ld_{Lo} (woman, oral): 200 mg/kg[9]
Ld_{Lo} (infant, oral): 934 mg/kg[9]
Ld_{Lo} (man, skin): 2.43 g/kg[9]
Ld_{Lo} (infant, skin): 1.20 g/kg[9]
LD_{50} (mouse, oral): 3.45 g/kg[9]
LD_{50} (mouse, IV): 1.24 g/kg
LD_{50} (mouse, SC): 1.74 g/kg
LD_{50} (rat, oral): 2.660 g/kg
LD_{50} (rat, IV): 1.33 g/kg
LD_{50} (rat, SC): 1.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Boric acid is irritating to the skin and is potentially toxic by inhalation. Gloves, eye protection, protective clothing, and a respirator are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IV injections; ophthalmic preparations; (auricular) otic solutions; topical preparations). Reported in the EPA TSCA Inventory. In the UK, the use of boric acid in cosmetics and toiletries is restricted. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sodium borate.

18 Comments

Boric acid has been used experimentally as a model oxo-acid to retard mannitol crystallization in the solid state.[10]

The EINECS number for boric acid is 233-139-2. The PubChem Compound ID (CID) for boric acid includes 7628 and 24492.

19 Specific References

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20 General References

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21 Authors

DD Ladipo, AC Bentham.

22 Date of Revision

19 January 2009.

Bronopol

1 Nonproprietary Names

BP: Bronopol

2 Synonyms

2-Bromo-2-nitro-1,3-propanediol; β-bromo-β-nitrotrimethyleneglycol; *Myacide*.

3 Chemical Name and CAS Registry Number

2-Bromo-2-nitropropane-1,3-diol [52-51-7]

4 Empirical Formula and Molecular Weight

$C_3H_6BrNO_4$ 200.00

5 Structural Formula

6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Bronopol 0.01–0.1% w/v is used as an antimicrobial preservative either alone or in combination with other preservatives in topical pharmaceutical formulations, cosmetics, and toiletries; the usual concentration is 0.02% w/v.

8 Description

Bronopol is a white or almost white crystalline powder; odorless or with a faint characteristic odor.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Antimicrobial activity Bronopol is active against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, with typical minimum inhibitory concentrations (MICs) between 10–50 µg/mL;[1–8] *see also* Table II. At room temperature, a 0.08% w/v aqueous solution may reduce the viability of culture collection strains of *Escherichia coli* and

Table I: Pharmacopeial specifications for bronopol.

Test	BP 2009
Identification	+
Characters	+
Acidity or alkalinity (1% w/v solution)	5.0–7.0
Related substances	+
Sulfated ash	⩽0.1%
Water	⩽0.5%
Assay (anhydrous basis)	99.0–101.0%

Table II: Minimum inhibitory concentrations (MICs) of bronopol.[2,9]

Microorganism	MIC (µg/mL)
Aspergillus niger	3200
Bacillus subtilis	12.5
Burkholderia (Pseudomonas) cepacia	25
Candida albicans	1600
Escherichia coli	12.5–50
Klebsiella aerogenes	25
Legionella pneumophilia	50
Penicillium roqueforti	400
Penicillium funiculosum	1600
Pityrosporum ovale	125
Proteus mirabilis	25–50
Proteus vulgaris	12.5–50
Pseudomonas aeruginosa	12.5–50
Saccharomyces cerevisiae	3200
Salmonella gallinarum	25
Staphylococcus aureus	12.5–50
Staphylococcus epidermidis	50
Streptococcus faecalis	50
Trichophyton mentagrophytes	200
Trichoderma viride	6400

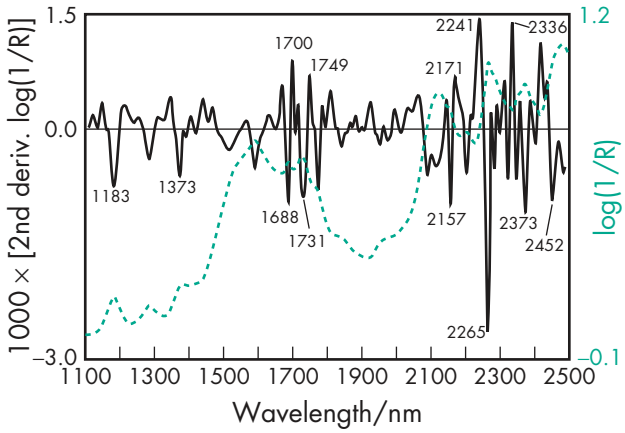

Figure 1: Near-infrared spectrum of bronopol measured by reflectance.

Pseudomonas aeruginosa by 100-fold or more in 15 minutes. Antimicrobial activity is not markedly influenced by pH in the range 5.0–8.0, nor by common anionic and nonionic surfactants, lecithin, or proteins.[2,5,6] Bronopol is less active against yeasts and molds, with typical MICs of 50–400 µg/mL or more, and has little or no useful activity against bacterial spores. *See also* Section 12.

Melting point 128–132°C

NIR spectra *see* Figure 1.

Partition coefficients

Mineral oil : water = 0.043 at 22–24°C;

Peanut oil : water = 0.11 at 22–24°C.

Solubility *see* Table III.

Table III: Solubility of bronopol.

Solvent	Solubility at 20°C
Cottonseed oil	Slightly soluble
Ethanol (95%)	1 in 2
Glycerol	1 in 100
Isopropyl myristate	1 in 200
Mineral oil	Slightly soluble
Propan-2-ol	1 in 4
Propylene glycol	1 in 2
Water	1 in 4

11 Stability and Storage Conditions

Bronopol is stable and its antimicrobial activity is practically unaffected when stored as a solid at room temperature and ambient relative humidity for up to 2 years.[3]

The pH of a 1.0% w/v aqueous solution is 5.0–6.0 and falls slowly during storage; solutions are more stable in acid conditions. Half-lives of bronopol in buffered aqueous solutions at 0.03% w/v are shown in Table IV.[9]

Microbiological assay results indicate longer half-lives than those obtained by HPLC and thus suggest that degradation products may contribute to antimicrobial activity. Formaldehyde and nitrites are among the decomposition products, but formaldehyde arises in such low concentrations that its antimicrobial effect is not likely to be significant. On exposure to light, especially under alkaline conditions, solutions become yellow or brown-colored but the degree of discoloration does not directly correlate with loss of antimicrobial activity.

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

Table IV: Half-lives of bronopol under different storage conditions.

Temperature (°C)	pH 4	pH 6	pH 8
5	>5 years	>5 years	6 months
25	>5 years	>5 years	4 months
40	2 years	4 months	8 days
60	2 weeks	<2 days	<1 day

12 Incompatibilities

Sulfhydryl compounds cause significant reductions in the activity of bronopol, and cysteine hydrochloride may be used as the deactivating agent in preservative efficacy tests; lecithin/polysorbate combinations are unsuitable for this purpose.[5] Bronopol is incompatible with sodium thiosulfate, with sodium metabisulfite, and with amine oxide or protein hydrolysate surfactants. Owing to an incompatibility with aluminum, the use of aluminum in the packaging of products that contain bronopol should be avoided.

13 Method of Manufacture

Bronopol is synthesized by the reaction of nitromethane with paraformaldehyde in an alkaline environment, followed by bromination. After crystallization, bronopol powder may be milled to produce a powder of the required fineness.

14 Safety

Bronopol is used widely in topical pharmaceutical formulations and cosmetics as an antimicrobial preservative.

Although bronopol has been reported to cause both irritant and hypersensitivity adverse reactions following topical use,[10–13] it is generally regarded as a nonirritant and nonsensitizing material at concentrations up to 0.1% w/v. At a concentration of 0.02% w/v, bronopol is frequently used as a preservative in 'hypoallergenic' formulations.

Animal toxicity studies have shown no evidence of phototoxicity or tumor occurrence when bronopol is applied to rodents topically or administered orally; and there is no *in vitro* or *in vivo* evidence of mutagenicity;[1] this is despite the demonstrated potential of bronopol to liberate nitrite on decomposition, which in the presence of certain amines may generate nitrosamines. Formation of nitrosamines in formulations containing amines may be reduced by limiting the concentration of bronopol to 0.01% w/v and including an antioxidant such as 0.2% w/v alpha tocopherol or 0.05% w/v butylated hydroxytoluene;[14] other inhibitor systems may also be appropriate.[15]

LD_{50} (dog, oral): 250 mg/kg [16]

LD_{50} (mouse, IP): 15.5 mg/kg

LD_{50} (mouse, IV): 48 mg/kg

LD_{50} (mouse, oral): 270 mg/kg

LD_{50} (mouse, SC): 116 mg/kg

LD_{50} (mouse, skin): 4.75 g/kg

LD_{50} (rat, IP): 26 mg/kg

LD_{50} (rat, IV): 37.4 mg/kg

LD_{50} (rat, oral): 180 mg/kg

LD_{50} (rat, SC): 170 mg/kg

LD_{50} (rat, skin): 1.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Bronopol may be harmful upon inhalation and the solid or concentrated solutions can be irritant to the skin and eyes. Eye protection, gloves, and dust respirator are recommended. Bronopol burns to produce toxic fumes.

16 Regulatory Status

Included in topical pharmaceutical formulations licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Bronopol owes its usefulness as a preservative largely to its activity against *Pseudomonas aeruginosa*, and its affinity for polar solvents, which prevents the loss of preservative into the oil phase of emulsions that is seen with some other preservatives. Other advantages include a low incidence of microbial resistance; low concentration exponent;[17] and good compatibility with most surfactants, other excipients, and preservatives, with which it can therefore be used in combination.

The major disadvantages of bronopol are relatively poor activity against yeasts and molds, instability at alkaline pH, and the production of formaldehyde and nitrite on decomposition, although there is no evidence of serious toxicity problems associated with bronopol that are attributable to these compounds.

The EINECS number for bronopol is200-143-0. The PubChem Compound ID (CID) for bronopol is 2450.

19 Specific References

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21 Authors

ME Quinn, PJ Sheskey.

22 Date of Revision

7 January 2009.

Butylated Hydroxyanisole

1 Nonproprietary Names

BP: Butylated Hydroxyanisole

PhEur: Butylhydroxyanisole

USP-NF: Butylated Hydroxyanisole

2 Synonyms

BHA; *tert*-butyl-4-methoxyphenol; butylhydroxyanisolum; 1,1-dimethylethyl-4-methoxyphenol; E320; *Nipanox BHA*; *Nipantiox 1-F*; *Tenox BHA*.

3 Chemical Name and CAS Registry Number

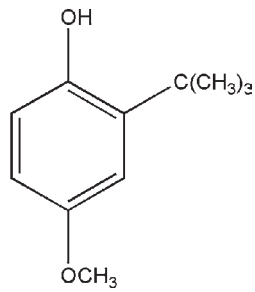
2-*tert*-Butyl-4-methoxyphenol [25013-16-5]

4 Empirical Formula and Molecular Weight

$C_{11}H_{16}O_2$ 180.25

The PhEur 6.0 describes butylated hydroxyanisole as 2-(1,1-dimethylethyl)-4-methoxyphenol containing not more than 10% of 3-(1,1-dimethylethyl)-4-methoxyphenol.

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Butylated hydroxyanisole is an antioxidant (*see* Table I) with some antimicrobial properties.[1–3] It is used in a wide range of cosmetics, foods, and pharmaceuticals. When used in foods, it is used to delay or prevent oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxyanisole is frequently used in combination with other antioxidants, particularly butylated hydroxytoluene and alkyl gallates, and with sequestrants or synergists such as citric acid.

FDA regulations direct that the total content of antioxidant in vegetable oils and direct food additives shall not exceed 0.02% w/w (200 ppm) of fat or oil content or essential (volatile) oil content of food.

USDA regulations require that the total content of antioxidant shall not exceed 0.01% w/w (100 ppm) of any one antioxidant or 0.02% w/w combined total of any antioxidant combination in animal fats.

Japanese regulations allow up to 1 g/kg in animal fats.

Table I: Antioxidant uses of butylated hydroxyanisole.

Antioxidant use	Concentration (%)
β-Carotene	0.01
Essential oils and flavoring agents	0.02–0.5
IM injections	0.03
IV injections	0.0002–0.0005
Oils and fats	0.02
Topical formulations	0.005–0.02
Vitamin A	10 mg per million units

8 Description

Butylated hydroxyanisole occurs as a white or almost white crystalline powder or a yellowish-white waxy solid with a faint, characteristic aromatic odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for butylated hydroxyanisole.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Residue on ignition	—	≤0.01%
Sulfated ash	≤0.1%	—
Related substances	+	—
Heavy metals	≤10 ppm	≤0.001%
Assay	—	≥98.5%

10 Typical Properties

Antimicrobial activity Activity is similar to that of the *p*-hydroxybenzoate esters (parabens). The greatest activity is against molds and Gram-positive bacteria, with less activity against Gram-negative bacteria.

Boiling point 264°C at 745 mmHg

Density (true) 1.117 g/cm^3

Flash point 130°C

Melting point 47°C (for pure 2-*tert*-butyl-4-methoxyphenol); *see also* Section 18.

NIR spectra *see* Figure 1.

Solubility Practically insoluble in water; soluble in methanol; freely soluble in ≥50% aqueous ethanol, propylene glycol, chloroform, ether, hexane, cottonseed oil, peanut oil, soybean oil, glyceryl monooleate, and lard, and in solutions of alkali hydroxides.

Viscosity (kinematic) 3.3 mm^2/s (3.3 cSt) at 99°C.

11 Stability and Storage Conditions

Exposure to light causes discoloration and loss of activity. Butylated hydroxyanisole should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Butylated hydroxyanisole is phenolic and undergoes reactions characteristic of phenols. It is incompatible with oxidizing agents

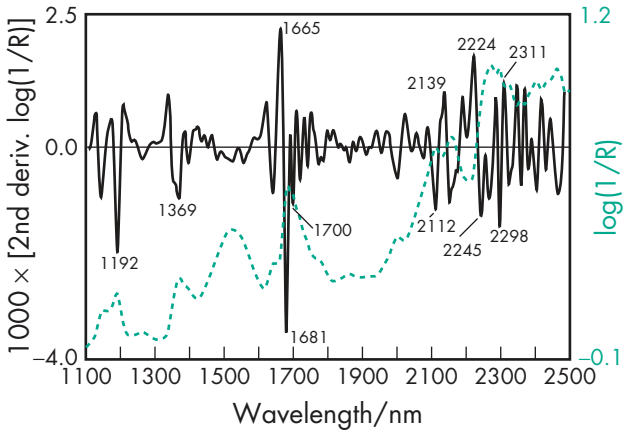


Figure 1: Near-infrared spectrum of butylated hydroxyanisole measured by reflectance.

and ferric salts. Trace quantities of metals and exposure to light cause discoloration and loss of activity.

13 Method of Manufacture

Prepared by the reaction of *p*-methoxyphenol with isobutene.

14 Safety

Butylated hydroxyanisole is absorbed from the gastrointestinal tract and is metabolized and excreted in the urine with less than 1% unchanged within 24 hours of ingestion.[4] Although there have been some isolated reports of adverse skin reactions to butylated hydroxyanisole,[5,6] it is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.

Concern over the use of butylated hydroxyanisole has occurred following long-term animal feeding studies. Although previous studies in rats and mice fed butylated hydroxyanisole at several hundred times the US-permitted level in the human diet showed no adverse effects, a study in which rats, hamsters, and mice were fed butylated hydroxyanisole at 1–2% of the diet produced benign and malignant tumors of the forestomach, but in no other sites. However, humans do not have any region of the stomach comparable to the rodent forestomach and studies in animals that also do not have a comparable organ (dogs, monkeys, and guinea pigs) showed no adverse effects. Thus, the weight of evidence does not support any relevance to the human diet where butylated hydroxyanisole is ingested at much lower levels.[7] The WHO acceptable daily intake of butylated hydroxyanisole has been set at 500 µg/kg body-weight.[7]

LD_{50} (mouse, oral): 1.1–2.0 g/kg[8]
LD_{50} (rabbit, oral): 2.1 g/kg
LD_{50} (rat, IP): 0.88 g/kg
LD_{50} (rat, oral): 2.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxyanisole may be irritant to the eyes and skin and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended. On combustion, toxic fumes may be given off.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM and IV injections, nasal sprays, oral capsules and tablets, and sublingual, 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

Butylated hydroxytoluene.

18 Comments

The commercially available material can have a wide melting point range (47–57°C) owing to the presence of varying amounts of 3-*tert*-butyl-4-methoxyphenol.

Tenox brands contain 0.1% w/w citric acid as a stabilizer.

A specification for butylated hydroxyanisole is contained in the Food Chemicals Codex (FCC).[9]

The EINECS number for butylated hydroxyanisole is 246-563-8. The PubChem Compound ID (CID) for butylated hydroxyanisole includes 8456 and 11954184.

19 Specific References

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21 Author

RT Guest.

22 Date of Revision

17 February 2009.

Butylated Hydroxytoluene

1 Nonproprietary Names

BP: Butylated Hydroxytoluene
PhEur: Butylhydroxytoluene
USP-NF: Butylated Hydroxytoluene

2 Synonyms

Agidol; BHT; 2,6-bis(1,1-dimethylethyl)-4-methylphenol; butylhydroxytoluene; butylhydroxytoluenum; *Dalpac*; dibutylated hydroxytoluene; 2,6-di-*tert*-butyl-*p*-cresol; 3,5-di-*tert*-butyl-4-hydroxytoluene; E321; *Embanox BHT*; *Impruvol*; *Ionol CP*; *Nipanox BHT*; *OHS28890*; *Sustane*; *Tenox BHT*; *Topanol*; *Vianol*.

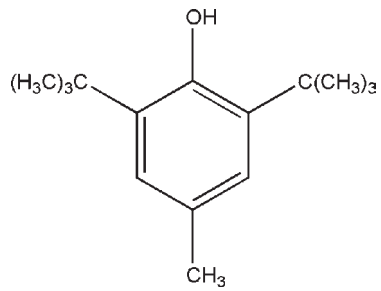
3 Chemical Name and CAS Registry Number

2,6-Di-*tert*-butyl-4-methylphenol [128-37-0]

4 Empirical Formula and Molecular Weight

$C_{15}H_{24}O$ 220.35

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Butylated hydroxytoluene is used as an antioxidant (*see* Table I) in cosmetics, foods, and pharmaceuticals.[1–4] It is mainly used to delay or prevent the oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxytoluene is also used at 0.5–1.0% w/w concentration in natural or synthetic rubber to provide enhanced color stability.

Butylated hydroxytoluene has some antiviral activity[5] and has been used therapeutically to treat herpes simplex labialis.[6]

8 Description

Butylated hydroxytoluene occurs as a white or pale yellow crystalline solid or powder with a faint characteristic phenolic odor.

Table I: Antioxidant uses of butylated hydroxytoluene.

Antioxidant use	Concentration (%)
β-Carotene	0.01
Edible vegetable oils	0.01
Essential oils and flavoring agents	0.02–0.5
Fats and oils	0.02
Fish oils	0.01–0.1
Inhalations	0.01
IM injections	0.03
IV injections	0.0009–0.002
Topical formulations	0.0075–0.1
Vitamin A	10 mg per million units

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for butylated hydroxytoluene.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Congealing temperature	—	⩾69.2°C
Freezing point	69–70°C	—
Residue on ignition	—	⩽0.002%
Sulfated ash	⩽0.1%	—
Heavy metals	—	⩽0.001%
Related substances	+	+
Assay	—	⩾99.0%

10 Typical Properties

Boiling point 265°C
Density (bulk) 0.48–0.60 g/cm^3
Density (true) 1.031 g/cm^3
Flash point 127°C (open cup)
Melting point 70°C
Moisture content ⩽0.05%
NIR spectra *see* Figure 1.
Partition coefficient Octanol : water = 4.17–5.80
Refractive index n_D^{75} = 1.4859
Solubility Practically insoluble in water, glycerin, propylene glycol, solutions of alkali hydroxides, and dilute aqueous mineral acids. Freely soluble in acetone, benzene, ethanol (95%), ether, methanol, toluene, fixed oils, and mineral oil. More soluble than butylated hydroxyanisole in food oils and fats.
Specific gravity
1.006 at 20°C;
0.890 at 80°C;
0.883 at 90°C;
0.800 at 100°C.
Specific heat
1.63 J/g/°C (0.39 cal/g/°C) for solid;
2.05 J/g/°C (0.49 cal/g/°C) for liquid.
Vapor density (relative) 7.6 (air = 1)
Vapor pressure
1.33 Pa (0.01 mmHg) at 20°C;
266.6 Pa (2 mmHg) at 100°C.

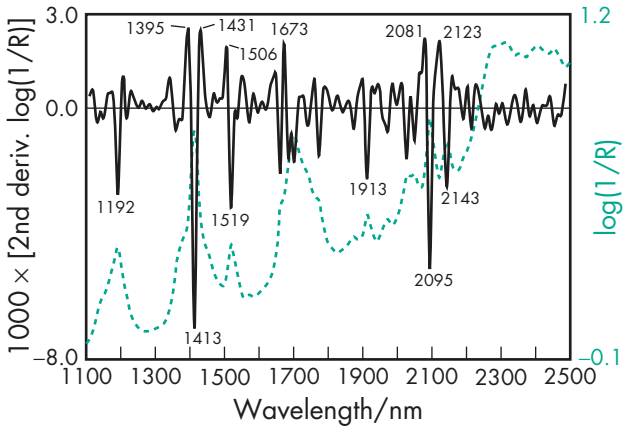


Figure 1: Near-infrared spectrum of butylated hydroxytoluene measured by reflectance.

Viscosity (kinematic) 3.47 mm^2/s (3.47 cSt) at 80°C.

11 Stability and Storage Conditions

Exposure to light, moisture, and heat causes discoloration and a loss of activity. Butylated hydroxytoluene should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Butylated hydroxytoluene is phenolic and undergoes reactions characteristic of phenols. It is incompatible with strong oxidizing agents such as peroxides and permanganates. Contact with oxidizing agents may cause spontaneous combustion. Iron salts cause discoloration with loss of activity. Heating with catalytic amounts of acids causes rapid decomposition with the release of the flammable gas isobutene.

13 Method of Manufacture

Prepared by the reaction of *p*-cresol with isobutene.

14 Safety

Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract and is metabolized and excreted in the urine mainly as glucuronide conjugates of oxidation products. Although there have been some isolated reports of adverse skin reactions, butylated hydroxytoluene is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.[7,8]

The WHO has set a temporary estimated acceptable daily intake for butylated hydroxytoluene at up to 125 µg/kg body-weight.[9]

Ingestion of 4 g of butylated hydroxytoluene, although causing severe nausea and vomiting, has been reported to be nonfatal.[10]

LD_{50} (guinea pig, oral): 10.7 g/kg[11]
LD_{50} (mouse, IP): 0.14 g/kg
LD_{50} (mouse, IV): 0.18 g/kg
LD_{50} (mouse, oral): 0.65 g/kg
LD_{50} (rat, oral): 0.89 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxytoluene may be irritant to the eyes and skin and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended. Closed containers may explode owing to pressure build-up when exposed to extreme heat.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM and IV injections, nasal sprays, oral capsules 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

Butylated hydroxyanisole.

18 Comments

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

The EINECS number for butylated hydroxytoluene is 204-881-4. The PubChem Compound ID (CID) for butylated hydroxytoluene is 31404.

19 Specific References

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21 Author

RT Guest.

22 Date of Revision

13 February 2009.

Butylene Glycol

1 Nonproprietary Names

None adopted.

2 Synonyms

Butane-1,3-diol; 1,3-butylene glycol; β-butylene glycol; 1,3-dihydroxybutane; methyltrimethylene glycol.

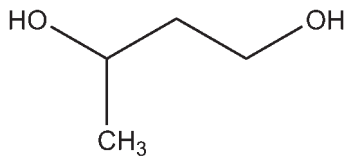
3 Chemical Name and CAS Registry Number

1,3-Butanediol [107-88-0]

4 Empirical Formula and Molecular Weight

$C_4H_{10}O_2$ 90.14

5 Structural Formula



6 Functional Category

Antimicrobial preservative; humectant; solvent; water-miscible cosolvent.

7 Applications in Pharmaceutical Formulation or Technology

Butylene glycol is used as a solvent and cosolvent for injectables.[1] It is used in topical ointments, creams, and lotions,[2–4] and it is also used as a vehicle in transdermal patches. Butylene glycol is a good solvent for many pharmaceuticals, especially estrogenic substances.[5]

In an oil-in-water emulsion, butylene glycol exerts its best antimicrobial effects at ~8% concentration.[6] Higher concentrations above 16.7% are required to inhibit fungal growth.[7]

8 Description

Butylene glycol occurs as a clear, colorless, viscous liquid with a sweet flavor and bitter aftertaste.

9 Pharmacopeial Specifications

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10 Typical Properties

Antimicrobial activity Butylene glycol is effective against Gram-positive and Gram-negative bacteria, molds, and yeast, though it is not sporicidal.[6]
Density 1.004–1.006 (at 20°C)
Flash point 115–121°C (open cup)
Hygroscopicity Absorbs 38.5% w/w of water in 144 hours at 81% RH.
Melting point −77°C
Refractive index $n_D^{20} = 1.440$
Solubility Miscible with acetone, ethanol (95%), castor oil, dibutyl phthalate, ether, water; practically insoluble in mineral oil, linseed oil, ethanolamine, aliphatic hydrocarbons; dissolves most essential oils and synthetic flavoring substances.
Specific heat 2.34 J/g (0.56 cal/g) at 20°C
Surface tension 37.8 mN/m (37.8 dyne/cm) at 25°C
Vapor density (relative) 3.1 (air = 1)
Vapor pressure 8 Pa (0.06 mmHg) at 20°C
Viscosity (dynamic) 104 mPa s (104 cP) at 25°C

11 Stability and Storage Conditions

Butylene glycol is hygroscopic and should be stored in a well-closed container in a cool, dry, well-ventilated place. When heated to decomposition, butylene glycol emits acrid smoke and irritating fumes.

12 Incompatibilities

Butylene glycol is incompatible with oxidizing reagents.

13 Method of Manufacture

Butylene glycol is prepared by catalytic hydrogenation of aldol using Raney nickel.

14 Safety

Butylene glycol is used in a wide variety of cosmetic formulations and is generally regarded as a relatively nontoxic material. It is mildly toxic by oral and subcutaneous routes.

In topical preparations, butylene glycol is regarded as minimally irritant. Butylene glycol can cause allergic contact dermatitis, with local sensitivity reported in patch tests.[3,9–12] Some local irritation is produced on eye contact.

LD_{50} (guinea pig, oral): 11.0 g/kg[8]
LD_{50} (mouse, oral): 12.98 g/kg
LD_{50} (rat, oral): 18.61 g/kg
LD_{50} (rat, SC): 20.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Butylene glycol should be handled in a well-ventilated environment; eye protection is recommended. Butylene glycol is combustible when exposed to heat or flame.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (transdermal patches). Included in licensed medicines in the UK (topical gel patches/medicated plasters).

17 Related Substances

Propylene glycol.

18 Comments

Butylene glycol is used in shaving lather preparations and cosmetics, where it can be used to replace glycerin.[2] Because of its high viscosity at low temperatures, heating may be required for pumping.

A specification for butylene glycol is included in the Food Chemicals Codex (FCC); *see* Table I.

The EINECS number for butylene glycol is 203-529-7. The PubChem Compound ID (CID) for butylene glycol is 7896.

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%

19 Specific References

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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*.

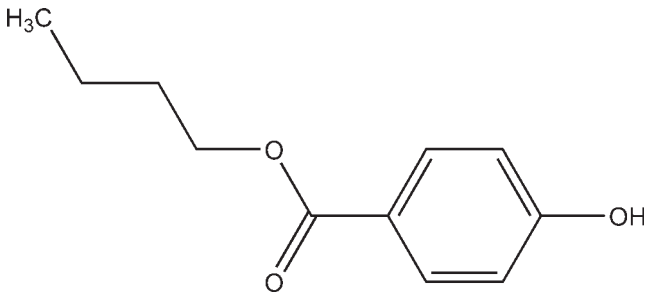
3 Chemical Name and CAS Registry Number

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.

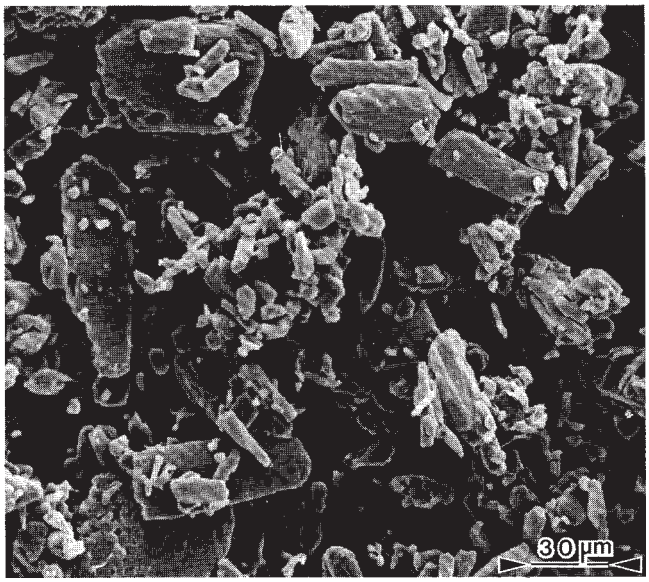
Table I: Uses of butylparaben.

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

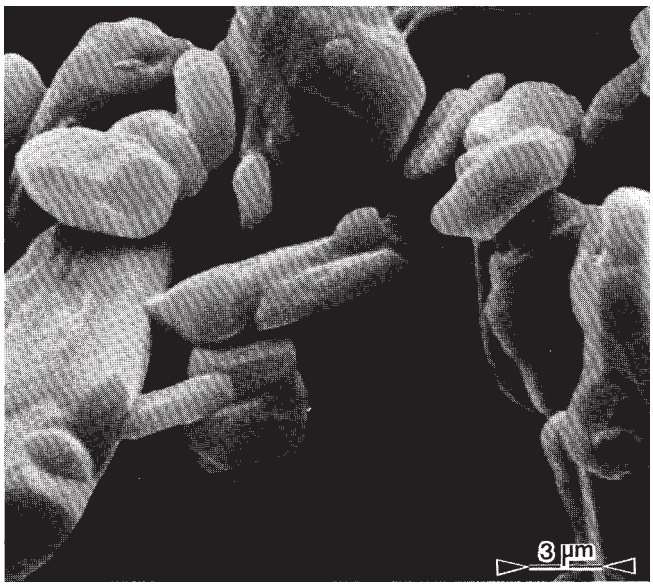
8 Description

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]

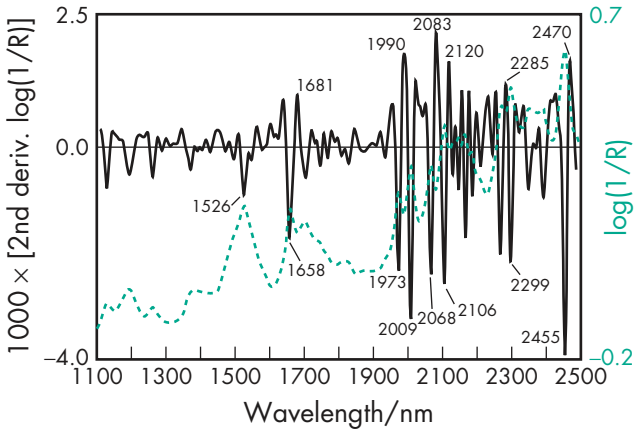


Figure 1: Near-infrared spectrum of butylparaben measured by reflectance.

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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22 Date of Revision

3 February 2009.