

Handbook of Pharmaceutical Excipients

Eighth edition

Edited by Paul J Sheskey, Walter G Cook and Colin G Cable



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EIGHTH EDITION

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LD₅₀ (mouse, oral): 0.338 g/kg

LD₅₀ (rat, IP): 0.0165 g/kg

LD₅₀ (rat, IV): 0.019 g/kg

LD₅₀ (rat, oral): 0.368 g/kg

LD₅₀ (rat, SC): 0.119 g/kg

15 Handling Precautions

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

Benzethonium chloride is highly flammable and should be kept away from sources of ignition. When heated to decomposition it emits very toxic fumes of hydrogen chloride, ammonia (NH₃), and nitrogen oxides (NO_x). Suitable eye, skin, and respiratory protection 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 Natural Health Products Ingredients Database.

17 Related Substances

Benalkonium chloride; cetrimide; cetrimonium bromide.

18 Comments

Benzethonium chloride has been used therapeutically as a disinfectant and topical anti-infective agent.⁽⁷⁻¹⁰⁾ However, its use in these applications has largely been superseded by other more effective antimicrobials and it is now largely used solely as a preservative in a limited number of pharmaceutical and cosmetic formulations.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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- 7 Shintre MS, et al. Efficacy of an alcohol-based healthcare hand rub containing synergistic combination of farnesol and benzethonium chloride. *Int J Hyg Environ Health* 2006; 209(5): 477-487.
- 8 Bearden DT, et al. Comparative *in vitro* activities of topical wound care products against community-associated methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 2008; 62(4): 769-772.
- 9 Suzuki T, et al. Bactericidal activity of topical antiseptics and their gargles against *Bordetella pertussis*. *J Infect Chemother* 2012; 18(2): 272-275.
- 10 Czerwinski SE, et al. Novel water-based antiseptic lotion demonstrates rapid, broad-spectrum kill compared with alcohol antiseptic. *J Infect Public Health* 2014; 7(3): 199-204.

20 General References

Lonza. Material safety data sheet: *Hyamine 1622*, 2012.

21 Author

ME Quinn.

22 Date of Revision

4 May 2017.



Benzoic Acid

1 Nonproprietary Names

BP: Benzoic Acid

JP: Benzoic Acid

PhEur: Benzoic Acid

USP-NF: Benzoic Acid

2 Synonyms

Acidum benzoicum; benzenecarboxylic acid; benzene formic acid; carboxybenzene; dracylic acid; E210; phenylcarboxylic acid; phenylformic acid; *Purox B*.

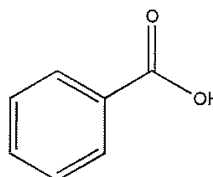
3 Chemical Name and CAS Registry Number

Benzoic acid [65-85-0]

4 Empirical Formula and Molecular Weight

C₇H₆O₂ 122.12

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Benzoic acid is widely used in pharmaceuticals (see Table I), as an antimicrobial preservative.⁽¹⁻³⁾ The greatest antimicrobial activity is seen at pH values between 2.5-4.5; see Section 10.

102 Benzoic Acid

Benzoic acid has been investigated for use in co-crystal formulations for improved physicochemical properties, such as solubility and dissolution rate.⁽⁴⁻⁶⁾ Benzoic acid spherical agglomerates have been studied for use in direct tableting.⁽⁷⁾

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 XVII	PhEur 9.2	USP 40-NF 35 S1
Identification	+	+	+
Characters	—	+	—
Melting point	121-124°C	121-124°C	121-123°C
Water	—	—	≤0.7%
Loss on drying	≤0.5%	—	—
Sulfated ash	—	≤0.1%	—
Residue on ignition	≤0.05%	—	≤0.05%
Readily carbonizable substances	+	+	+
Readily oxidizable substances	+	+	+
Heavy metals	≤20 ppm	—	≤10 µg/g
Halogenated compounds and halides	—	≤300 ppm	—
Chlorinated compounds	+	—	—
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.⁽⁸⁾ It has been reported that antimicrobial activity is enhanced by the addition of protamine, a basic protein.⁽⁹⁾

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/cm³ for solid at 24°C;

1.075 g/cm³ 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.⁽¹⁰⁾

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

Partition coefficients

Benzene : water = 0.0044;⁽¹¹⁾

Cyclohexane : water = 0.30;⁽¹²⁾

Octanol : water = 1.87.⁽¹³⁾

Refractive index

n_D¹⁵ = 1.5397 for solid;

n_D¹³² = 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 ⁽¹²⁾
Ethanol	1 in 2.7 at 15°C
	1 in 2.2
Ethanol (76%)	1 in 3.72 ⁽¹⁴⁾
Ethanol (54%)	1 in 6.27 ⁽¹⁴⁾
Ethanol (25%)	1 in 68 ⁽¹⁴⁾
Ether	1 in 3
Fixed oils	Freely soluble
Methanol	1 in 1.8
Toluene	1 in 11
Water	1 in 300

Spectroscopy

IR spectrum see Figure 1.

NIR spectrum see Figure 2.

Raman spectrum see Figure 3.

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.⁽¹⁵⁾

When added to a suspension, benzoic acid dissociates, with the benzoate anion adsorbing onto the suspended drug particles. This

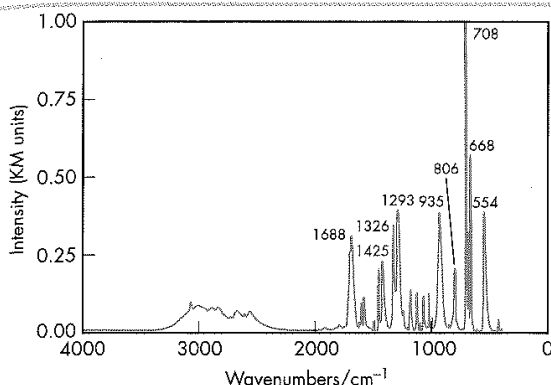


Figure 1: Infrared spectrum of benzoic acid measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

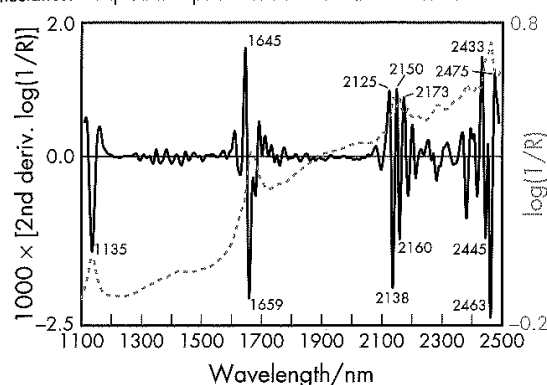


Figure 2: Near-infrared spectrum of benzoic acid measured by reflectance.

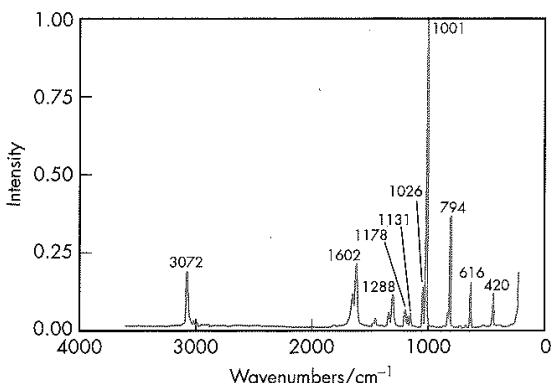


Figure 3: Raman spectrum of benzoic acid measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

adsorption alters the charge at the surface of the particles, which may in turn affect the physical stability of the suspension.⁽¹⁶⁻¹⁸⁾ The addition of sodium azide has been shown to increase the stability of benzoic acid in skin permeation experiments.⁽¹⁹⁾

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

12 Incompatibilities

Benzoic acid undergoes typical reactions of an organic acid, e.g. with alkalis or heavy metals. Preservative activity may be reduced by interaction with kaolin.⁽²⁰⁾

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 benzo-trichloride 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. The yield of benzoic acid 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;⁽²¹⁾ care should be taken when administering benzoic acid to patients with chronic liver disease.⁽²²⁾ Benzoic acid is a gastric irritant, and a mild irritant to the skin.⁽²³⁻²⁶⁾ It is also a mild irritant to the eyes and mucous membranes.⁽²⁷⁾ 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.⁽²⁸⁾ It has been reported that asthmatics may become adversely affected by benzoic acid contained in some antiasthma drugs.⁽²⁹⁾ Benzoic acid may also cause genotoxic effects.⁽³⁰⁾

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.^(31,32) The minimum lethal human oral dose of benzoic acid is 500 mg/kg body-weight.^(33,34)

LD₅₀ (cat, oral): 2 g/kg⁽³³⁾

LD₅₀ (dog, oral): 2 g/kg⁽³³⁾

LD₅₀ (mouse, IP): 1.46 g/kg⁽³³⁾

LD₅₀ (mouse, oral): 1.94 g/kg⁽³³⁾

LD₅₀ (rat, oral): 1.7 g/kg⁽³³⁾

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, sprays, suspensions, syrups and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian Health Products Ingredients Database.

17 Related Substances

Potassium benzoate; sodium benzoate.

18 Comments

Benzoic acid is also used as an antimicrobial preservative in cosmetics and foods.

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.

Benzoic acid also has a long history of use as an antifungal agent⁽³⁵⁾ in topical therapeutic preparations such as Whitfield's ointment (benzoic acid 6% and salicylic acid 3%).

A specification for benzoic acid is contained in the *Food Chemicals Codex* (FCC).⁽³⁶⁾

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

RT Guest.

22 Date of Revision

4 May 2017.

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; Nipanax BHT; OHS28890; Sustane; Tenox BHT; Topanol; Vianol.

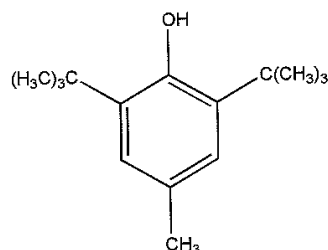
3 Chemical Name and CAS Registry Number

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

4 Empirical Formula and Molecular Weight

C₁₅H₂₄O 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.^(1–5) 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.⁽⁶⁾

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

8 Description

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

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Boiling point 265°C
 Density (bulk) 0.48–0.60 g/cm³
 Density (true) 1.031 g/cm³
 Flash point 127°C (open cup)
 Melting point 70°C
 Moisture content ≤0.05%

Table II: Pharmacopetal specifications for butylated hydroxytoluene.

Test	PhEur 9.2	USP 40-NF 35 S1
Identification	+	+
Characters	+	-
Appearance of solution	+	-
Congeeing temperature	-	≥69.2°C
Freezing point	69–70°C	-
Residue on ignition	-	≤0.002%
Sulfated ash	≤0.1%	-
Heavy metals	-	≤10 ppm
Related substances	+	+
Assay	-	99.0–101.5%

Partition coefficient Octanol : water = 4.17–5.80

Refractive index $n_D^{25} = 1.4859$

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.

Spectroscopy

IR spectrum *see* Figure 1.

NIR spectrum *see* Figure 2.

Raman spectrum *see* Figure 3.

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.

Viscosity (kinematic) 3.47 mm²/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

Butylated hydroxytoluene is 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

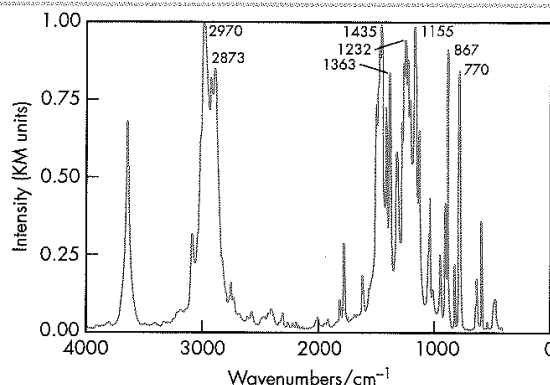


Figure 1: Infrared spectrum of butylated hydroxytoluene measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

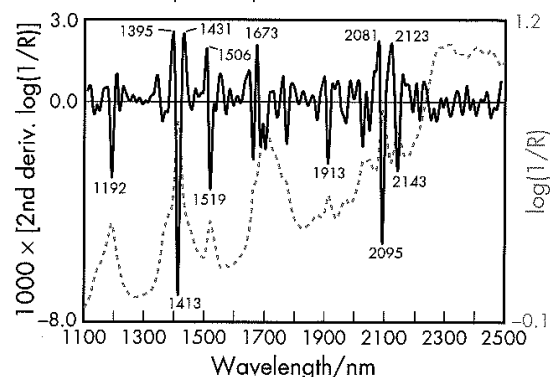


Figure 2: Near-infrared spectrum of butylated hydroxytoluene measured by reflectance.

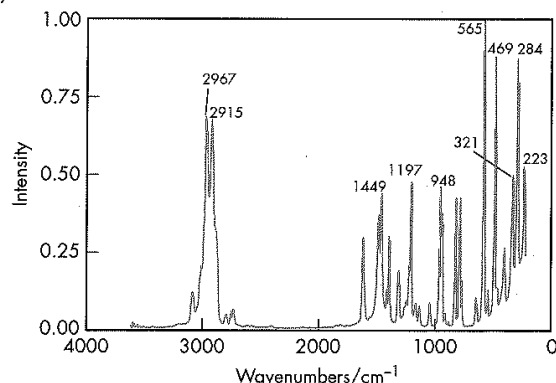


Figure 3: Raman spectrum of butylated hydroxytoluene measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

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⁾

LD₅₀ (guinea pig, oral): 10.7 g/kg⁽¹¹⁾

LD₅₀ (mouse, IP): 0.14 g/kg

128 Butylene Glycol

LD₅₀ (mouse, IV): 0.18 g/kg
LD₅₀ (mouse, oral): 0.65 g/kg
LD₅₀ (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 Natural Health Products Ingredients Database.

17 Related Substances

Butylated hydroxyanisole.

18 Comments

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⁽¹²⁾ and has been used therapeutically to treat herpes simplex labialis.⁽¹³⁾

A specification for butylated hydroxytoluene is contained in the *Food Chemicals Codex* (FCC).⁽¹⁴⁾

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

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21 Author

RT Guest.

22 Date of Revision

4 May 2017.

Butylene Glycol

1 Nonproprietary Names

USP–NF: Butylene Glycol

2 Synonyms

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

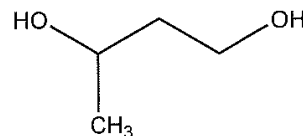
3 Chemical Name and CAS Registry Number

Butane-1,3-diol [107-88-0]

4 Empirical Formula and Molecular Weight

C₄H₁₀O₂ 90.12

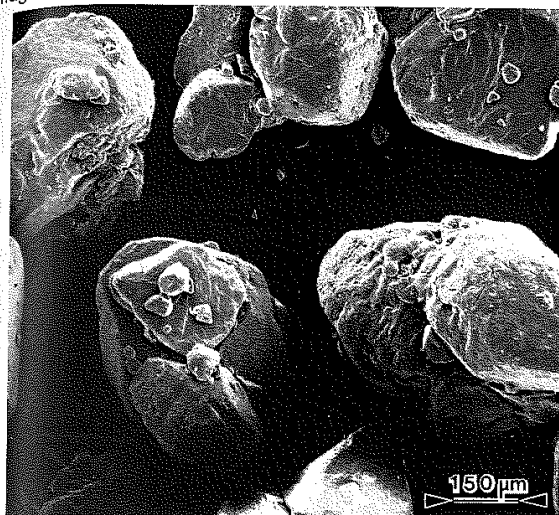
5 Structural Formula



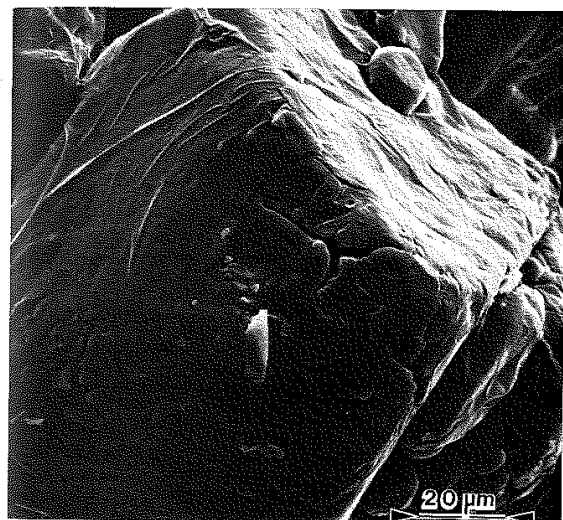
6 Functional Category

Antimicrobial preservative; humectant; solvent; transdermal delivery component.

SEM 1: Excipient: citric acid monohydrate; manufacturer: Pfizer Ltd; magnification: 600 $\times$.



SEM 2: Excipient: citric acid monohydrate; manufacturer: Pfizer Ltd; magnification: 600 $\times$.



9 Pharmacopeial Specifications

The pharmacopeial specifications for citric acid monohydrate have undergone harmonization of many attributes for JP, PhEur, and USP–NF.

See Table II. See also Sections 17 and 18.

Note that the JP XVII, PhEur 9.2 and USP 40–NF 35 S1 have separate monographs for the monohydrate and anhydrous material.

10 Typical Properties

Acidity/alkalinity pH = 2.2 (1% w/v aqueous solution)

Dissociation constant

pK_{a1}: 3.128 at 25°C;

pK_{a2}: 4.761 at 25°C;

pK_{a3}: 6.396 at 25°C.

Density 1.542 g/cm³

Heat of combustion –1972 kJ/mol (–471.4 kcal/mol)

Table II: Pharmacopeial specifications for citric acid monohydrate (and anhydrous).

Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Identification	+	+	+
Characters ^(a)	–	+	–
Appearance of solution	+	+	+
Water			
(hydrous form)	7.5–9.0%	7.5–9.0%	7.5–9.0%
(anhydrous form)	≤1.0%	≤1.0%	≤1.0%
Sterility ^(a)	–	–	+
Bacterial endotoxins ^(a)	–	<0.5 IU/mg ^(b)	+
Residue on ignition	≤0.1%	–	≤0.1%
Sulfated ash	–	≤0.1%	–
Calcium	–	–	–
Aluminum	–	≤0.2 ppm	≤0.2 ppm ^(c)
Oxalic acid	≤360 ppm	≤360 ppm	≤0.036%
Sulfate	≤150 ppm	≤150 ppm	≤0.015%
Heavy metals ^(a)	≤10 ppm	–	≤10 μg/g
Readily carbonizable substances	+	+	+
Assay (anhydrous basis)	99.5–100.5%	99.5–100.5%	99.5–100.5%

(a) These tests have not been fully harmonized at the time of publication.

(b) If intended for use in parenteral preparations.

(c) Where it is labeled as intended for use in dialysis.

Heat of solution –16.3 kJ/mol (–3.9 kcal/mol) at 25°C

Hygroscopicity At relative humidities less than about 65%, citric acid monohydrate effloresces at 25°C, the anhydrous acid being formed at relative humidities less than about 40%. At relative humidities between about 65% and 75%, citric acid monohydrate absorbs insignificant amounts of moisture, but under more humid conditions substantial amounts of water are absorbed.

Melting point ≈100°C (softens at 75°C)

Particle size distribution Various grades of citric acid monohydrate with different particle sizes are commercially available.

Solubility Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.

Spectroscopy

IR spectrum see Figure 1.

NIR spectrum see Figure 2.

Raman spectrum see Figure 3.

Viscosity (dynamic) 6.5 mPa s (6.5 cP) for a 50% w/v aqueous solution at 25°C.

See also Section 17.

11 Stability and Storage Conditions

Citric acid monohydrate loses water of crystallization in dry air or when heated to about 40°C. It is slightly deliquescent in moist air. Dilute aqueous solutions of citric acid may ferment on standing.

The bulk monohydrate or anhydrous material should be stored in airtight containers in a cool, dry place.

12 Incompatibilities

Citric acid is incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates. It is potentially explosive in combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.

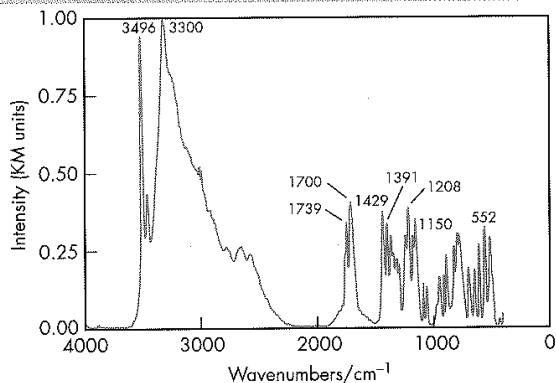


Figure 1: Infrared spectrum of citric acid monohydrate measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

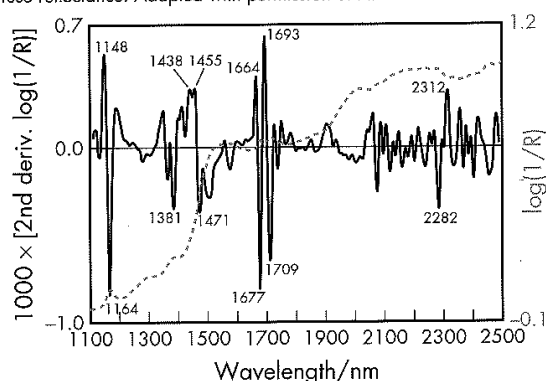


Figure 2: Near-infrared spectrum of citric acid monohydrate measured by reflectance.

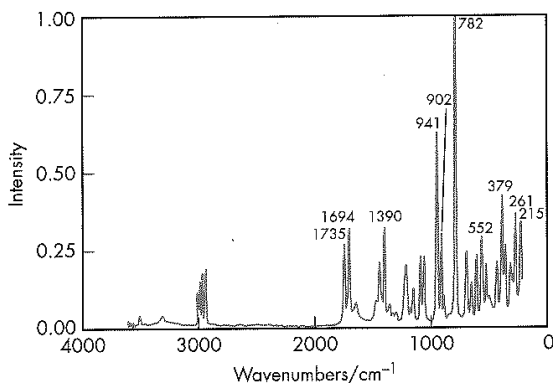


Figure 3: Raman spectrum of citric acid monohydrate measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

13 Method of Manufacture

Citric acid occurs naturally in a number of plant species and may be extracted from lemon juice, which contains 5–8% citric acid, or pineapple waste. Anhydrous citric acid may also be produced industrially by mycological fermentation of crude sugar solutions such as molasses, using strains of *Aspergillus niger*. Citric acid is purified by recrystallization; the anhydrous form is obtained from a hot concentrated aqueous solution and the monohydrate from a cold concentrated aqueous solution.

14 Safety

Citric acid is found naturally in the body, mainly in the bones, and is commonly consumed as part of a normal diet. Orally ingested citric acid is absorbed and is generally regarded as a nontoxic material when used as an excipient. However, excessive or frequent consumption of citric acid has been associated with erosion of the teeth.⁽⁵⁾

Citric acid and citrates also enhance intestinal aluminum absorption in renal patients, which may lead to increased, harmful serum aluminum levels. It has therefore been suggested that patients with renal failure taking aluminum compounds to control phosphate absorption should not be prescribed citric acid or citrate-containing products.⁽⁶⁾

See Section 17 for anhydrous citric acid animal toxicity data.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Direct contact with eyes can cause serious damage. Citric acid should be handled in a well-ventilated environment or a dust mask should be worn. It is combustible.

16 Regulatory Status

GRAS listed. The anhydrous form is accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; IM, IV, and other injections; ophthalmic preparations; oral capsules, solutions, suspensions and tablets; topical and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in Japan and the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Anhydrous citric acid; fumaric acid; malic acid; sodium citrate dihydrate; tartaric acid.

Anhydrous citric acid

Empirical formula $C_6H_8O_7$

Molecular weight 192.12

CAS number [77-92-9]

Synonyms Acidum citricum anhydricum; citric acid; E330; 2-hydroxy- β -1,2,3-propanetricarboxylic acid; 2-hydroxypropane 1,2,3-tricarboxylic acid.

Appearance Odorless or almost odorless, colorless crystals or a white crystalline powder. Crystal structure is monoclinic holohedral.

Dissociation constants

pK_{a1} : 3.128 at 25°C;

pK_{a2} : 4.761 at 25°C;

pK_{a3} : 6.396 at 25°C.

Density 1.665 g/cm³

Heat of combustion -1985 kJ/mol (-474.5 kcal/mol)

Hygroscopicity At relative humidities between about 25–50%, anhydrous citric acid absorbs insignificant amounts of water at 25°C. However, at relative humidities between 50% and 75%, it absorbs significant amounts, with the monohydrate being formed at relative humidities approaching 75%. At relative humidities greater than 75% substantial amounts of water are absorbed by the monohydrate.

Melting point 153°C

Solubility Soluble 1 in 1 part of ethanol (95%) and 1 in 1 of water; sparingly soluble in ether.

Safety

LD₅₀ (mouse, IP): 0.9 g/kg⁽⁷⁾

LD₅₀ (mouse, IV): 0.04 g/kg

LD₅₀ (mouse, oral): 5.04 g/kg

LD₅₀ (mouse, SC): 2.7 g/kg

LD₅₀ (rabbit, IV): 0.33 g/kg

LD₅₀ (rat, IP): 0.88 g/kg

LD₅₀ (rat, oral): 3.0 g/kg

LD₅₀ (rat, SC): 5.5 g/kg

Comments Anhydrous citric acid is listed in the PhEur 9.2 and USP 40–NF 35 S1. Anhydrous citric acid 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 USP–NF, the General Chapter 5.8 in PhEur, along with the ‘State of Work’ document on the PhEur EDQM website, and also the General Information Chapter G10 in the JP.

18 Comments

Citric acid monohydrate has undergone harmonization of many attributes for JP, PhEur, and USP–NF by the Pharmacopeial Discussion Group. For further information see the General Chapter 5.8 in PhEur, along with the ‘State of Work’ document on the PhEur EDQM website, and also the General Information Chapter G10 in the JP.

Citric acid monohydrate has been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery.⁽⁸⁾

Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

A specification for citric acid monohydrate is contained in the *Food Chemicals Codex* (FCC).⁽⁹⁾

The EINECS number for citric acid is 201-069-1. The PubChem Compound ID (CID) for citric acid monohydrate is 22230.

19 Specific References

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21 Author

GE Amidon.

22 Date of Revision

4 May 2017.

Coconut Oil

1 Nonproprietary Names

BP: Coconut Oil

JP: Coconut Oil

PhEur: Coconut Oil, Refined

USP–NF: Coconut Oil

2 Synonyms

Aceite de coco; cocois oleum raffinatum; coconut butter; coconut palm oil; copra oil; oleum cocois; *Pureco* 76; refined coconut oil.

3 Chemical Name and CAS Registry Number

Coconut oil [8001-31-8]

4 Empirical Formula and Molecular Weight

Coconut oil contains triglycerides, the fatty acid constituents of which are mainly lauric and myristic acids with smaller proportions of capric, caproic, caprylic, oleic, palmitic and stearic acids.

The PhEur 9.2 and USP 40–NF 35 S1 state that the fatty acid composition for coconut oil is caproic acid ($\leq 1.5\%$), caprylic acid (5.0 – 11.0%), capric acid (4.0 – 9.0%), lauric acid (40.0 – 50.0%), myristic acid (15.0 – 20.0%), palmitic acid (7.0 – 12.0%), stearic acid (1.5 – 5.0%), arachidic acid ($\leq 0.2\%$), palmitoleic acid ($\leq 1.0\%$), oleic acid (4.0 – 10.0%), linoleic acid (1.0 – 3.0%), linolenic acid ($\leq 0.2\%$), and eicosenoic acid ($\leq 0.2\%$).

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; ointment base.

7 Applications in Pharmaceutical Formulation or Technology

Coconut oil has traditionally been used in ointments where it forms a readily absorbable base. It has been used particularly in preparations intended for application to the scalp, where it could

Table II: FCC⁽⁵⁾ and JPE⁽¹⁰⁾ specifications for diethyl sebacate.

Test	FCC 10 S2	JPE 2004
Description	+	+
Identification	+	+
Acid value	≤1.0	≤0.5
Refractive index at 20°C	1.435–1.438	1.435–1.437
Specific gravity at 25°C	0.960–0.965	0.958–0.968
Ester value	—	411–435
Iodine value	—	≤0.5
Heavy metals	—	≤20 ppm
Arsenic	—	≤2 ppm
Residue on ignition	—	≤0.10%
Assay	≥98%	—

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20 General References

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21 Authors

ME Quinn, RC Rowe.

22 Date of Revision

4 May 2017.

Diethylene Glycol Monoethyl Ether

1 Nonproprietary Names

BP: Diethylene Glycol Monoethyl Ether
PhEur: Diethylene Glycol Monoethyl Ether
USP–NF: Diethylene Glycol Monoethyl Ether

2 Synonyms

Carbitol; DEGEE; DGME; diethyleneglycoli aether monoethilicus; 3,6-dioxo-1-octanol; ethoxydiglycol; ethyl carbitol; ethyl digol; ethyl dioxitol; 1-hydroxy-3,6-dioxaoctane; *Transcutol HP*; *Transcutol P*.

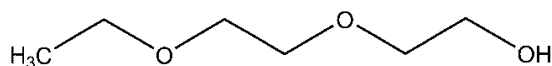
3 Chemical Name and CAS Registry Number

2-(2-Ethoxyethoxy)ethanol [111-90-0]

4 Empirical Formula and Molecular Weight

C₆H₁₄O₃ 134.17

5 Structural Formula



6 Functional Category

Solubilizing agent; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Diethylene glycol monoethyl ether is a solubilizing agent with broad chemical compatibility and widely used in oral, dermal, and parenteral pharmaceutical preparations. It is used as a cosolvent in oral drug delivery systems to enhance drug solubility, with the level of use limited to 10%. Purified diethylene glycol monoethyl ether is also used in some injectable products.⁽¹⁾

Diethylene glycol monoethyl ether has been reported to enhance skin penetration for a variety of drugs, and is used in creams, lotions, microemulsions, and aqueous gels.^(2–14) Diethylene glycol monoethyl ether is also used in cosmetic formulations.

8 Description

Diethylene glycol monoethyl ether is a clear, colorless, hygroscopic liquid with a mild odor.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Autoignition temperature

201°C for *Carbitol*;⁽¹⁵⁾

204°C for *Transcutol*.⁽¹⁶⁾

Boiling point

201°C for *Carbitol*;

198°C for *Transcutol*.

Density 0.988 g/cm³

Table 1: Pharmacopeial specifications for diethylene glycol monoethyl ether.

Test	PhEur 9.2	USP 40-NF 35 S1
Identification	+	+
Characters	+	-
Relative density	≈ 0.991	-
Refractive index at 20°C	1.426–1.428	1.426–1.428
Acid value	≤ 0.1	≤ 0.1
Peroxide value	≤ 8.0	≤ 8.0
Limit of free ethylene oxide	≤ 1 ppm	≤ 1 µg/g
2-Methoxyethanol	≤ 50 ppm	≤ 50 µg/g
2-Ethoxyethanol	≤ 160 ppm	≤ 160 µg/g
Ethylene glycol	≤ 620 ppm	≤ 620 µg/g
Diethylene glycol	≤ 250 ppm	≤ 150 µg/g
Total impurities	≤ 0.2%	-
Water	≤ 0.1%	≤ 0.1%
Assay	-	99–101%

Evaporation rate0.01 for *Carbitol*;0.02 for *Transcutol* (*n*-butyl acetate = 1.0).**Explosive limit**

1.2% volume at 135°C (lower limit);

23.5% volume at 182°C (upper limit) for *Transcutol*.**Flash point**90°C for *Carbitol*;96.1°C for *Transcutol*.**Freezing point**-43°C for *Carbitol*;-105°C for *Transcutol*.

Hygroscopicity At a relative humidity of 8–50% the equilibrium moisture content at 25°C is approx. 8% w/w, but at a relative humidity of 70% it is approx. 24% w/w.

Partition coefficient Log *P* (octanol : water) = -0.54

Solubility Soluble in water; miscible in acetone, benzene, chloroform, ethanol (95%), ether, and pyridine; partially soluble in vegetable oils; insoluble in mineral oils.

Specific heat 2.193 J/g°C (0.52 cal/g°C) at 25°C for *Carbitol*

Spectroscopy

IR spectrum see Figure 1.

Raman spectrum see Figure 2.

Vapor density 4.6 (air = 1)

Vapor pressure9.33 Pa (0.07 mmHg) at 20°C for *Carbitol*;16.0 Pa (0.12 mmHg) at 20°C for *Transcutol*.

Viscosity 4.5 mPa s (4.5 cP) at 25°C for *Carbitol*.

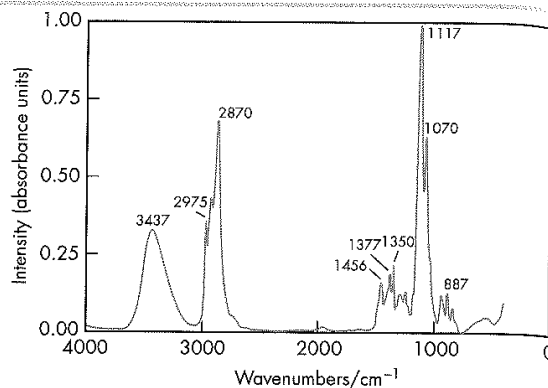
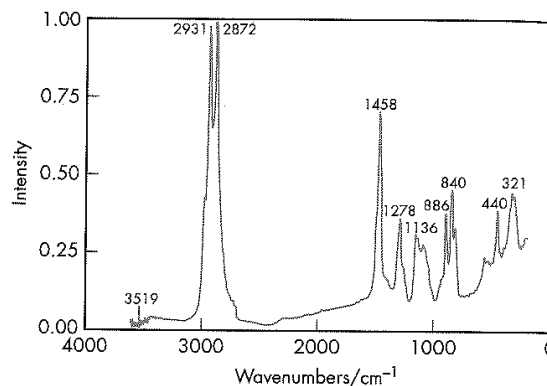
11 Stability and Storage Conditions

Diethylene glycol monoethyl ether is very stable and inert in its original container. It is hygroscopic and sensitive to water uptake and oxidation. If the drug being formulated is sensitive to oxidation, the addition of a suitable antioxidant prior to processing is required.

Store in a cool, dry, well-ventilated area in a tightly closed container filled with nitrogen. Keep away from sources of ignition.

12 Incompatibilities**13 Method of Manufacture**

Diethylene glycol monoethyl ether is obtained by *O*-alkylation of ethanol with two ethylene oxide units.

**Figure 1:** Infrared spectrum of diethylene glycol monoethyl ether measured by transmission. Adapted with permission of Informa Healthcare.**Figure 2:** Raman spectrum of diethylene glycol monoethyl ether measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.**14 Safety**

Diethylene glycol monoethyl ether is used in a wide variety of pharmaceutical formulations for oral, dermal, and parenteral administration, and as a cosmetic ingredient. It is generally regarded as nonirritant and nontoxic.

The Cosmetic Ingredient Review (CIR) Expert Panel has evaluated diethylene glycol monoethyl ether and found it to be safe as presently used in cosmetics at a maximum concentration of 50%.⁽¹⁷⁾

The acute toxicity of diethylene glycol monoethyl ether after oral, IV, and dermal application as well as inhalation has been studied and can be regarded as very low in all species investigated. The LD₅₀ values for acute oral, acute IV, and acute dermal toxicity were found to be generally much higher than 2 g/kg body weight, and the available LC₅₀ value for acute inhalation was >5 mg/L (i.e. 5.24 mg/L) in rat,⁽¹⁸⁾ in each case above the limit doses for classification.

LD₅₀ (rat, oral): >5 g/kg⁽¹⁹⁾

LD₅₀ (mouse, IV): 3.2 g/kg⁽²⁰⁾

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantities of material handled. Diethylene glycol monoethyl ether should be used with adequate ventilation. Avoid contact with eyes, skin, and clothing. Wear suitable protective clothing.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (topical and transdermal gels). Approved in the US as an indirect food additive. Included in nonparenteral formulations available in the UK and France. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

18 Comments

A number of studies have shown that the inclusion of diethylene glycol monoethyl ether can improve localized drug delivery by increasing drug retention in the skin. This is associated with the swelling of lipid bilayer structures which subsequently act as a depot for drug-solvent complexes, which enables the slow and localized diffusion of the drug over time.^(3-5,14)

The EINECS number for diethylene glycol monoethyl ether is 203-919-7. The PubChem Compound ID (CID) for diethylene glycol monoethyl ether is 8146.

19 Specific References

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21 Author

C Subra.

22 Date of Revision

4 May 2017.

Difluoroethane (HFC)

1 Nonproprietary Names

None adopted.

2 Synonyms

Dymel 152a; ethylene fluoride; *Freon 152a*; *Genetron 152a*; halocarbon 152a; HFC 152a; propellant 152a; R-152a; refrigerant 152a; *Solkane 152a*.

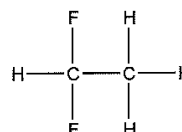
3 Chemical Name and CAS Registry Number

1,1-Difluoroethane [75-37-6]

4 Empirical Formula and Molecular Weight

C₂H₄F₂ 66.05

5 Structural Formula



Edetate Disodium

1 Nonproprietary Names

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

2 Synonyms

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

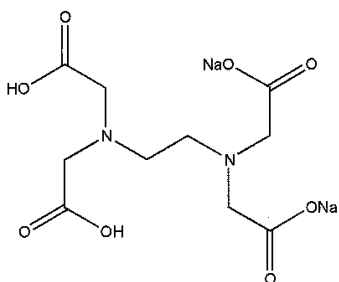
3 Chemical Name and CAS Registry Number

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

4 Empirical Formula and Molecular Weight

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

5 Structural Formula



6 Functional Category

Complexing agent.

7 Applications in Pharmaceutical Formulation or Technology

Edetate disodium is used as a complexing agent in a wide range of pharmaceutical preparations, including mouthwashes, ophthalmic preparations, and topical preparations,⁽¹⁻³⁾ typically at concentrations between 0.005 and 0.1% w/v.

Edetate disodium forms stable water-soluble complexes (chelates) with alkaline earth and heavy-metal ions. The chelated form has few of the properties of the free ion, and for this reason chelating agents are often described as 'removing' ions from solution, a process known as sequestering. The stability of the metal-edetate complex is dependent on the metal ion involved and the pH.

Edetate disodium has been used experimentally to investigate the stability and skin penetration capacity of captopril gel, in which edetate disodium was shown to exert a potent stabilizing effect, and may be used in the development of a transdermal drug delivery system.⁽⁴⁾ A chitosan-EDTA conjugate has been investigated as a novel polymer for use in topical gels. The conjugate was shown to

be stable, colorless, and transparent, and it also demonstrated antimicrobial effects.⁽⁵⁾ Studies have shown that edetate disodium may be effective in retarding microbial growth in propofol formulations⁽⁶⁾ and for the prevention of biofilm formation in catheters.⁽⁷⁾

Research has also been done to prepare and characterize hot melt dispersion formulations of mini-pellets containing EDTA.⁽⁸⁾ A salt complex of iron and EDTA has been used to develop chewable and orodispersible tablets in studies in humans and rats.⁽⁹⁾

See also Edetic Acid.

8 Description

Edetate disodium occurs as a white, crystalline, odorless powder with a slightly acidic taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for edetate disodium.

Test	JP XVII	PhEur 9.2	USP 40-NF 35 S1
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	4.3–4.7	4.0–5.5	4.0–6.0
Iron	—	≤80 ppm	—
Calcium	—	—	+
Heavy metals	≤10 ppm	—	≤0.005%
Cyanide	+	—	—
Arsenic	≤2 ppm	—	—
Limit of nitrilotriacetic acid	—	≤0.1%	≤0.1%
Residue on ignition	37.0–39.0%	—	—
Loss on drying	—	—	8.7–11.4%
Assay	≥99.0%	98.5–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity pH 4.3–4.7 (1% w/v solution in carbon dioxide-free water)

Density (bulk) 980 kg/m³ (for *Versene*)

Freezing point depression 0.14°C (1% w/v aqueous solution)

Melting point Decomposition at 252°C for the dihydrate.

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

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

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

Spectroscopy

IR spectrum see Figure 1.

NIR spectrum see Figure 2.

Raman spectrum see Figure 3.

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

11 Stability and Storage Conditions

Edetate salts are more stable than edetic acid (see also Edetic Acid). However, edetate disodium dihydrate loses its water of crystal-

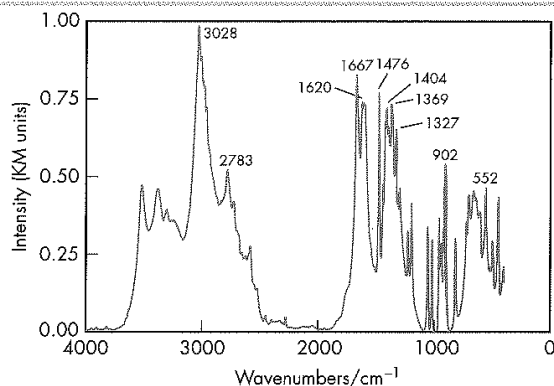


Figure 1: Infrared spectrum of edetate disodium dihydrate measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

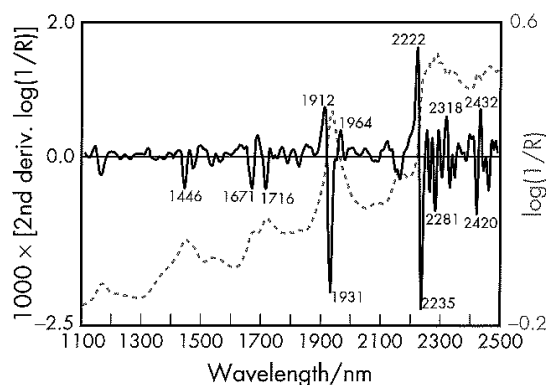


Figure 2: Near-infrared spectrum of edetate disodium dihydrate measured by reflectance.

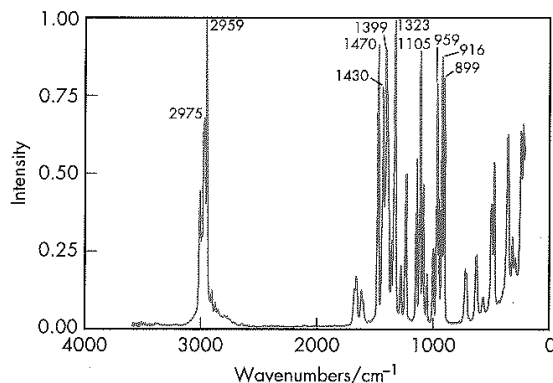


Figure 3: Raman spectrum of edetate disodium dihydrate measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

lization when heated to 120°C. Aqueous solutions of edetate disodium may be sterilized by autoclaving, and should be stored in an alkali-free container.

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

12 Incompatibilities

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

The addition of edetate disodium to phenylmercuric nitrate⁽¹⁰⁾ and thimerosal^(10,11) has also been reported to reduce the antimicrobial efficacy of the preservative.

See also Edetic Acid.

13 Method of Manufacture

Edetate disodium may be prepared by the reaction of edetic acid and sodium hydroxide.

14 Safety

Edetate disodium is used widely in topical, oral, and parenteral pharmaceutical formulations; it is used extensively in cosmetic and food products. Edetate disodium and edetate calcium disodium are used in a greater number and variety of pharmaceutical formulations than is edetic acid. Both edetate disodium and edetate calcium disodium are poorly absorbed from the gastrointestinal tract and are associated with few adverse effects when used as excipients in pharmaceutical formulations.

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

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

Although edetate disodium is generally considered safe, there have been reports of edetate disodium toxicity in patients receiving chelation therapy,⁽¹²⁾ and between 1971 and 2007, four deaths attributed to the therapeutic use of edetate disodium were reported to the FDA.⁽¹³⁾

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

The WHO has set an estimated acceptable daily intake for disodium EDTA in foodstuffs of up to 2.5 mg/kg body-weight.⁽¹⁴⁾ See also Edetic Acid.

LD₅₀ (mouse, IP): 0.26 g/kg⁽¹⁵⁾

LD₅₀ (mouse, IV): 0.056 g/kg⁽¹⁵⁾

LD₅₀ (mouse, OP): 2.05 g/kg⁽¹⁵⁾

LD₅₀ (rabbit, IV): 0.047 g/kg⁽¹⁵⁾

LD₅₀ (rabbit, OP): 2.3 g/kg⁽¹⁵⁾

LD₅₀ (rat, OP): 2.0 g/kg⁽¹⁵⁾

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (inhalations; injections; ophthalmic, otic, oral, rectal, topical, intrauterine, nasal, transdermal, urethral, iontophoresis and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Edetic acid.

18 Comments

Many solutions used for the cleaning, storage, and wetting of contact lenses contain edetate disodium.^(16,17) Therapeutically, edetate disodium is used as an anticoagulant as it will chelate calcium and prevent the coagulation of blood *in vitro*.⁽¹⁸⁾ Concentrations of 0.1% w/v are used in small volumes for hematological testing and 0.3% w/v in transfusions. Studies have shown how edetate disodium is facilitated by methylsulfonylmethane to cross biological membranes for regional chelation therapy.⁽¹⁹⁾ It is also used therapeutically in the treatment of hypercalcemia.⁽¹³⁾

Edetate disodium is used as a water softener as it will chelate calcium and magnesium ions present in hard water.

A specification for edetate disodium is contained in the *Food Chemicals Codex* (FCC).⁽²⁰⁾

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

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21 Authors

SL Cantor, S Shah.

22 Date of Revision

4 May 2017.

590 Medium-chain Triglycerides

minutes, with no significant increase in blood-glucose levels during this time.⁽³⁾

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral, tablet). Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Dextrose; mannitol.

18 Comments

Included in the BP 2017 as a general reagent. D-Mannose is a naturopathic remedy for urinary tract infections.

D-Mannose has recently been investigated as a surface modifier for nanoparticles and liposomes to enhance oral and alveolar delivery by macrophage targeting.⁽⁴⁻⁷⁾ Research has also shown that D-mannose is useful in freeze-dried suspensions to prevent aggregation.⁽⁸⁾

The EINECS number for D-mannose is 222-392-4. The PubChem Compound ID (CID) for D-mannose is 18950.

19 Specific References

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20 General References

21 Authors

ME Quinn, RC Rowe.

22 Date of Revision

21 April 2017.

Medium-chain Triglycerides

1 Nonproprietary Names

BP: Medium-chain Triglycerides

PhEur: Triglycerides, Medium-Chain

USP-NF: Medium-Chain Triglycerides

2 Synonyms

Bergabest; caprylic/capric triglyceride; *Captex 300*; *Captex 355*; *Coconad*; *Crodamol GTCC*; *Delios*; glyceryl tricaprylate/caprate; *Kollisolv MCT*; *Labrafac CC*; *Labrafac Lipo*; *Labrafac WL1349*; MCT oil; *Miglyol 810*; *Miglyol 812*; *Myritol*; *Neobee M5*; *Nesatol*; oleum neutrale; oleum vegetable tenue; *ProKote 2855*; *Stelliesters MCT*; thin vegetable oil; triglycerida saturata media; *Waglinol 3/9280*.

3 Chemical Name and CAS Registry Number

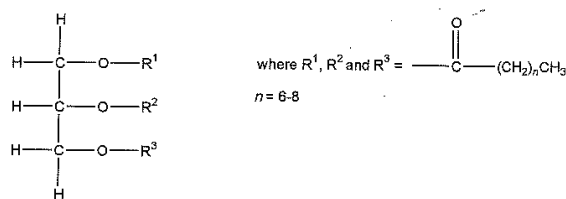
Medium-chain triglycerides [438544-49-1]

4 Empirical Formula and Molecular Weight

≈ 500 (average)

The PhEur 9.2 describes medium-chain triglycerides as the fixed oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineensis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid and of capric acid. They contain not less than 95% of saturated fatty acids.

5 Structural Formula



See also Section 4.

6 Functional Category

Emulsifying agent; solvent; suppository base; suspending agent; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Medium-chain triglycerides have been used in a variety of pharmaceutical formulations including oral, parenteral, and topical preparations.

In oral formulations, medium-chain triglycerides are used as the base for the preparation of oral emulsions, microemulsions, self-emulsifying systems, solutions, or suspensions of drugs that are unstable or insoluble in aqueous media, e.g. calciferol. Medium-

chain triglycerides have also been investigated as intestinal absorption enhancers^(1,2) and have additionally been used as a filler in capsules and sugar-coated tablets, and as a lubricant or antiadhesion agent in tablets.

In parenteral formulations, medium-chain triglycerides have similarly been used in the production of emulsions, solutions, or suspensions intended for intravenous administration.⁽³⁻⁹⁾ In rectal formulations, medium-chain triglycerides have been used in the preparation of suppositories containing labile materials. In cosmetics and topical pharmaceutical preparations, medium-chain triglycerides are used as a component of ointments, creams, and liquid emulsions.⁽⁵⁾

An emulsion of medium-chain triglycerides has shown significant potential as an effective antimicrobial alternative to chlorhexidine- and xylitol-based products for use against animal pathogens.⁽¹⁰⁾

Although similar to long-chain triglycerides, medium-chain triglycerides have a number of advantages in pharmaceutical formulations, which include better spreading properties on the skin; no impedance of skin respiration; good penetration properties; good emollient and cosmetic properties; no visible film on the skin surface; good compatibility; good solvent properties; and good stability against oxidation.

8 Description

A colorless to slightly yellowish oily liquid that is practically odorless and tasteless. It solidifies at about 0°C. The oil is free from catalytic residues or the products of cracking.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for medium-chain triglycerides.

Test	PhEur 9.2	USP 40-NF 35 S1
Identification	+	+
Characters	+	—
Appearance	+	+
Alkaline impurities	+	+
Relative density	0.95	0.93–0.96
Refractive index	1.446	1.440–1.452
Viscosity	25–33 mPa s	25–33 mPa s
Acid value	≤0.2	≤0.2
Hydroxyl value	≤10	≤10
Iodine value	≤1.0	≤1.0
Peroxide value	≤1.0	≤1.0
Saponification value	310–360	310–360
Unsaponifiable matter	—	≤0.5%
Composition of fatty acids		
Caproic acid	≤2.0%	≤2.0%
Caprylic acid	50.0–80.0%	50.0–80.0%
Capric acid	20.0–50.0%	20.0–50.0%
Lauric acid	≤3.0%	≤3.0%
Myristic acid	≤1.0%	≤1.0%
Chain length ≥C ₁₆	≤1.0%	—
Heavy metals	—	10 µg/g
Water	≤0.2%	≤0.2%
Sulfated ash	≤1.0%	—
Total ash	—	≤0.1%
Chromium ^(a)	≤0.05 ppm	≤0.05 µg/g
Copper ^(a)	≤0.1 ppm	≤0.1 µg/g
Lead ^(a)	≤0.1 ppm	≤0.1 µg/g
Nickel ^(a)	≤0.2 ppm	≤0.1 µg/g
Tin ^(a)	≤0.1 ppm	≤0.1 µg/g

^(a) For medium-chain triglycerides intended for use in parenteral nutrition.

10 Typical Properties

Acid value

- ≤0.1 for *Crodamol GTCC*;
- ≤0.1 for *Miglyol 810*;
- ≤0.1 for *Miglyol 812*;
- ≤0.05 for *Neobee M5*.

Cloud point

- ≤5°C for *Crodamol GTCC*;
- ≈10°C for *Miglyol 810*;
- ≈10°C for *Miglyol 812*.

Color

- ≤60 (Hazen color index) for *Crodamol GTCC*;
- ≤90 (Hazen color index) for *Miglyol 810*;
- ≤60 (Hazen color index) for *Miglyol 812*;
- ≤100 (Hazen color index) for *Neobee M5*.

Density

- 0.94–0.96 g/cm³ for *Crodamol GTCC* at 20°C;
- 0.94–0.95 g/cm³ for *Miglyol 810* at 20°C;
- 0.94–0.95 g/cm³ for *Miglyol 812* at 20°C;
- 0.94 g/cm³ for *Neobee M5* at 20°C.

Freezing point

- 5°C for *Neobee M5*

Hydroxyl value

- ≤8 for *Neobee M5*

Iodine number

- ≤1.0 for *Crodamol GTCC*;
- ≤0.5 for *Miglyol 810*;
- ≤0.5 for *Miglyol 812*;
- ≤0.5 for *Neobee M5*.

Moisture content

- ≤0.15% w/w for *Crodamol GTCC*;
- ≤0.10% w/w for *Miglyol 810*;
- ≤0.10% w/w for *Miglyol 812*;
- ≤0.15% w/w for *Neobee M5*.

Peroxide value

- ≤1.0 for *Miglyol 810*;
- ≤1.0 for *Miglyol 812*;
- ≤0.5 for *Neobee M5*.

Refractive index

- 1.4485–1.4500 for *Crodamol GTCC* at 20°C;
- 1.4485–1.4505 for *Miglyol 810* at 20°C;
- 1.4490–1.4510 for *Miglyol 812* at 20°C;
- 1.4480–1.4510 for *Neobee M5* at 20°C.

Saponification value

- 325–345 for *Crodamol GTCC*;
- 335–355 for *Miglyol 810*;
- 325–345 for *Miglyol 812*;
- 335–360 for *Neobee M5*.

Solubility Soluble in all proportions at 20°C in acetone, benzene, 2-butanone, carbon tetrachloride, chloroform, dichloromethane, ethanol, ethanol (95%), ether, ethyl acetate, petroleum ether, special petroleum spirit (boiling range 80–110°C), propan-2-ol, toluene, and xylene. Miscible with long-chain hydrocarbons and triglycerides; practically insoluble in water.

Surface tension

- 32.2 mN/m for *Crodamol GTCC* at 25°C;
- 31.0 mN/m for *Miglyol 810* at 20°C;
- 31.1 mN/m for *Miglyol 812* at 20°C;
- 32.3 mN/m for *Neobee M5* at 25°C.

Viscosity (dynamic)

- 27–30 mPa s (27–30 cP) for *Miglyol 810* at 20°C;

28–32 mPa s (28–32 cP) for *Miglyol 812* at 20°C;
23 mPa s (23 cP) for *Neobee M5* at 25°C.

11 Stability and Storage Conditions

Medium-chain triglycerides are stable over the wide range of storage temperatures that can be experienced in tropical and temperate climates. Ideally, however, they should be stored at temperatures not exceeding 25°C and not exposed to temperatures above 40°C for long periods. At low temperatures, samples of medium-chain triglycerides may become viscous or solidify. Samples should therefore be well melted and mixed before use, although overheating should be avoided.

In the preparation of microemulsions and self-emulsifying systems, emulsions, or aqueous suspensions of medium-chain triglycerides, care should be taken to avoid microbiological contamination of the preparation, since lipase-producing microorganisms, which become active in the presence of moisture, can cause hydrolysis of the triglycerides. Hydrolysis of the triglycerides is revealed by the characteristic unpleasant odor of free medium-chain fatty acids.

Medium-chain triglycerides may be sterilized by maintaining at 170°C for 1 hour.

Medium-chain triglycerides should be stored protected from light in a well-filled and well-closed container. When stored dry, in sealed containers, medium-chain triglycerides remain stable for many years.

12 Incompatibilities

Preparations containing medium-chain triglycerides should not come into contact with polystyrene containers or packaging components since the plastic rapidly becomes brittle upon contact. Low-density polyethylene should also not be used as a packaging material as the medium-chain triglycerides readily penetrate the plastic, especially at high temperatures, forming an oily film on the outside. High-density polyethylene is a suitable packaging material. Closures based on phenol resins should be tested before use for compatibility with medium-chain triglycerides. Polyvinyl chloride packaging should also be tested for compatibility since medium-chain triglycerides can dissolve some plasticizers, such as phthalates, out of the plastic.

Materials recommended as safe for packaging medium-chain triglycerides are low-density polyethylene, polypropylene, glass, and metal.

13 Method of Manufacture

Medium-chain triglycerides are obtained from the fixed oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. Hydrolysis of the fixed oil followed by distillation yields the required fatty acids, which are then re-esterified to produce the medium-chain triglycerides.

Although the PhEur 9.2 specifies that medium-chain fatty acids are obtained from coconut oil, medium-chain triglycerides are also to be found in substantial amounts in the kernel oils of certain other types of palm-tree, e.g. palm kernel oil and babassu oil. Some animal products, such as milk-fat, also contain small amounts (up to 4%) of the medium-chain fatty acid esters.

14 Safety

Medium-chain triglycerides are used in a variety of pharmaceutical formulations including oral, parenteral, and topical products, and are generally regarded as essentially nontoxic and nonirritant materials.

In acute toxicology studies in animals and humans, no irritant or other adverse reactions have been observed; for example, when they were patch-tested on more than 100 individuals, no irritation was

produced on either healthy or eczematous skin. Medium-chain triglycerides are not irritating to the eyes.

Similarly, chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglycerides following inhalation or intraperitoneal, oral, and parenteral administration.

In humans, administration of 0.5 g/kg body-weight medium-chain triglycerides to healthy individuals produced no change in blood or serum triglycerides compared to subjects receiving the same dose of the long-chain triglyceride triolein.

In patients consuming diets based on medium-chain triglycerides, adverse effects reported include abdominal pain and diarrhea.

LD₅₀ (mouse, IV): 3.7 g/kg

LD₅₀ (mouse, oral): 29.6 g/kg

LD₅₀ (rat, oral): 33.3 g/kg

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral, sublingual, topical and transdermal preparations). Included in nonparenteral and parenteral medicines licensed in Europe. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Coconut oil; suppository bases, hard fat; vegetable oil, hydrogenated.

18 Comments

Medium-chain triglycerides may also be known as fractionated coconut oil, which contains three saturated lipid chains bound to a glycerin backbone, and are distinguished from other triglycerides by the length of the carbon chains, normally between 6 and 10.

Therapeutically, medium-chain triglycerides have been used as nutritional agents.⁽¹¹⁾ Diets containing medium-chain triglycerides are used in conditions associated with the malabsorption of fat, such as cystic fibrosis, since medium-chain triglycerides are more readily digested than long-chain triglycerides. Medium-chain triglycerides have been investigated particularly for their use in total parenteral nutrition regimens in combination with long-chain triglycerides.^(4,12)

A specification for medium-chain fatty acid triglycerides is included in the *Japanese Pharmaceutical Excipients* (JPE).⁽¹³⁾

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20 General References

Akkar A, *et al.* Solubilizing poorly soluble antimycotic agents by emulsification via a solvent-free process. *AAPS Pharm Sci Tech* 2004; 5: E24.

21 Author

G Moss.

22 Date of Revision

4 May 2017.

Meglumine

1 Nonproprietary Names

BP: Meglumine
JP: Meglumine
PhEur: Meglumine
USP–NF: Meglumine

2 Synonyms

Meglumin; meglumina; megluminum; 1-methylamino-1-deoxy-D-glucitol; N-methylglucamine; N-methyl-D-glucamine.

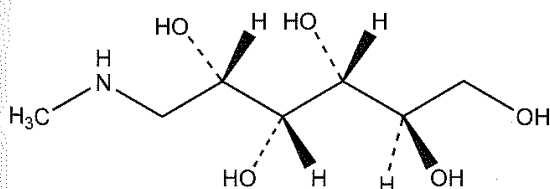
3 Chemical Name and CAS Registry Number

1-Deoxy-1-(methylamino)-D-glucitol [6284-40-8]

4 Empirical Formula and Molecular Weight

C₇H₁₇NO₅ 195.21

5 Structural Formula



6 Functional Category

Buffering agent.

7 Applications in Pharmaceutical Formulation or Technology

Meglumine is an organic base used as a pH-adjusting agent and solubilizing agent, primarily in the preparation of soluble salts of iodinated organic acids used as X-ray contrast media.

8 Description

Meglumine occurs as a white to slightly yellow-colored crystalline powder; it is odorless or with a slight odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for meglumine.

Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Identification	+	+	+
Appearance of solution	+	+	+
Melting range	128–131°C	128°C	128–132°C
Specific optical rotation	–16.0° to –17.0°	–16.0° to –17.0°	–15.7° to –17.3°
Reducing substances	–	≤0.2%	–
Loss on drying	≤0.5%	≤0.5%	≤1.0%
Residue on ignition	≤0.1%	≤0.1%	≤0.1%
Absence of reducing substances	+	–	+
Bacterial endotoxins	–	≤1.5 IU/g	–
Heavy metals	≤10 ppm	≤10 ppm	≤0.002%
Iron	–	≤10 ppm	–
Arsenic	≤1 ppm	–	–
Chloride	≤0.009%	≤100 ppm	–
Sulfate	≤0.019%	≤150 ppm	–
Nickel	–	≤5 ppm	–
Aluminum	–	≤5 ppm	–
Assay (dried basis)	≥99.0%	99.0–101.0%	99.0–100.5%

10 Typical Properties

Acidity/alkalinity pH = 10.5 (1% w/v aqueous solution).

Dissociation constant pK_a = 9.5 at 20°C

Melting point 128–132°C

Osmolarity A 5.02% w/v aqueous solution is iso-osmotic with serum.

Solubility see Table II.

Specific rotation [α]_D²⁰ = –16.5° (10% w/v aqueous solution)

Propylene Glycol

1 Nonproprietary Names

BP: Propylene Glycol
JP: Propylene Glycol
PhEur: Propylene Glycol
USP-NF: Propylene Glycol

2 Synonyms

1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol; propylenglycolum.

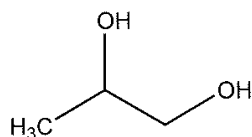
3 Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]
(-)-1,2-Propanediol [4254-14-2]
(+)-1,2-Propanediol [4254-15-3]
(±)-Propane-1,2-diol [4254-16-4]

4 Empirical Formula and Molecular Weight

C₃H₈O₂ 76.09

5 Structural Formula



6 Functional Category

Antimicrobial preservative; humectant; plasticizing agent; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, humectant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. See Table I.

It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics.

Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

The effect of propylene glycol on the freeze-thaw of injectable formulations has been investigated.^(1,2) An investigation into skin penetration enhancers found propylene glycol altered the skin barrier properties, therefore may have potential use in treatment of impaired skin barrier conditions.⁽³⁾

Propylene glycol has also been investigated in various delivery systems, including self-emulsifying and mucoadhesive systems,⁽⁴⁻¹²⁾ as a plasticizer in hot-melt extruded sustained-release formulations,⁽¹³⁾ and in a formulation to improve the stability of photosensitive drugs.⁽¹⁴⁾

8 Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid, with a sweet, slightly acrid taste resembling that of glycerin.

Table I: Uses of propylene glycol.

Use	Dosage form	Concentration (%)
Humectant	Topicals	≈15
Preservative	Solutions, semisolids	15-30
Solvent or cosolvent	Aerosol solutions	10-30
	Oral solutions	10-25
	Parenterals	10-60
	Topicals	5-80

9 Pharmacopeial Specifications

See Table II. See also Section 18.

Table II: Pharmacopeial specifications for propylene glycol.

Test	JP XVII	PhEur 9.2	USP 40-NF 35 S1
Identification	+	+	+
Appearance	—	+	—
Specific gravity	1.035-1.040	1.035-1.040	1.035-1.037
Acidity	+	+	+
Water	≤0.5%	≤0.2%	≤0.2%
Residue on ignition	≤0.005%	—	≤3.5 mg/50 g
Sulfated ash	—	≤0.01%	—
Chloride	≤0.007%	—	≤70 ppm
Sulfate	≤0.002%	—	≤60 ppm
Heavy metals	≤5 ppm	—	≤5 ppm
Refractive index	—	1.431-1.433	—
Oxidizing substances	—	+	—
Reducing substances	—	+	—
Arsenic	≤2 ppm	—	—
Glycerin	+	—	—
Boiling point	184-189°C	184-189°C	—
Assay	—	—	≥99.5%

10 Typical Properties

Autoignition temperature 371°C

Boiling point 187-188°C

Density 1.0361 g/cm³ at 20°C⁽¹⁵⁾

Dissociation constant pK_a = 14.8 at 25°C^(16,17)

Flammability

Upper limit, 12.5% v/v in air;

lower limit, 2.6% v/v in air.

Flash point

99°C (open cup);⁽¹⁸⁾

104°C (closed cup).⁽¹⁸⁾

Heat of combustion 1803.3 kJ/mol (431.0 kcal/mol)

Heat of vaporization 705.4 J/g (168.6 cal/g) at bp

Melting point -59°C

Osmolarity A 2.0% v/v aqueous solution is iso-osmotic with serum.

Partition coefficient Log P (octanol : water) = -0.92^(17,18)

Refractive index n_D^{20} = 1.4324

Specific rotation

$[\alpha]_D^{20}$ = -15.0° (neat) for (R)-form;

$[\alpha]_D^{20}$ = +15.8° (neat) for (S)-form.

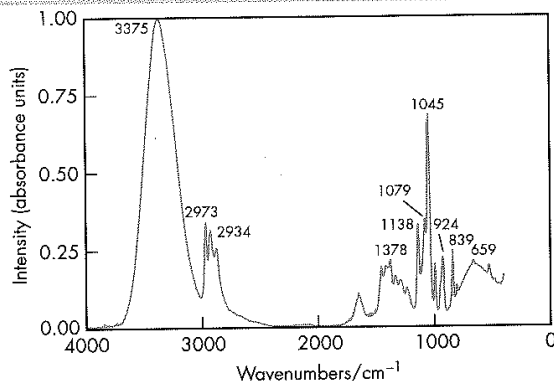


Figure 1: Infrared spectrum of propylene glycol measured by transmission. Adapted with permission of Informa Healthcare.

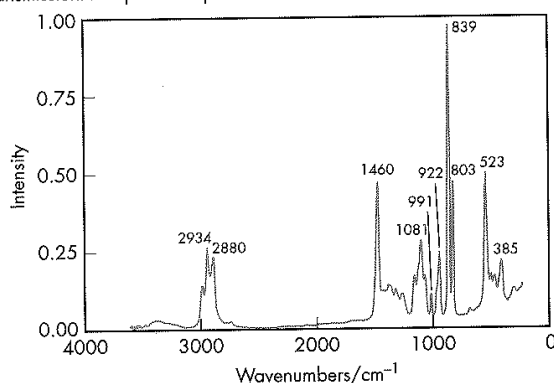


Figure 2: Raman spectrum of propylene glycol measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

Solubility Miscible with acetone, chloroform, ethanol (95%), methanol; glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Specific heat 2.47 J/g (0.590 cal/g) at 20°C.

Spectroscopy

IR spectrum see Figure 1.

Raman spectrum see Figure 2.

Surface tension 40.1 mN/m (40.1 dynes/cm) at 25°C.

Vapor density (relative) 2.62 (air = 1)

Vapor pressure 9.33 Pa (0.07 mmHg) at 20°C.

Viscosity (dynamic) 58.1 mPa s (58.1 cP) at 20°C.

11 Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. When heated to decomposition, propylene glycol emits acrid smoke and toxic fumes of CO and CO₂.

Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving.

Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

13 Method of Manufacture

Propylene is converted to chlorohydrin by chlorine water and hydrolyzed to 1,2-propylene oxide. With further hydrolysis, 1,2-propylene oxide is converted to propylene glycol.⁽¹⁹⁾

14 Safety

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material. It is also used extensively in foods and cosmetics. As a likely consequence of its metabolism and excretion, propylene glycol is less toxic than other glycols. Propylene glycol is rapidly absorbed from the gastrointestinal tract; there is also evidence that it is absorbed topically when applied to damaged skin. It is extensively metabolized in the liver, mainly to lactic and pyruvic acids, and is also excreted unchanged in the urine.^(20,21)

In topical preparations, propylene glycol is regarded as minimally irritant,⁽²²⁾ although it is more irritant than glycerin. There have been some reports of contact dermatitis associated with propylene glycol,⁽²³⁻²⁵⁾ and some local irritation is produced upon application to mucous membranes or when it is used under occlusive conditions.⁽²⁶⁾ Systemic dermatitis has been documented after ingestion of propylene glycol through food or medicine,⁽²⁷⁾ while parenteral administration may cause pain or irritation when propylene glycol is used in high concentration.

Propylene glycol is estimated to be one-third as intoxicating as ethanol, with administration of large volumes being associated with adverse effects most commonly on the central nervous system, especially in neonates and children.⁽²⁸⁻³¹⁾ Other adverse reactions reported, though generally isolated, include: ototoxicity;⁽³²⁾ cardiovascular effects; seizures; and hyperosmolarity⁽³³⁾ and lactic acidosis, both of which occur most frequently in patients with renal impairment. Adverse effects are more likely to occur following consumption of large quantities of propylene glycol or on administration to neonates, children under 4 years of age, pregnant women, and patients with hepatic or renal failure. Adverse events may also occur in patients treated with disulfiram or metronidazole.⁽³⁴⁾

An intravenous acetaminophen preparation containing propylene glycol was administered to 60 neonates in a prospective cohort study; it was found that a median exposure of 34.1 mg/kg a day was tolerated well.⁽³⁵⁾ However, the same authors caution that neonates have a lower tolerance limit to propylene glycol than adults, and more research is needed in neonates.⁽³⁶⁾ On the basis of metabolic and toxicological data, the WHO has set an acceptable daily intake of propylene glycol at up to 25 mg/kg body-weight.⁽³⁷⁾ Formulations containing 35% propylene glycol can cause hemolysis in humans.

In animal studies, there has been no evidence that propylene glycol is teratogenic or mutagenic. Rats can tolerate a repeated oral daily dose of up to 30 mL/kg body-weight in the diet over 6 months, while the dog is unaffected by a repeated oral daily dose of 2 g/kg in the diet for 2 years.⁽³⁸⁾

LD₅₀ (mouse, IP): 9.72 g/kg⁽³⁹⁾

LD₅₀ (mouse, IV): 6.63 g/kg

LD₅₀ (mouse, oral): 22.0 g/kg

LD₅₀ (mouse, SC): 17.37 g/kg

LD₅₀ (rat, IM): 14.0 g/kg

LD₅₀ (rat, IP): 6.66 g/kg

LD₅₀ (rat, IV): 6.42 g/kg

LD₅₀ (rat, oral): 20.0 g/kg

LD₅₀ (rat, SC): 22.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylene glycol should be handled in

a well-ventilated environment; eye protection and gloves are recommended. In the UK, the long-term (8-hour TWA) workplace exposure limit for propylene glycol vapor and particulates is 474 mg/m^3 (150 ppm) and 10 mg/m^3 for particulates.⁽⁴⁰⁾

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (buccal films, dental preparations; IM and IV injections; inhalations; ophthalmic, oral, otic, percutaneous, rectal, topical, photopheresis, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Propylene glycol alginate.

18 Comments

Propylene glycol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Chapter 5.8 in PhEur, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter G10 in the JP.

As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol. In addition to its uses as an excipient, propylene glycol is used in veterinary medicine as an oral glucogenic in ruminants.⁽⁴¹⁾

A possible hepatoprotective effect of propylene glycol due to the inhibition of CYP2E1 has been found in a single-blinded crossover study in 15 healthy subjects taking liquid and solid preparations of acetaminophen.⁽⁴²⁾

Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavors in preference to ethanol, since its lack of volatility provides a more uniform flavor.

A specification for potassium glycol is contained in the *Food Chemicals Codex* (FCC).⁽⁴³⁾

The EINECS number for propylene glycol is 200-338-0. The PubChem Compound ID (CID) for propylene glycol is 1030.

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21 Author

S Driver.

22 Date of Revision

4 May 2017.

Propylene Glycol Alginate

1 Nonproprietary Names

USP–NF: Propylene Glycol Alginate

2 Synonyms

Alginic acid, propylene glycol ester; E405; hydroxypropyl alginate; *Kelcoloid*; *Kimiloid*; *Manucol Ester*; PGA; *Profoam*; propane-1,2-diol alginate; *TIC Pretested*.

3 Chemical Name and CAS Registry Number

Propylene glycol alginate [9005-37-2]

4 Empirical Formula and Molecular Weight

Propylene glycol alginate is a propylene glycol ester of alginic acid, a linear glycuronan polymer consisting of a mixture of β -(1 $\rightarrow$ 4)-D-mannosyluronic acid and α -(1 $\rightarrow$ 4)-L-gulosyluronic acid residues.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; foam stabilizing agent; suspending agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Propylene glycol alginate is used as a stabilizing, suspending, gelling, and emulsifying agent in oral and topical pharmaceutical formulations. Typically, a concentration of 0.3–5.0% w/v is used, although this may vary depending upon the specific application and the grade of propylene glycol alginate used.

8 Description

Propylene glycol alginate occurs as a white to yellowish colored, practically odorless and tasteless, fibrous or granular powder.

9 Pharmacopeial Specifications

See Table I. See also Section 18.

Table I: Pharmacopeial specifications for propylene glycol alginate.

Test	USP 40–NF 35 S1
Identification	+
Microbial limits	≤200 cfu/g
Loss on drying	≤20.0%
Ash	≤10.0%
Arsenic	≤3 ppm
Lead	≤10 ppm
Heavy metals	≤40 ppm
Free carboxyl groups	+
Esterified carboxyl groups	+
Assay (of alginates)	+

10 Typical Properties

Solubility Soluble in dilute organic acids and water, forming stable, viscous, colloidal solutions at pH 3. Depending upon the degree of esterification, propylene glycol alginate is also soluble in aqueous ethanol/water mixtures containing up to 60% w/w of ethanol (95%). The interfacial and foaming properties of propylene glycol alginate aqueous solutions have been studied, and were found to be affected by the degree of esterification and molecular weight.⁽¹⁾

Spectroscopy

NIR spectrum see Figure 1.

Viscosity (dynamic) The viscosity of aqueous solutions depends upon the grade of material used. Typically, a 1% w/v aqueous solution has a viscosity of 20–400 mPa s (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions. See also Sodium Alginate.

11 Stability and Storage Conditions

Propylene glycol alginate is a stable material, although it will gradually become less soluble if stored at elevated temperatures for extended periods.

Sodium Citrate Dihydrate

1 Nonproprietary Names

BP: Sodium Citrate
JP: Sodium Citrate Hydrate
PhEur: Sodium Citrate
USP-NF: Sodium Citrate

2 Synonyms

Citric acid trisodium salt; E331; natrii citras; sodium citrate tertiary; trisodium citrate.

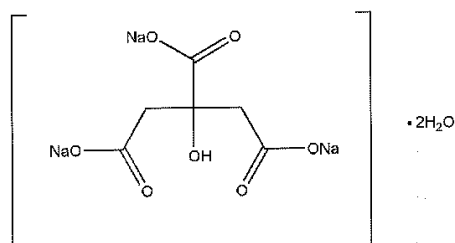
3 Chemical Name and CAS Registry Number

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate
[6132-04-3]

4 Empirical Formula and Molecular Weight

$C_6H_5Na_3O_7 \cdot 2H_2O$ 294.10

5 Structural Formula



6 Functional Category

Alkalizing agent; buffering agent; complexing agent; emulsifying agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium citrate, as either the dihydrate or anhydrous material, is widely used in pharmaceutical formulations; see Table I. It is also used as a complexing agent to bind metal ions in solution. The anhydrous material is used in effervescent tablet formulations.⁽¹⁾

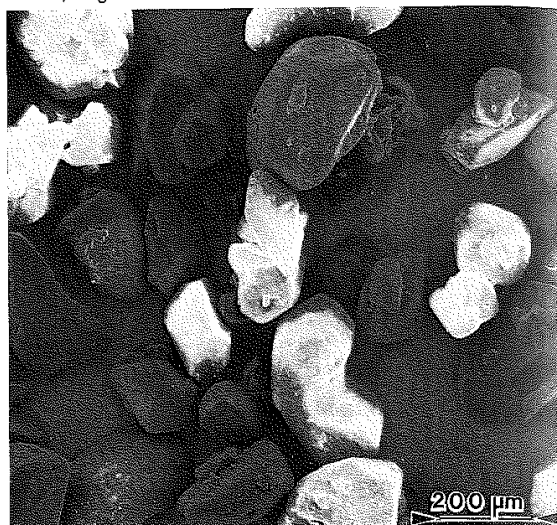
Table I: Uses of sodium citrate dihydrate.

Use	Concentration (%)
Buffering agent	0.3–2.0
Injections	0.02–4.0
Ophthalmic solutions	0.1–2.0
Complexing agent	0.3–2.0

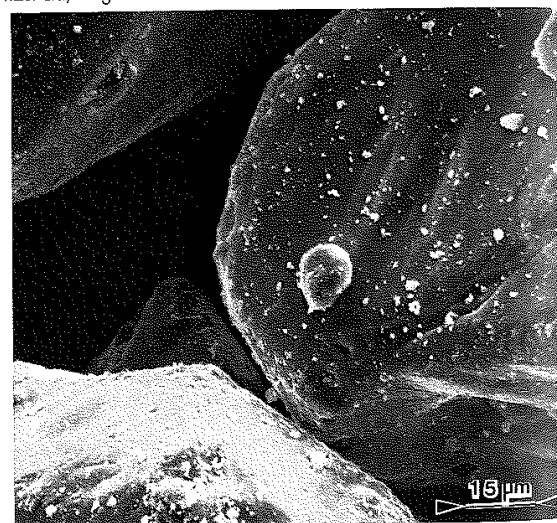
8 Description

Sodium citrate dihydrate consists of odorless, colorless, monoclinic crystals, or a white crystalline powder with a cooling, saline taste. It is slightly deliquescent in moist air, and in warm dry air it is efflorescent. Although most pharmacopeias specify that sodium citrate is the dihydrate, the USP 40–NF 35 S1 states that sodium citrate may be either the dihydrate or anhydrous material.

SEM 1: Excipient: sodium citrate dihydrate (granular); manufacturer: Pfizer Ltd; magnification: 60×.



SEM 2: Excipient: sodium citrate dihydrate (granular); manufacturer: Pfizer Ltd; magnification: 600×.



9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity pH = 7.0–9.0 (5% w/v aqueous solution)

Density (bulk) 1.12 g/cm³

Density (tapped) 0.99 g/cm³

Density (true) 1.19 g/cm³

Melting point Converts to the anhydrous form at 150°C.

Osmolarity A 3.02% w/v aqueous solution is iso-osmotic with serum.

Table II: Pharmacopeial specifications for sodium citrate dihydrate.

Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Identification	+	+	+
Characters	—	+	—
pH	7.5–8.5	—	—
Appearance of solution	+	+	—
Acidity or alkalinity	—	+	+
Loss on drying	10.0–13.0%	—	—
Water	—	11.0–13.0%	10.0–13.0%
Oxalate	+	≤300 ppm	—
Sulfate	≤0.048%	≤150 ppm	—
Heavy metals	≤10 ppm	—	≤10 ppm
Arsenic	≤2 ppm	—	—
Chloride	≤0.015%	≤50 ppm	—
Tartrate	+	—	+
Readily carbonizable substances	+	+	—
Pyrogens	—	+(a)	—
Assay (anhydrous basis)	99.0–101.0%	99.0–101.0%	99.0–100.5%

(a) If intended for use in large-volume preparations for parenteral use, compliance with a test for pyrogens may be required.

Particle size distribution Various grades of sodium citrate dihydrate with different particle sizes are commercially available.

Solubility Soluble 1 in 1.5 of water, 1 in 0.6 of boiling water; practically insoluble in ethanol (95%).

Spectroscopy

IR spectrum *see* Figure 1.

NIR spectrum *see* Figure 2.

Raman spectrum *see* Figure 3.

11 Stability and Storage Conditions

Sodium citrate dihydrate is a stable material. Aqueous solutions may be sterilized by autoclaving. On storage, aqueous solutions may cause the separation of small, solid particles from glass containers.

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

12 Incompatibilities

Aqueous solutions are slightly alkaline and will react with acidic substances. Alkaloidal salts may be precipitated from their aqueous or hydro-alcohol solutions. Calcium and strontium salts will cause precipitation of the corresponding citrates. Other incompatibilities include bases, reducing agents, and oxidizing agents.

13 Method of Manufacture

Sodium citrate is prepared by adding sodium carbonate to a solution of citric acid until effervescence ceases. The resulting solution is filtered and evaporated to dryness.

14 Safety

After ingestion, sodium citrate is absorbed and metabolized to bicarbonate. Although it is generally regarded as a nontoxic and nonirritant excipient, excessive consumption may cause gastrointestinal discomfort or diarrhea. Therapeutically, in adults, up to 15 g daily of sodium citrate dihydrate may be administered orally, in divided doses, as an aqueous solution to relieve the painful irritation caused by cystitis.

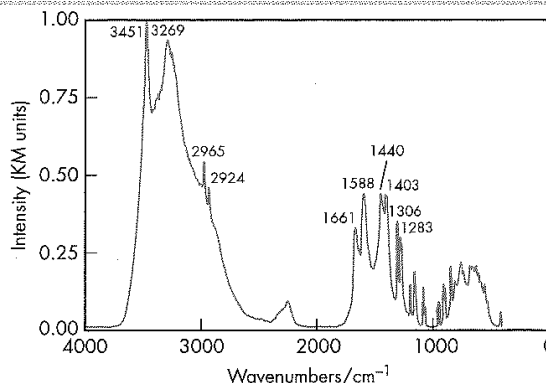


Figure 1: Infrared spectrum of sodium citrate dihydrate measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

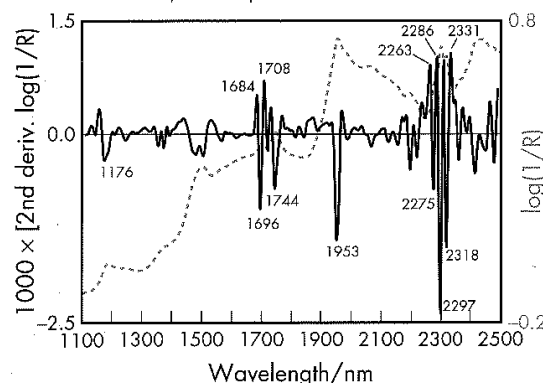


Figure 2: Near-infrared spectrum of sodium citrate dihydrate measured by reflectance.

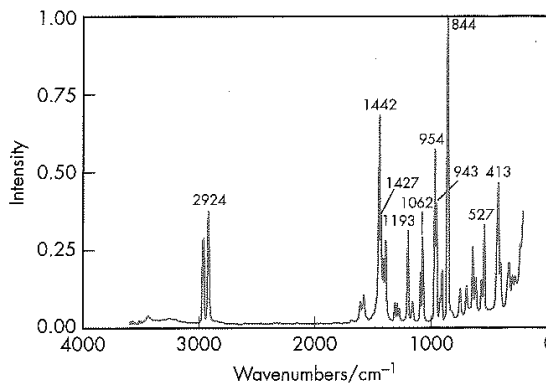


Figure 3: Raman spectrum of sodium citrate dihydrate measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

Citrates and citric acid enhance intestinal aluminum absorption in renal patients, which may lead to increased, harmful serum aluminum levels. It has therefore been suggested that patients with renal failure taking aluminum compounds to control phosphate absorption should not be prescribed citrate- or citric acid-containing products.⁽²⁾

See Section 17 for anhydrous sodium citrate animal toxicity data.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium citrate dihydrate dust may be irritant to the eyes and respiratory tract. Eye protection and gloves are recommended. Sodium citrate should be handled in a well-ventilated environment or a dust mask should be worn.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; injections; ophthalmic products; oral solutions, suspensions, syrups and tablets; nasal, otic, rectal, topical, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Anhydrous sodium citrate; citric acid monohydrate.

Anhydrous sodium citrate

Empirical formula $C_6H_5Na_3O_7$

Molecular weight 258.07

CAS number [68-04-2]

Synonyms Anhydrous trisodium citrate; citric acid trisodium salt anhydrous; trisodium 2-hydroxy-1,2,3-propanetricarboxylic acid.

Appearance Colorless crystals or a white crystalline powder.

Safety

LD₅₀ (mouse, IP): 1.36 g/kg⁽³⁾

LD₅₀ (mouse, IV): 0.17 g/kg

LD₅₀ (rabbit, IV): 0.45 g/kg

LD₅₀ (rat, IP): 1.55 g/kg

18 Comments

Each gram of sodium citrate dihydrate represents approximately 10.2 mmol of sodium and 3.4 mmol of citrate. Each gram of anhydrous sodium citrate represents approximately 11.6 mmol of sodium and 3.9 mmol of citrate.

Therapeutically, sodium citrate is used to relieve the painful irritation caused by cystitis, and also to treat dehydration and acidosis due to diarrhea; see Section 14.

Sodium citrate, as either the dihydrate or anhydrous material, is used in food products, primarily to adjust the pH of solutions.

Sodium citrate is additionally used as a blood anticoagulant either alone or in combination with other citrates such as disodium hydrogen citrate.

The EINECS number for sodium citrate is 200-675-3. The PubChem Compound ID (CID) for sodium citrate dihydrate is 71474.

19 Specific References

- 1 Anderson NR, *et al.* Quantitative evaluation of pharmaceutical effervescent systems II: stability monitoring of reactivity and porosity measurements. *J Pharm Sci* 1982; 71: 7-13.
- 2 Main J, Ward MK. Potentiation of aluminum absorption by effervescent analgesic tablets in a haemodialysis patient. *Br Med J* 1992; 304: 1686.
- 3 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 12th edn. New York: Wiley, 2012: 4464.

20 General References**21 Author**

GE Amidon.

22 Date of Revision

4 May 2017.



Sodium Cyclamate

1 Nonproprietary Names

BP: Sodium Cyclamate

PhEur: Sodium Cyclamate

2 Synonyms

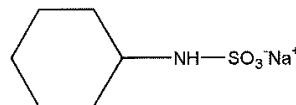
Cyclamate sodium; cyclohexylsulfamic acid monosodium salt; E952; natrii cyclamas; sodium cyclohexanesulfamate.

3 Chemical Name and CAS Registry Number

Sodium N-cyclohexylsulfamate [139-05-9]

4 Empirical Formula and Molecular Weight

$C_6H_{12}NNaO_3S$ 201.22

5 Structural Formula**6 Functional Category**

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium cyclamate is used as an intense sweetening agent in pharmaceutical formulations. In dilute solution, up to about 0.17% w/v, the sweetening power is approximately 30 times that of sucrose. However, at higher concentrations this is reduced and at a concentration of 0.5% w/v a bitter taste becomes noticeable.

14 Safety

Microcrystalline wax is mainly used in topical pharmaceutical formulations but is also used in some oral products. It is generally regarded as a nontoxic and nonirritating material.

15 Handling Precautions

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

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral capsules; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Paraffin; wax, white; wax, yellow.

18 Comments

Rheological studies of a model ointment containing microcrystalline wax, white petroleum, and mineral oil showed that while the latter two substances control the rheology of the ointment, microcrystalline wax incorporates itself into the existing white petroleum structure and builds up the structure of the ointment.⁽⁵⁾

Waxes have been combined in melt-extruded drug delivery systems.

A specification for refined microcrystalline wax (petroleum wax) is contained in the *Food Chemicals Codex* (FCC).⁽⁶⁾

19 Specific References

- 1 De Brabander C, *et al.* Bioavailability of ibuprofen from matrix minitabets based on a mixture of starch and microcrystalline wax. *Int J Pharm* 2000; 208: 81–86.
- 2 De Brabander C, *et al.* Matrix minitabets based on starch/microcrystalline wax mixtures. *Int J Pharm* 2000; 199: 195–203.
- 3 Vergote GJ, *et al.* Oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen. *Int J Pharm* 2001; 219: 81–87.
- 4 Motycka S, Nairn J. Influence of wax coatings on release rate of anions from ion-exchange resin beads. *J Pharm Sci* 1978; 67: 500–503.
- 5 Pena LE, *et al.* Structural rheology of a model ointment. *Pharm Res* 1994; 11: 875–881.
- 6 *Food Chemicals Codex*. [online] Bethesda, MD: United States Pharmacopeia. <http://publications.usp.org> (accessed 31 March 2017).

20 General References

- Hasa D, *et al.* Melt-extruded helical waxy matrices as a new sustained drug delivery system. *Eur J Pharm Biopharm* 2011; 79(3): 592–600.
- Paramelt B.V. Basewax 7796. Product literature. <http://www.paramelt.com/additives-modifiers-wax.aspx> (accessed 21 October 2015).
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- Tennant DR. The usage, occurrences and dietary intakes of white mineral oils and waxes in Europe. *Food Chem Toxicol* 2004; 42: 481–492.

21 Author

AH Kibbe.

22 Date of Revision

4 May 2017.

Wax, Nonionic Emulsifying

1 Nonproprietary Names

BP: Cetomacrogol Emulsifying Wax

USP–NF: Emulsifying Wax

2 Synonyms

Collone NI; Crodex N; Emulgade 1000NI; Kerawax; Lipowax P; Masurf Emulsifying Wax; Permulin D; Polawax; Ritachol 2000; T-Wax.

3 Chemical Name and CAS Registry Number

Nonionic emulsifying wax [97069-99-0]

See also Section 4

4 Empirical Formula and Molecular Weight

The USP 40–NF 35 S1 designates nonionic emulsifying wax as emulsifying wax that is prepared from cetostearyl alcohol and contains a polyoxyethylene derivative of a fatty acid ester of sorbitan. However, the BP 2017 describes nonionic emulsifying wax as cetomacrogol emulsifying wax prepared from cetostearyl alcohol and macrogol cetostearyl ether (22). The UK and US materials are therefore constitutionally different. See also Section 18.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; solubilizing agent; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

Nonionic emulsifying wax is used as an emulsifying agent in the production of oil-in-water emulsions that are unaffected by moderate concentrations of electrolytes and are stable over a wide pH range. The concentration of wax used alters the consistency of a product owing to its 'self-bodying action'; at concentrations up to about 5% a product is pourable.

Concentrations of about 15% of nonionic emulsifying wax are commonly used in creams, but concentrations as high as 25% may be employed, e.g. in chlorhexidine cream BP. Nonionic emulsifying wax is particularly recommended for use with salts of polyvalent metals and medicaments based on nitrogenous compounds. Creams are susceptible to microbial spoilage and should be adequately preserved.

Nonionic emulsifying wax is also used in nonaqueous ointment bases, such as cetomacrogol emulsifying ointment BP, and in barrier creams. It has also been investigated for its effects on the physical

W

1024 Wax, Nonionic Emulsifying

properties of cetyltrimethyl ammonium bromide (CTAB)-based solid lipid nanoparticles.⁽¹⁾

8 Description

Nonionic emulsifying wax occurs as a white or off-white waxy solid or flakes, which melt when heated to give a clear, almost colorless liquid. Nonionic emulsifying wax has a faint odor, which is characteristic of cetostearyl alcohol.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for nonionic emulsifying wax.

Test	BP 2017	USP 40-NF 35 S1
Identification	+	—
Characters	+	—
Melting range	—	50–54°C
Solidifying point	45–53°C	—
pH (3% dispersion)	—	5.5–7.0
Alkalinity	+	—
Acid value	≤0.5	—
Hydroxyl value	175–192	178–192
Iodine value	—	≤3.5
Refractive index (at 60°C)	1.435–1.439	—
Saponification value	≤2.0	≤14
Sulfated ash	≤0.1%	—

10 Typical Properties

Density 0.94 g/cm³

Flash point >150°C for Masurf Emulsifying Wax NF

Solubility The BP 2017 specifies that cetomacrogol emulsifying wax is practically insoluble in water, forming an emulsion, and is moderately soluble in ethanol (96%), and partly soluble in ether.

Spectroscopy

NIR spectrum see Figure 1.

11 Stability and Storage Conditions

Nonionic emulsifying wax is stable and should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Nonionic emulsifying wax is incompatible with tannin, phenol and phenolic materials, resorcinol, and benzocaine. It may reduce the antibacterial efficacy of quaternary ammonium compounds.

13 Method of Manufacture

The BP 2017 specifies that cetomacrogol emulsifying wax (nonionic emulsifying wax) may be prepared by melting and mixing together 800 g of cetostearyl alcohol and 200 g of macrogol cetostearyl ether (22). The mixture is then stirred until cold.

The USP 40–NF 35 S1 formula for nonionic emulsifying wax is a mixture of unstated proportions of cetostearyl alcohol and a polyoxyethylene derivative of a fatty acid ester of sorbitan.

14 Safety

Nonionic emulsifying wax is used in cosmetics and topical pharmaceutical formulations, and is generally regarded as a nontoxic and nonirritant material.

15 Handling Precautions

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

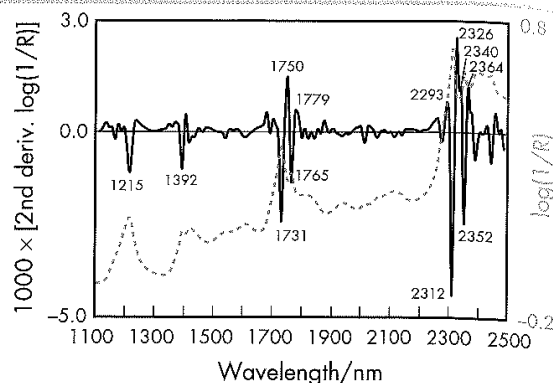


Figure 1: Near-infrared spectrum of nonionic emulsifying wax measured by reflectance.

16 Regulatory Status

Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Cationic emulsifying wax; cetostearyl alcohol; polyoxyethylene alkyl ethers; wax, anionic emulsifying.

It should be noted that there are many similar nonionic emulsifying waxes composed of different nonionic surfactants and fatty alcohols.

Cationic emulsifying wax

Synonyms cetrimide emulsifying wax; *Crodex C*.

Method of manufacture Cetrimide emulsifying wax is prepared similarly to nonionic emulsifying wax and contains 90 g of cetostearyl alcohol and 10 g of cetrimide.

Comments Cationic emulsifying wax is claimed to be of particular value in cosmetic and pharmaceutical formulations when cationic characteristics are important. Thus it can be used in medicated creams, germicidal creams, ointments and lotions, hair conditioners, baby creams, and skin care products in which cationic compounds are included. Cationic emulsifying wax is compatible with cationic and nonionic materials, but is incompatible with anionic surfactants and drugs. Additional antimicrobial preservatives should be included in creams. Cetrimide may cause irritation to the eye; see Cetrimide.

18 Comments

The nomenclature for emulsifying wax is confusing since there are three groups of emulsifying waxes with different titles in Europe, the UK, and US; see Table II.

Table II: Nomenclature for emulsifying wax.

	Europe	UK	US
Nonionic	—	Cetomacrogol emulsifying wax	Emulsifying wax
Anionic	Cetostearyl alcohol (type A), emulsifying Cetostearyl alcohol (type B), emulsifying	Emulsifying wax	—
Cationic	—	Cetrimide emulsifying wax	—

The waxes have similar physical properties but vary in the type of surfactant used, which, in turn, affects the range of compatibilities.

Emulsifying wax BP and emulsifying wax USP–NF contain anionic and nonionic surfactants, respectively, and are therefore not interchangeable in formulations.

19 Specific References

- 1 Siddiqui A, *et al.* The effect of emulsifying wax on the physical properties of CTAB-based solid lipid nanoparticles (SLN). *Pharm Dev Technol* 2014; 19(1): 125–128.

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Eccleston GM. Properties of fatty alcohol mixed emulsifiers and emulsifying waxes. In: Florence AT, ed. *Materials Used in Pharmaceutical Formulation: Critical Reports on Applied Chemistry*. 6. Oxford: Blackwell Scientific, 1984; 124–156.

Eccleston GM. Functions of mixed emulsifiers and emulsifying waxes in dermatological lotions and creams. *Colloids Surf A Physicochem Eng Asp* 1997; 123–124: 169–182.

Hadgraft JW. The emulsifying properties of polyethyleneglycol ethers of cetostearyl alcohol. *J Pharm Pharmacol* 1954; 6: 816–829.

Mason Chemical Company. Product literature: *Masurf Emulsifying Wax NF* 2005.

Lake OA, *et al.* Analysis of creams. III. Application of gas-liquid chromatography. Part I. *Pharm Weekbl Sci* 1982; 4: 42(2): 48.

21 Author

G Moss.

22 Date of Revision

4 May 2017.



Wax, White

1 Nonproprietary Names

BP: White Beeswax

JP: White Beeswax

PhEur: Beeswax, White

USP–NF: White Wax

2 Synonyms

Bleached wax; cera alba; E901.

3 Chemical Name and CAS Registry Number

White beeswax [8012-89-3]

4 Empirical Formula and Molecular Weight

White wax is the chemically bleached form of natural beeswax; *see* Section 13.

Beeswax consists of 70–75% of a mixture of various esters of straight-chain monohydric alcohols with even-numbered carbon chains from C₂₄ to C₃₆ esterified with straight-chain acids. These straight-chain acids also have even numbers of carbon atoms up to C₃₆ together with some C₁₈ hydroxy acids. The chief ester is myricyl palmitate. Also present are free acids (about 14%) and carbohydrates (about 12%) as well as approximately 1% free wax alcohols and stearic esters of fatty acids.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; emulsion stabilizing agent; modified-release agent; stiffening agent.

7 Applications in Pharmaceutical Formulation or Technology

White wax is a chemically bleached form of yellow wax and is used in similar applications: for example, to increase the consistency of creams and ointments, and to stabilize water-in-oil emulsions.

White wax is used to polish sugar-coated tablets and to adjust the melting point of suppositories.

White wax is also used as a film coating in sustained-release tablets.⁽¹⁾ White beeswax microspheres may be used in oral dosage forms to retard the absorption of an active ingredient from the stomach, allowing the majority of absorption to occur in the intestinal tract. Wax has been incorporated in dosage forms intended to float in the stomach fluids to prolong drug release, with mixed results.⁽²⁾ Wax coatings can also be used to affect the release of drug from ion-exchange resin beads.^(3–5)

See also Wax, Yellow and Microcrystalline Wax.

8 Description

White wax consists of tasteless, white or slightly yellow-colored sheets or fine granules with some translucence. Its odor is similar to that of yellow wax but is less intense.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for white wax

Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Characters	+	+	—
Melting range	60–67°C	61–66°C	62–65°C
Relative density	—	≈0.960	—
Acid value	5–9 or 17–22	17–24	17–24
Ester value	—	70–80	72–79
Saponification value	80–100	87–104	—
Ceresin, paraffins, and certain other waxes	—	+	—
Purity	+	—	—
Glycerols and other polyols	—	+	—
Saponification cloud test	—	—	+
Fats or fatty acids, Japan wax, rosin, and soap	—	—	+

Edetate Disodium

1 Nonproprietary Names

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

2 Synonyms

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

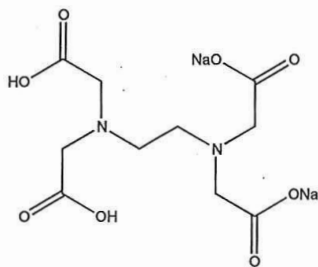
3 Chemical Name and CAS Registry Number

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

4 Empirical Formula and Molecular Weight

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

5 Structural Formula



6 Functional Category

Complexing agent.

7 Applications in Pharmaceutical Formulation or Technology

Edetate disodium is used as a complexing agent in a wide range of pharmaceutical preparations, including mouthwashes, ophthalmic preparations, and topical preparations,⁽¹⁻³⁾ typically at concentrations between 0.005 and 0.1% w/v.

Edetate disodium forms stable water-soluble complexes (chelates) with alkaline earth and heavy-metal ions. The chelated form has few of the properties of the free ion, and for this reason chelating agents are often described as 'removing' ions from solution, a process known as sequestering. The stability of the metal-edetate complex is dependent on the metal ion involved and the pH.

Edetate disodium has been used experimentally to investigate the stability and skin penetration capacity of captopril gel, in which edetate disodium was shown to exert a potent stabilizing effect, and may be used in the development of a transdermal drug delivery system.⁽⁴⁾ A chitosan-EDTA conjugate has been investigated as a novel polymer for use in topical gels. The conjugate was shown to

be stable, colorless, and transparent, and it also demonstrated antimicrobial effects.⁽⁵⁾ Studies have shown that edetate disodium may be effective in retarding microbial growth in propofol formulations⁽⁶⁾ and for the prevention of biofilm formation in catheters.⁽⁷⁾

Research has also been done to prepare and characterize hot melt dispersion formulations of mini-pellets containing EDTA.⁽⁸⁾ A salt complex of iron and EDTA has been used to develop chewable and orodispersible tablets in studies in humans and rats.⁽⁹⁾

See also Edetic Acid.

8 Description

Edetate disodium occurs as a white, crystalline, odorless powder with a slightly acidic taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for edetate disodium.

Test	JP XVII	PhEur 9.2	USP 40-NF 35 S1
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	4.3–4.7	4.0–5.5	4.0–6.0
Iron	—	≤80 ppm	—
Calcium	—	—	+
Heavy metals	≤10 ppm	—	≤0.005%
Cyanide	+	—	—
Arsenic	≤2 ppm	—	—
Limit of nitrilotriacetic acid	—	≤0.1%	≤0.1%
Residue on ignition	37.0–39.0%	—	—
Loss on drying	—	—	8.7–11.4%
Assay	≥99.0%	98.5–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity pH 4.3–4.7 (1% w/v solution in carbon dioxide-free water)

Density (bulk) 980 kg/m³ (for *Versene*)

Freezing point depression 0.14°C (1% w/v aqueous solution)

Melting point Decomposition at 252°C for the dihydrate.

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

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

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

Spectroscopy

IR spectrum see Figure 1.

NIR spectrum see Figure 2.

Raman spectrum see Figure 3.

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

11 Stability and Storage Conditions

Edetate salts are more stable than edetic acid (see also Edetic Acid). However, edetate disodium dihydrate loses its water of crystal-

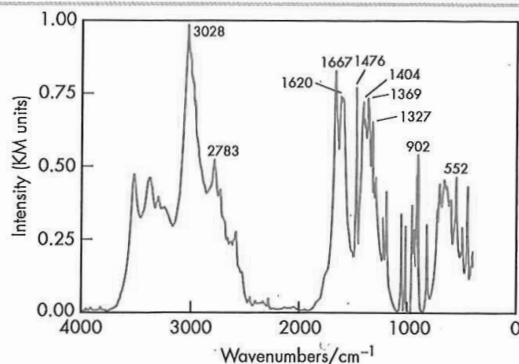


Figure 1: Infrared spectrum of edetate disodium dihydrate measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

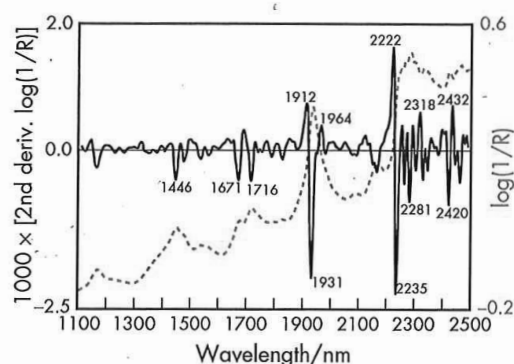


Figure 2: Near-infrared spectrum of edetate disodium dihydrate measured by reflectance.

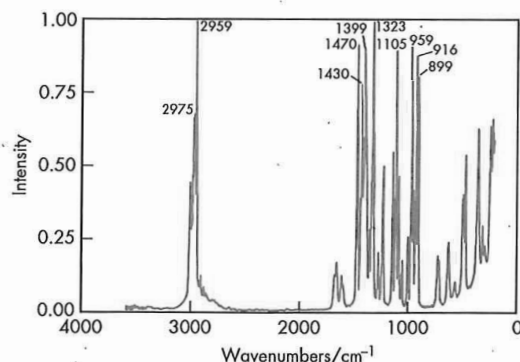


Figure 3: Raman spectrum of edetate disodium dihydrate measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

lization when heated to 120°C. Aqueous solutions of edetate disodium may be sterilized by autoclaving, and should be stored in an alkali-free container.

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

12 Incompatibilities

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

The addition of edetate disodium to phenylmercuric nitrate⁽¹⁰⁾ and thimerosal^(10,11) has also been reported to reduce the antimicrobial efficacy of the preservative.

See also Edetic Acid.

13 Method of Manufacture

Edetate disodium may be prepared by the reaction of edetic acid and sodium hydroxide.

14 Safety

Edetate disodium is used widely in topical, oral, and parenteral pharmaceutical formulations; it is used extensively in cosmetic and food products. Edetate disodium and edetate calcium disodium are used in a greater number and variety of pharmaceutical formulations than is edetic acid. Both edetate disodium and edetate calcium disodium are poorly absorbed from the gastrointestinal tract and are associated with few adverse effects when used as excipients in pharmaceutical formulations.

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

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

Although edetate disodium is generally considered safe, there have been reports of edetate disodium toxicity in patients receiving chelation therapy,⁽¹²⁾ and between 1971 and 2007, four deaths attributed to the therapeutic use of edetate disodium were reported to the FDA.⁽¹³⁾

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

* The WHO has set an estimated acceptable daily intake for disodium EDTA in foodstuffs of up to 2.5 mg/kg body-weight.⁽¹⁴⁾ See also Edetic Acid.

LD₅₀ (mouse, IP): 0.26 g/kg⁽¹⁵⁾

LD₅₀ (mouse, IV): 0.056 g/kg⁽¹⁵⁾

LD₅₀ (mouse, OP): 2.05 g/kg⁽¹⁵⁾

LD₅₀ (rabbit, IV): 0.047 g/kg⁽¹⁵⁾

LD₅₀ (rabbit, OP): 2.3 g/kg⁽¹⁵⁾

LD₅₀ (rat, OP): 2.0 g/kg⁽¹⁵⁾

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (inhalations; injections; ophthalmic, otic, oral, rectal, topical, intrauterine, nasal, transdermal, urethral, iontophoresis and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Edetic acid.

18 Comments

Many solutions used for the cleaning, storage, and wetting of contact lenses contain edetate disodium.^(16,17) Therapeutically, edetate disodium is used as an anticoagulant as it will chelate calcium and prevent the coagulation of blood *in vitro*.⁽¹⁸⁾ Concentrations of 0.1% w/v are used in small volumes for hematological testing and 0.3% w/v in transfusions. Studies have shown how edetate disodium is facilitated by methylsulfonylmethane to cross biological membranes for regional chelation therapy.⁽¹⁹⁾ It is also used therapeutically in the treatment of hypercalcemia.⁽¹³⁾

Edetate disodium is used as a water softener as it will chelate calcium and magnesium ions present in hard water.

A specification for edetate disodium is contained in the *Food Chemicals Codex* (FCC).⁽²⁰⁾

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

19 Specific References

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- 2 Kaur IP, et al. Formulation and evaluation of ophthalmic preparations of acetazolamide. *Int J Pharm* 2000; 199: 119-127.
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