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21 Authors

ME Quinn, PJ Sheskey.

22 Date of Revision

7 January 2009.

Sodium Propionate

1 Nonproprietary Names

BP: Sodium Propionate

PhEur: Sodium Propionate

USP-NF: Sodium Propionate

2 Synonyms

E281; ethylformic acid, sodium salt, hydrate; methylacetic acid, sodium salt, hydrate; natrii propionas; sodium propanoate hydrate; sodium propionate hydrate.

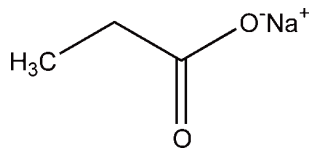
3 Chemical Name and CAS Registry Number

Propionic acid, sodium salt, hydrate [6700-17-0]
Propionic acid, sodium salt, anhydrous [137-40-6]

4 Empirical Formula and Molecular Weight

$C_3H_5NaO_2 \cdot xH_2O$ 114.06 (for monohydrate)
$C_3H_5NaO_2$ 96.06 (for anhydrous)

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

As an excipient, sodium propionate is used in oral pharmaceutical formulations as an antimicrobial preservative. Like propionic acid, sodium propionate and other propionic acid salts are fungistatic and bacteriostatic against a number of Gram-positive cocci. Propionates are more active against molds than is sodium benzoate, but have essentially no activity against yeasts; *see* Section 10.

Therapeutically, sodium propionate has been used topically in concentrations up to 10% w/w alone or in combination with other propionates, caprylates, or other antifungal agents, in the form of ointments or solutions for the treatment of dermatophyte infections. Eye drops containing 5% w/v sodium propionate have also been used. *See* Section 18.

In food processes, particularly baking, sodium propionate is used as an antifungal agent; it may also be used as a flavoring agent in food products. In veterinary medicine, sodium propionate is used therapeutically as a glucogenic substance in ruminants.[1]

8 Description

Sodium propionate occurs as colorless transparent crystals or as a granular, free-flowing, crystalline powder. It is odorless, or with a slight characteristic odor, and is deliquescent in moist air. Sodium propionate has a characteristic, slightly cheeselike taste, although by itself it is unpalatable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium propionate.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	–
Appearance of solution	+	–
Alkalinity	–	+
pH	7.8–9.2	–
Water	–	⩽1.0%
Heavy metals	⩽10 ppm	⩽0.001%
Related substances	+	–
Readily oxidizable substances	+	–
Iron	⩽10 ppm	–
Loss on drying	0.5%	–
Assay (dried basis)	99.0–101.0%	99.0–100.5%

10 Typical Properties

Antimicrobial activity Sodium propionate, propionic acid, and other propionates possess mainly antifungal activity and are used as preservatives primarily against molds; they exhibit essentially no activity against yeasts. Although, in general, propionates exhibit little activity against bacteria, sodium propionate is effective against *Bacillus mesenterium*, the organ-

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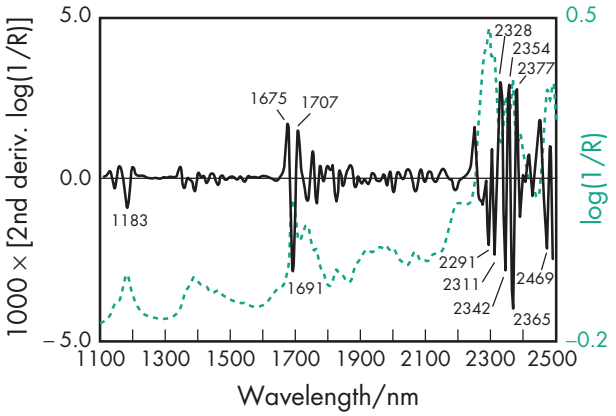

Figure 1: Near-infrared spectrum of sodium propionate measured by reflectance.

ism that causes 'rope' in bread. Antimicrobial activity is largely dependent upon the presence of the free acid and hence propionates exhibit optimum activity at acid pH, notably at less than pH 5. Synergistic effects occur between propionates and carbon dioxide or sorbic acid. *See also* Propionic acid.

NIR spectra *see* Figure 1.

Solubility Soluble 1 in 24 of ethanol (95%), 1 in 1 of water, and 1 in 0.65 of boiling water; practically insoluble in chloroform and ether.

11 Stability and Storage Conditions

Sodium propionate is deliquescent and should therefore be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Incompatibilities for sodium propionate are similar to those of other weak organic acids.

13 Method of Manufacture

Sodium propionate is prepared by the reaction of propionic acid with sodium carbonate or sodium hydroxide.

14 Safety

Sodium propionate and other propionates are used in oral pharmaceutical formulations, food products, and cosmetics. The free acid, propionic acid, occurs naturally at levels up to 1% w/w in certain cheeses.

Following oral consumption, propionate is metabolized in mammals in a manner similar to that of fatty acids. Toxicity studies in animals have shown sodium propionate and other propionates to be relatively nontoxic materials.[2,3] In veterinary medicine, sodium propionate is used as a therapeutic agent for cattle and sheep.[1]

In humans, 6 g of sodium propionate has been administered daily without harm.[2] However, allergic reactions to propionates can occur.

LD_{50} (mouse, oral): 6.33 g/kg[4]

LD_{50} (mouse, SC): 2.1 g/kg

LD_{50} (rabbit, skin): 1.64 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium propionate may be irritant to the eyes and skin. Gloves, eye protection, and a dust-mask are recommended. When heated to decomposition, sodium propionate emits toxic fumes of sodium monoxide, Na_2O.

In the UK, the workplace exposure limits for propionic acid are 31 mg/m^3 (10 ppm) long-term (8-hour TWA) and 46 mg/m^3 (15 ppm) short-term.[5]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. In cheese products, propionates are limited to 0.3% w/w concentration; a limit of 0.32% w/w is applied in flour and white bread rolls, while a limit of 0.38% w/w is applied in whole wheat products.

Included in the FDA Inactive Ingredients Database (oral capsules, powder, suspensions, and syrups). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Anhydrous sodium propionate; calcium propionate; potassium propionate; propionic acid; zinc propionate.

Anhydrous sodium propionate

Empirical formula $C_3H_5O_2Na$
Molecular weight 96.06
CAS number [137-40-6]
Synonyms E281; propanoic acid, sodium salt, anhydrous.
Safety

LD_{50} (mouse, oral): 2.35 g/kg[4]

LD_{50} (rat, oral): 3.92 g/kg

Calcium propionate

Empirical formula $C_6H_{10}O_4Ca$
Molecular weight 186.22
CAS number [4075-81-4]
Synonyms Calcium dipropionate; E282; propanoic acid, calcium salt; propionic acid, calcium salt.
Appearance White crystalline powder.
Solubility Soluble in water; slightly soluble in ethanol (95%) and methanol; practically insoluble in acetone and benzene.
Method of manufacture Prepared by the reaction of propionic acid and calcium hydroxide.
Comments Occurs as the monohydrate or trihydrate.

Potassium propionate

Empirical formula $C_3H_5O_2K$
Molecular weight 112.17
CAS number [327-62-8]
Synonyms E283; propanoic acid, potassium salt; propionic acid, potassium salt.
Appearance White crystalline powder.
Comments Occurs as the anhydrous form and the monohydrate. Decomposes in moist air to give off propionic acid.

Zinc propionate

Empirical formula $C_6H_{10}O_4Zn$
Molecular weight 211.52
CAS number [557-28-8]
Synonyms Propanoic acid, zinc salt; propionic acid, zinc salt.
Appearance White platelets or needlelike crystals (for the monohydrate).
Solubility The anhydrous form is soluble 1 in 36 of ethanol (95%) at 15°C, 1 in 6 of boiling ethanol (95%), and 1 in 3 of water at 15°C.
Method of manufacture Prepared by dissolving zinc oxide in dilute propionic acid solution.
Comments Occurs as the anhydrous form and the monohydrate. Decomposes in moist air to give off propionic acid.

18 Comments

Propionates are used as antimicrobial preservatives in preference to propionic acid since they are less corrosive.

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The therapeutic use of sodium propionate in topical antifungal preparations has largely been superseded by a new generation of antifungal drugs.

A specification for sodium propionate is contained in the Food Chemicals Codex (FCC).[6]

The EINECS number for sodium propionate is 205-290-4. The PubChem Compound ID (CID) for sodium propionate is 23663426.

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T Sakurai.

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Sodium Starch Glycolate

1 Nonproprietary Names

BP: Sodium Starch Glycolate
PhEur: Sodium Starch Glycolate
USP-NF: Sodium Starch Glycolate

2 Synonyms

Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; *Explosol*; *Explotab*; *Glycolys*; *Primojel*; starch carboxymethyl ether, sodium salt; *Tablo*; *Vivastar P.*

3 Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

4 Empirical Formula and Molecular Weight

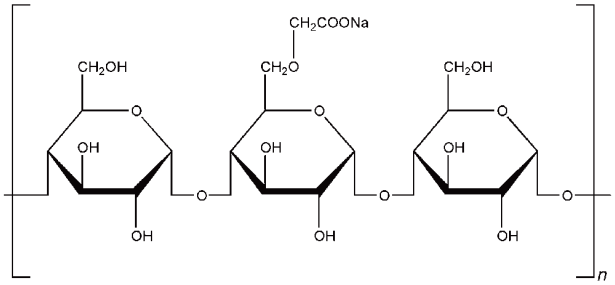
The USP32–NF27 describes two types of sodium starch glycolate, Type A and Type B, and states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch or of a crosslinked carboxymethyl ether of starch.

The PhEur 6.0 describes three types of material: Type A and Type B are described as the sodium salt of a crosslinked partly *O*-carboxymethylated potato starch. Type C is described as the sodium salt of a partly *O*-carboxymethylated starch, crosslinked by physical dehydration. Types A, B, and C are differentiated by their pH, sodium, and sodium chloride content.

The PhEur and USP–NF monographs have been harmonized for Type A and Type B variants.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5×10^5–1×10^6.

5 Structural Formula



6 Functional Category

Tablet and capsule disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule[1–6] and tablet formulations.[7–10] It is commonly used in tablets prepared by either direct-compression[11–13] or wet-granulation processes.[14–16] The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.[17–20]

Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.[10–12]

Sodium starch glycolate has also been investigated for use as a suspending vehicle.[21]

8 Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of: granules, irregularly shaped, ovoid or pear-shaped, 30–100 µm in size, or rounded, 10–35 µm in size; compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

10 Typical Properties

Acidity/alkalinity *See* Section 9.

Density (bulk)

0.756 g/cm^3 for *Glycolys*;
0.81 g/cm^3 for *Primojel*;
0.67 g/cm^3 for *Tablo*.

Density (tapped)

0.945 g/cm^3 for *Glycolys*;
0.98 g/cm^3 for *Primojel*;
0.83 g/cm^3 for *Tablo*.

Density (true)

1.56 g/cm^3 for *Primojel*;
1.49 g/cm^3 for *Tablo*.

Melting point Does not melt, but chars at approximately 200°C.

NIR spectra *see* Figure 1.

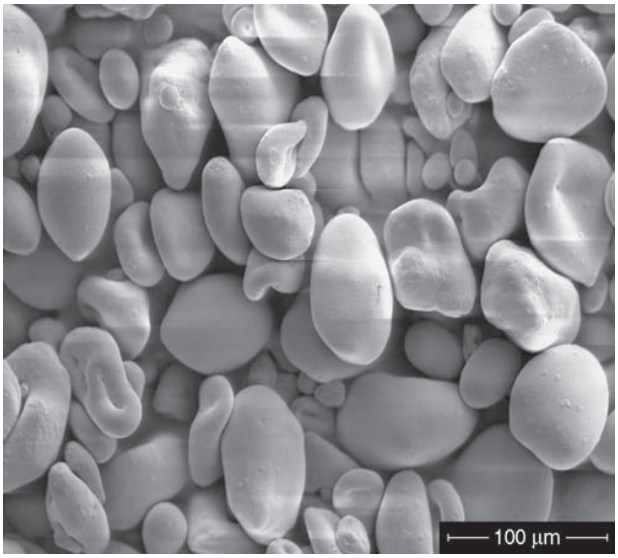
Particle size distribution 100% of particles less than 106 µm in size. Average particle size (d_{50}) is 38 µm and 42 µm for *Primojel* by microscopy and sieving, respectively.

Solubility Practically insoluble in methylene chloride. It gives a translucent suspension in water.

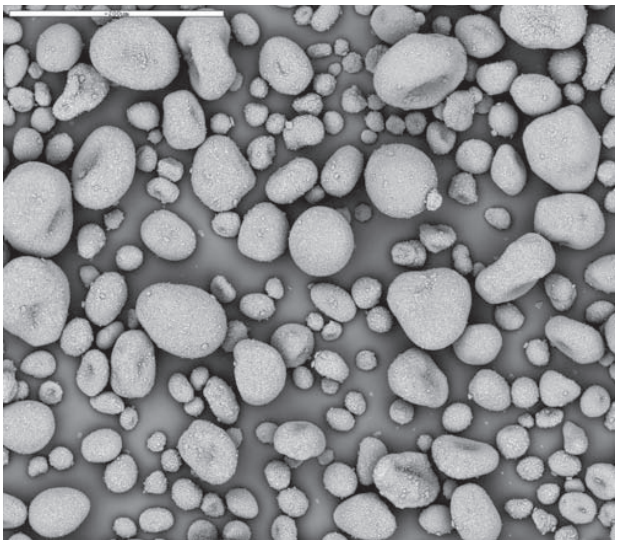
Specific surface area

0.24 m^2/g for *Glycolys*;
0.185 m^2/g for *Primojel*;
0.335 m^2/g for *Tablo*.

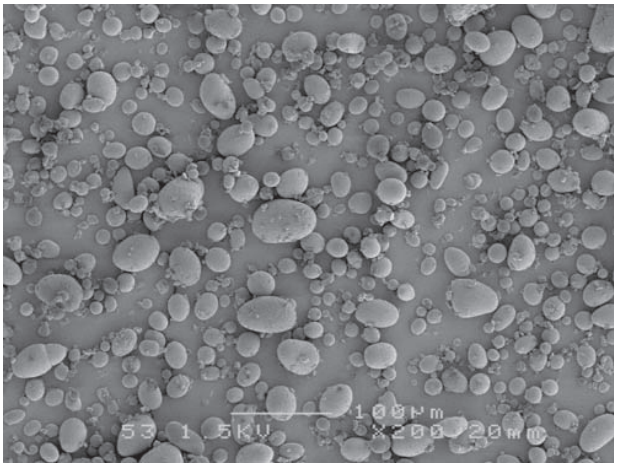
SEM 1: Excipient: sodium starch glycolate (*Explotab*); manufacturer: JRS Pharma; magnification: 300×; voltage: 5 kV.



SEM 2: Excipient: sodium starch glycolate (*Glycolys*); manufacturer: Roquettes Frères.



SEM 3: Excipient: sodium starch glycolate (*Primojel*); manufacturer: DMV-Fonterra Excipients; magnification: 200×; voltage: 1.5 kV.



SEM 4: Excipient: sodium starch glycolate (*Vivastar P*); manufacturer: JRS Pharma; magnification: 300×; voltage: 5 kV.

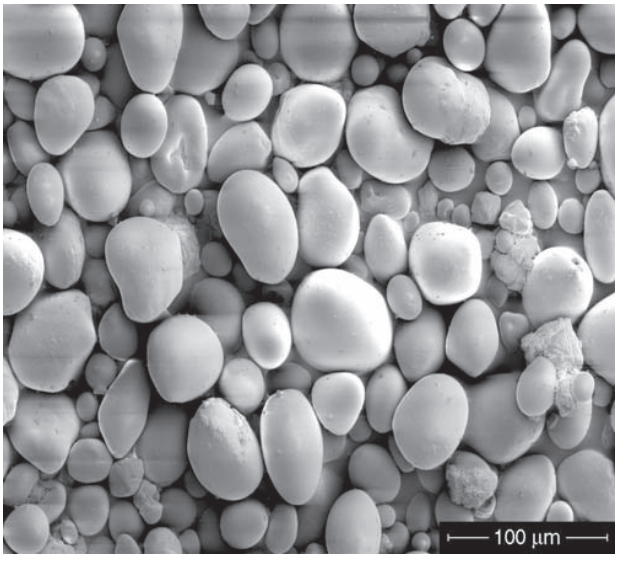


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Table I: Pharmacopeial specifications for sodium starch glycolate.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Appearance of solution	+	—
pH	+	+
Type A	5.5–7.5	5.5–7.5
Type B	3.0–5.0	3.0–5.0
Type C	5.5–7.5	—
Heavy metals	⩽20 ppm	⩽0.002%
Iron	⩽20 ppm	⩽0.002%
Loss on drying	+	⩽10%
Type A	⩽10.0%	—
Type B	⩽10.0%	—
Type C	⩽7.0%	—
Microbial limits	+[a]	+[a]
Sodium chloride	+	⩽7.0%
Type A	⩽7.0%	—
Type B	⩽7.0%	—
Type C	⩽1.0%	—
Sodium glycolate	+	⩽2.0%
Type A	⩽2.0%	—
Type B	⩽2.0%	—
Type C	⩽2.0%	—
Assay (of Na)	+	+
Type A	2.8–4.2%	2.8–4.2%
Type B	2.0–3.4%	2.0–3.4%
Type C	2.8–5.0%	—

(a) Complies with tests for *Salmonella* and *Escherichia coli*.

Swelling capacity In water, sodium starch glycolate swells to up to 300 times its volume.

Viscosity (dynamic) ⩽200 mPa s (200 cP) for a 4% w/v aqueous dispersion; viscosity is 4.26 mPa s for a 2% w/v aqueous dispersion (depending on source and grade).

11 Stability and Storage Conditions

Tablets prepared with sodium starch glycolate have good storage properties.[22–24] Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

12 Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.[25]

13 Method of Manufacture

Sodium starch glycolate is a substituted derivative of potato starch. Typically, commercial products are also crosslinked using either sodium trimetaphosphate (Types A and B) or dehydration (Type C).[26]

Starch is carboxymethylated by reacting it with sodium chloroacetate in an alkaline, nonaqueous medium, typically denatured ethanol or methanol, followed by neutralization with citric acid, acetic acid, or some other acid. *Vivastar P* is manufactured in methanolic medium, and *Explotab* in ethanolic medium.

14 Safety

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

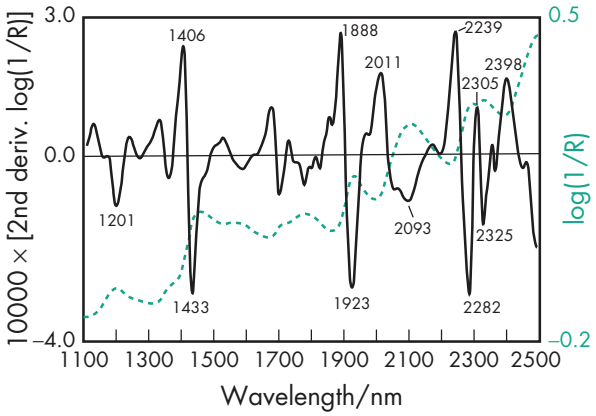

Figure 1: Near-infrared spectrum of sodium starch glycolate measured by reflectance.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Pregelatinized starch; starch.

18 Comments

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

The physical properties of sodium starch glycolate, and hence its effectiveness as a disintegrant, are affected by the degree of crosslinkage, extent of carboxymethylation, and purity.[27,28]

Sodium starch glycolate has been reported to interact with glycopeptide antibiotics,[29,30] basic drugs, and increase the photostability of norfloxacin.[31] The solubility of the formulation matrix and mode of incorporation in wet granulation can affect the disintegration time; disintegration times can be slower in tablets containing high levels of soluble excipients.[32]

Commercially, sodium starch glycolate is available in a number of speciality grades, e.g. low pH (*Explotab Low pH*, *Glycolys Low pH*); low viscosity (*Explotab CLV*, *Glycolys LV*); low solvent (*Vivastar PSF*); and low moisture *Glycolys LM*.

A specification for sodium starch glycolate is included in the *Japanese Pharmaceutical Excipients* (JPE).[33]

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21 Author

PM Young.

22 Date of Revision

3 February 2009.

Sodium Stearyl Fumarate

1 Nonproprietary Names

BP: Sodium Stearyl Fumarate

PhEur: Sodium Stearyl Fumarate

USP-NF: Sodium Stearyl Fumarate

2 Synonyms

Fumaric acid, octadecyl ester, sodium salt; natrii stearylis fumaras; *Pruv*; sodium monostearyl fumarate.

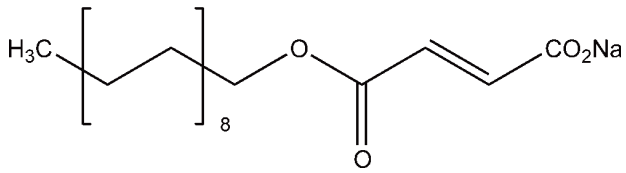
3 Chemical Name and CAS Registry Number

2-Butenedioic acid, monooctadecyl ester, sodium salt [4070-80-8]

4 Empirical Formula and Molecular Weight

$C_{22}H_{39}NaO_4$ 390.5

5 Structural Formula



6 Functional Category

Tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.[1–9] It is also used in certain food applications; *see* Section 16.

8 Description

Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.

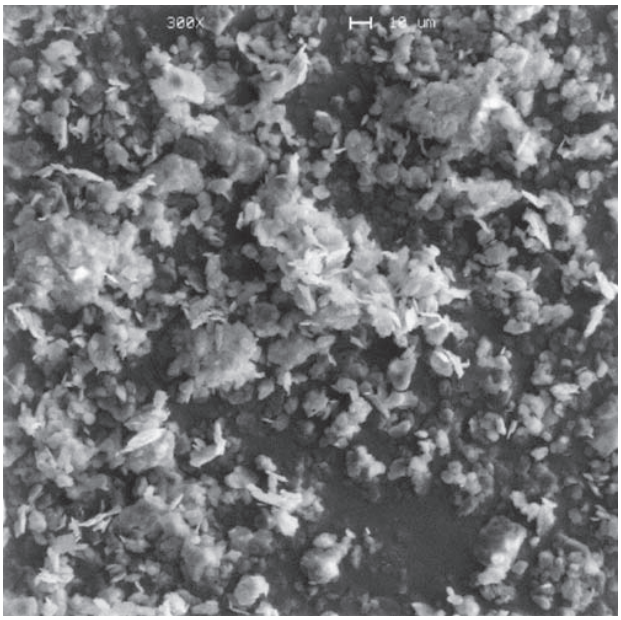
9 Pharmacopeial Specifications

See Table I.

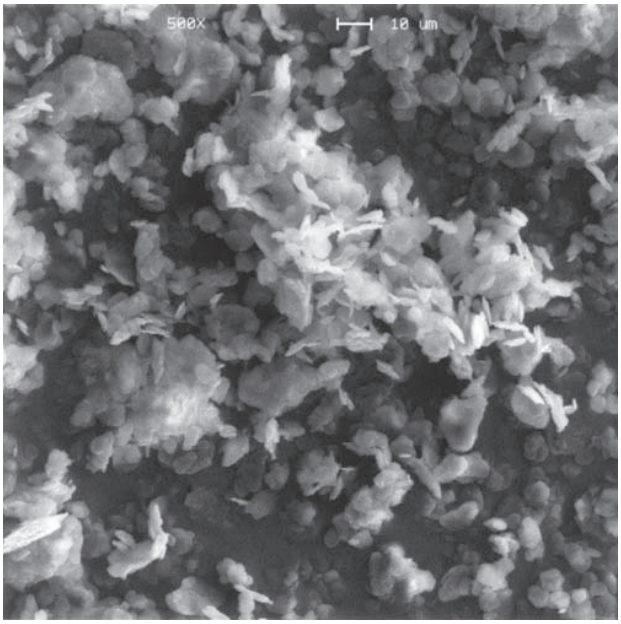
Table I: Pharmacopeial specifications for sodium stearyl fumarate.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Water	⩽5.0%	⩽5.0%
Lead	—	⩽0.001%
Heavy metals	—	⩽0.002%
Related substances	⩽5.0%	—
Sodium stearyl maleate	—	⩽0.25%
Stearyl alcohol	—	⩽0.5%
Saponification value (anhydrous basis)	—	142.2–146.0
Assay (anhydrous basis)	99.0–101.5%	99.0–101.5%

SEM 1: Excipient: sodium stearyl fumarate; manufacturer: JRS Pharma LP; lot no.: 255-01; magnification: 300×.



SEM 2: Excipient: sodium stearyl fumarate; manufacturer: JRS Pharma LP; lot no.: 255-01; magnification: 500×.



10 Typical Properties

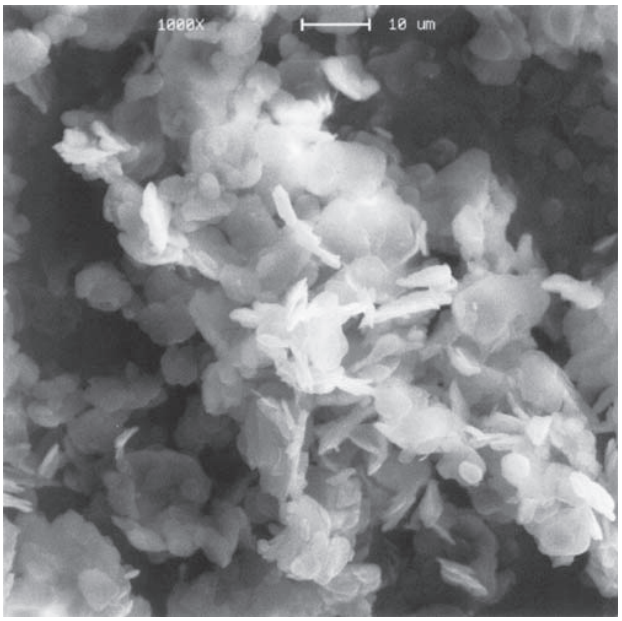
Acidity/alkalinity pH = 8.3 for a 5% w/v aqueous solution at 90°C.

Density 1.107 g/cm^3

Density (bulk) 0.2–0.35 g/cm^3

Density (tapped) 0.3–0.5 g/cm^3

SEM 3: Excipient: sodium stearyl fumarate; manufacturer: JRS Pharma LP; lot no.: 255-01; magnification: 1000×.



Melting point 224–245°C (with decomposition)
Solubility *see* Table II.
Specific surface area 1.2–2.0 m^2/g

Table II: Solubility of sodium stearyl fumarate.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Practically insoluble
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Methanol	Slightly soluble
Water	1 in 20 000 at 25°C 1 in 10 at 80°C 1 in 5 at 90°C

S

11 Stability and Storage Conditions

At ambient temperature, sodium stearyl fumarate is stable for up to 3 years when stored in amber glass bottles with polyethylene screw caps.

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

12 Incompatibilities

Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.[10]

13 Method of Manufacture

Stearyl alcohol is reacted with maleic anhydride. The product of this reaction then undergoes an isomerization step followed by salt formation to produce sodium stearyl fumarate.

14 Safety

Sodium stearyl fumarate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

Metabolic studies of sodium stearyl fumarate in the rat and dog indicated that approximately 80% was absorbed and 35% was rapidly metabolized. The fraction absorbed was hydrolyzed to stearyl alcohol and fumaric acid, with the stearyl alcohol further oxidized to stearic acid. In the dog, sodium stearyl fumarate that was not absorbed was excreted unchanged in the feces within 24 hours.[11]

Stearyl alcohol and stearic acid are naturally occurring constituents in various food products, while fumaric acid is a normal constituent of body tissue. Stearates and stearyl citrate have been reviewed by the WHO and an acceptable daily intake for stearyl citrate has been set at up to 50 mg/kg body-weight.[12] The establishment of an acceptable daily intake for stearates[12] and fumaric acid[13] was thought unnecessary.

Disodium fumarate has been reported to have a toxicity not greatly exceeding that of sodium chloride.[14,15]

See Fumaric Acid, Stearic Acid, and Stearyl Alcohol for further information.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium stearyl fumarate should be handled in a well-ventilated environment; eye protection is recommended.

16 Regulatory Status

GRAS listed. Permitted by the FDA for direct addition to food for human consumption as a conditioning or stabilizing agent in various bakery products, flour-thickened foods, dehydrated potatoes, and processed cereals up to 0.2–1.0% by weight of the food. Included in nonparenteral medicines licensed in the UK. Included in the FDA Inactive Ingredients Database (oral capsules and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Sodium stearyl fumarate is supplied in a pure form and is often of value when the less pure stearate-type lubricants are unsuitable owing to chemical incompatibility. Sodium stearyl fumarate is less hydrophobic than magnesium stearate or stearic acid and has a less retardant effect on tablet dissolution than magnesium stearate.

A specification for sodium stearyl fumarate is contained in the Food Chemicals Codex (FCC).[16]

The EINECS number for sodium stearyl fumarate is 223-781-1. The PubChem Compound ID (CID) for sodium stearyl fumarate is 23665634.

19 Specific References

1 Surén G. Evaluation of lubricants in the development of tablet formula. *Dansk Tidsskr Farm* 1971; **45**: 331–338.
2 Hölzer AW, Sjögren J. Evaluation of sodium stearyl fumarate as a tablet lubricant. *Int J Pharm* 1979; **2**: 145–153.
3 Hölzer AW, Sjögren J. Evaluation of some lubricants by the comparison of friction coefficients and tablet properties. *Acta Pharm Suec* 1981; **18**: 139–148.
4 Saleh SI *et al*. Evaluation of some water soluble lubricants for direct compression. *Lab Pharm Prob Tech* 1984; **32**: 588–591.
5 Chowhan ZT, Chi L-H. Drug–excipient interactions resulting from powder mixing IV: role of lubricants and their effect on in vitro dissolution. *J Pharm Sci* 1986; **75**: 542–545.
6 Shah NH *et al*. Evaluation of two new tablet lubricants sodium stearyl fumarate and glyceryl behenate. Measurement of physical parameters (compaction, ejection and residual forces) in the tableting process and the effect on the dissolution rate. *Drug Dev Ind Pharm* 1986; **12**: 1329–1346.
7 Davies PN *et al*. Some pitfalls in accelerated stability testing with tablet and capsule lubricants. *J Pharm Pharmacol* 1987; **39**: 86P.

8 Mu X *et al*. Investigations into the food effect on a polysaccharide dosage form. *Eur J Pharm Sci* 1996; **4**(Suppl. 1): S184.
9 Michoel A *et al*. Comparative evaluation of co-processed lactose and microcrystalline cellulose with their physical mixtures in the formulation of folic acid tablets. *Pharm Dev Technol* 2002; **7**(1): 79–87.
10 Pesonen T *et al*. Incompatibilities between chlorhexidine diacetate and some tablet excipients. *Drug Dev Ind Pharm* 1995; **21**: 747–752.
11 Figdor SK, Pinson R. The absorption and metabolism of orally administered tritium labelled sodium stearyl fumarate in the rat and dog. *J Agric Food Chem* 1970; **18**(5): 872–877.
12 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
13 FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-fifth report of the FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1990; No. 789.
14 Bodansky O *et al*. The toxicity and laxative action of sodium fumarate. *J Am Pharm Assoc (Sci)* 1942; **31**: 1–8.
15 Locke A *et al*. The comparative toxicity and cathartic efficiency of disodium tartrate and fumarate, and magnesium fumarate, for the mouse and rabbit. *J Am Pharm Assoc (Sci)* 1942; **31**: 12–14.
16 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 912.

20 General References

Nicklasson M, Brodin A. The coating of disk surfaces by tablet lubricants, determined by an intrinsic rate of dissolution method. *Acta Pharm Suec* 1982; **19**: 99–108.
Zanowiak P. Lubrication in solid dosage form design and manufacture. Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology.*, vol. **9**: New York: Marcel Dekker, 1994; 87–111.

21 Author

PJ Weller.

22 Date of Revision

16 January 2009.

Sodium Sulfite

1 Nonproprietary Names

BP: Anhydrous Sodium Sulphite
JP: Dried Sodium Sulfite
PhEur: Sodium Sulphite, Anhydrous
USP-NF: Sodium Sulfite

2 Synonyms

Disodium sulfite; exsiccated sodium sulfite; E221; natrii sulfis anhydricus; sulfurous acid disodium salt.

3 Chemical Name and CAS Registry Number

Sodium sulfite [7757-83-7]

4 Empirical Formula and Molecular Weight

Na_2SO_3 126.04

5 Structural Formula

See Section 4.

6 Functional Category

Antimicrobial preservative; antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium sulfite is used as an antioxidant in applications similar to those for sodium metabisulfite.[1] It is also an effective antimicrobial preservative, particularly against fungi at low pH (0.1% w/v of sodium sulfite is used). Sodium sulfite is used in cosmetics, food products, and pharmaceutical applications such as parenteral formulations, inhalations, oral formulations, and topical preparations.

See also Sodium Metabisulfite.

8 Description

Sodium sulfite occurs as an odorless white powder or hexagonal prisms. Note that the commercially available sodium sulfite is often presented as a white to tan- or pink-colored powder that would not conform to the pharmacopeial specification.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium sulfite.

Test	JP XV	PhEur 6.0	USP32–NF27
Characters	+	+	–
Identification	+	+	+
Appearance of solution	–	+	+
Heavy metals	⩽20 ppm	⩽10 ppm	⩽10 µg/g
Arsenic	⩽4 ppm	–	–
Iron	–	⩽10 ppm	⩽10 µg/g
Selenium	–	⩽10 ppm	⩽10 µg/g
Thiosulfates	+	⩽0.1%	⩽0.1%
Zinc	–	⩽25 ppm	⩽25 µg/g
Assay	⩾97%	95.0–100.5%	95.0–100.5%

10 Typical Properties

Acidity/alkalinity pH = 9 for an aqueous solution.
Density 2.633 g/cm^3
Hygroscopicity Hygroscopic.
Solubility Soluble 1 in 3.2 parts of water; soluble in glycerin; practically insoluble in ethanol (95%).

11 Stability and Storage Conditions

Sodium sulfite should be stored in a well-closed container in a cool, dry, place. In solution, sodium sulfite is slowly oxidized to sulfate by

dissolved oxygen; strong acids lead to formation of sulfurous acid/sulfur dioxide. On heating, sodium sulfite decomposes liberating sulfur oxides.

12 Incompatibilities

Sodium sulfite is incompatible with acids, oxidizing agents, many proteins, and vitamin B_1.

See also Sodium Metabisulfite.

13 Method of Manufacture

Sodium bisulfite is prepared by reacting sulfur dioxide gas with sodium hydroxide solution. The solid material is obtained by evaporation of water. Further neutralization with sodium hydroxide while keeping the temperature above 33.6°C leads to crystallization of the anhydrous sodium sulfite (below this temperature the heptahydrate form is obtained).

14 Safety

Sodium sulfite is widely used in food and pharmaceutical applications as an antioxidant. It is generally regarded as relatively nontoxic and nonirritant when used as an excipient.[2,3] However, contact dermatitis and hypersensitivity reactions have been reported.[4,5] The acceptable daily intake for sodium sulfite has been set at up to 350 µg/kg body-weight daily.[6]

LD_{50} (mouse, IP): 0.950 g/kg[7]
LD_{50} (mouse, IV): 0.130 g/kg
LD_{50} (mouse, oral): 0.820 g/kg
LD_{50} (rabbit, IV): 0.065 g/kg
LD_{50} (rabbit, oral): 1.181 g/kg
LD_{50} (rat, IV): 0.115 g/kg

15 Handling Precautions

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

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in FDA Inactive Ingredients Database (epidural, IM, IV, and SC injections; inhalation solution; ophthalmic solutions; oral syrups and suspensions; otic solutions; topical creams and emulsions). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Sodium sulfite heptahydrate; sodium metabisulfite.

Sodium sulfite heptahydrate

Synonyms Natrii sulfis heptahydricus
CAS number [7785-83-7]
Molecular weight 252.15
Description Colorless crystals.
Density 1.56 g/cm^3
Solubility 1 in 1.6 of water; 1 in 30 of glycerin; sparingly soluble in ethanol (95%).
Comments Sodium sulfite heptahydrate is included in the PhEur 6.0. The heptahydrate is unstable, oxidizing in the air to the sulfate.

18 Comments

A specification for sodium sulfite is contained in the Food Chemicals Codex (FCC).[8]

The EINECS number for sodium sulfite is 231-821-4. The PubChem Compound ID (CID) for sodium sulfite is 24437.

19 Specific References

1 Islam MS *et al*. Photoprotection of daunorubicin hydrochloride with sodium sulfite. *PDA J Pharm Sci Technol* 1995; **49**: 122–126.
2 Nair B, Elmore AR. Final report on the safety assessment of sodium sulfite, potassium sulfite, ammonium sulfite, sodium bisulfite, ammonium bisulfite, sodium metabisulfite and potassium metabisulfite. *Int J Toxicol* 2003; **22**(2): 63–88.
3 Gunnisson AF. Sulphite toxicity: a critical review of *in vitro* and *in vivo* data. *Food Cosmet Toxicol* 1981; **19**: 667–682.
4 Vissers-Croughs KJ *et al*. Allergic contact dermatitis from sodium sulfite. *Contact Dermatitis* 1988; **18**(4): 252–253.
5 Gunnisson AF, Jacobsen DW. Sulphite hypersensitivity: a critical review. *CRC Crit Review Toxicol* 1987; **17**(3): 185–214.
6 FAO/WHO. Evaluation of certain food additives and contaminants. Thirtieth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1987: No. 751.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3281–3282.
8 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 913.

20 General References

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21 Author

HJ de Jong.

22 Date of Revision

14 January 2009.

Sodium Thiosulfate

1 Nonproprietary Names

BP: Sodium Thiosulphate
JP: Sodium Thiosulfate Hydrate
PhEur: Sodium Thiosulfate
USP-NF: Sodium Thiosulfate

2 Synonyms

Ametox; disodium thiosulfate; disodium thiosulfate pentahydrate; natrii thiosulfas; natrium thiosulfuricum; sodium hyposulfite; sodium subsulfite; *Sodothiol*; *Sulfothiorine*; thiosulfuric acid disodium salt.

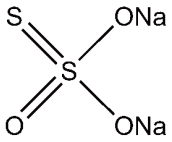
3 Chemical Name and CAS Registry Number

Sodium thiosulfate anhydrous [7772-98-7]
Sodium thiosulfate pentahydrate [10102-17-7]

4 Empirical Formula and Molecular Weight

$Na_2S_2O_3$ 158.11 (for anhydrous)
$Na_2S_2O_3 \cdot 5H_2O$ 248.2 (for pentahydrate)

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium thiosulfate is used as an antioxidant in pharmaceuticals (ophthalmic, intravenous, and oral preparations). It has also been used for its antifungal properties[1] and as a reagent in analytical chemistry.

8 Description

Sodium thiosulfate occurs as odorless and colorless crystals, a crystalline powder or granules. It is efflorescent in dry air and deliquescent in moist air.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity Aqueous solution practically neutral at pH 6.5–8.0 (pentahydrate).
Density 1.69 g/cm^3 (pentahydrate)
Hygroscopicity Slightly deliquesces in moist air (pentahydrate).
Melting point 48°C (pentahydrate)
Solubility Soluble in water; practically insoluble in ethanol (95%).

SEM 1: Excipient: sodium thiosulfate; magnification: 100×; voltage: 10 kV.

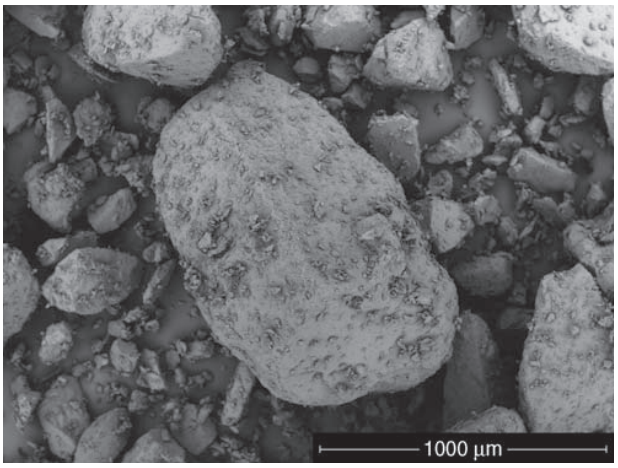


Table I: Pharmacopeial specifications for sodium thiosulfate.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	–	+	–
pH	6.0–8.0	6.0–8.4	–
Appearance of solution	+	+	–
Water	–	–	32.0–37%
Calcium	+	–	+
Heavy metals	⩽20 ppm	⩽10 ppm	⩽0.002%
Arsenic	⩽5 ppm	–	–
Loss on drying	+	–	–
Sulfides	–	+	–
Sulfates and sulfites	–	⩽0.2%	–
Assay (dried basis)	99.0–101.0%	99.0–101.0%	99.0–100.5%

11 Stability and Storage Conditions

Sodium thiosulfate decomposes on heating. The bulk powder should be stored in a cool place, and the container should be kept tightly closed in a dry and well-ventilated place. It should not be stored near acids.

12 Incompatibilities

Sodium thiosulfate is incompatible with iodine, with acids, and with lead, mercury, and silver salts. It may reduce the activity of some preservatives, including bronopol, phenylmercuric salts, and thimerosal.[1]

13 Method of Manufacture

On an industrial scale, sodium thiosulfate is produced chiefly from liquid waste products of sodium sulfide or sulfur dye manufacture. Small-scale synthesis is done by boiling an aqueous solution of sodium sulfite with sulfur.[2,3]

14 Safety

Sodium thiosulfate is used in ophthalmic, intravenous, and oral pharmaceutical preparations. Apart from osmotic disturbances, sodium thiosulfate is relatively nontoxic. It is moderately toxic by

the subcutaneous route and mildly irritating to respiratory tract and skin. Large oral doses have a cathartic action.[1]

LD_{50} (IP, mouse) 5.6 g/kg[4]
LD_{50} (IV, mouse) 2.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Protective gloves are recommended for prolonged or repeated contact use. Hazardous products (sulfur oxides) are formed when heated to decomposition.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (IV solutions; ophthalmic solutions and suspensions; oral capsules, solutions, and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Sodium thiosulfate has been used as an antidote to cyanide poisoning.[5,6] Thiosulfate acts as a sulfur donor for the conversion of cyanide to thiocyanate (which can then be safely excreted in the urine), catalyzed by the enzyme rhodanase.

There is a specification for sodium thiosulfate in the Food Chemicals Codex (FCC).[7]

The EINECS number for sodium thiosulfate is 231-867-5. The PubChem Compound ID (CID) for sodium thiosulfate pentahydrate is 516922.

19 Specific References

1 Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 36th edn. London, UK: Pharmaceutical Press, 2009; 1466.
2 Lowenheim FA, Moran MK, eds. *Faith, Keyes & Clarks Industrial Chemicals*, 4th edn. New York: Wiley-Interscience, 1975; 769–773.
3 Holleman AF, Wiberg E. *Inorganic Chemistry.* San Diego: Academic Press, 2001; 1937.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3284–3285.
5 Frankenberg L, Sörbo B. Effect of cyanide antidotes on the metabolic conversion of cyanide to thiocyanate. *Arch Toxicol* 1975; **14**: 81–89.
6 Sylvester DM *et al.* Effects of thiosulfate on cyanide pharmacokinetics in dogs. *Toxicol Appl Pharmacol* 1983; **69**: 265–271.
7 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 914.

20 General References

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21 Authors

JC Hooton, N Sandler.

22 Date of Revision

16 February 2009.

Sorbic Acid

S

1 Nonproprietary Names

BP: Sorbic Acid
PhEur: Sorbic Acid
USP-NF: Sorbic Acid

2 Synonyms

Acidum sorbicum; E200; (2-butenylidene) acetic acid; crotylidene acetic acid; hexadienic acid; hexadienoic acid; 2,4-hexadienoic acid; 1,3-pentadiene-1-carboxylic acid; 2-propenylacrylic acid; (*E*,*E*)-sorbic acid; *Sorbistat K*.

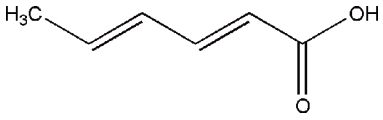
3 Chemical Name and CAS Registry Number

(*E*,*E*)-Hexa-2,4-dienoic acid [22500-92-1]

4 Empirical Formula and Molecular Weight

$C_6H_8O_2$ 112.13

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Sorbic acid is an antimicrobial preservative[1] with antibacterial and antifungal properties used in pharmaceuticals, foods, enteral preparations, and cosmetics. Generally, it is used at concentrations of 0.05–0.2% in oral and topical pharmaceutical formulations, especially those containing nonionic surfactants. Sorbic acid is also used with proteins, enzymes, gelatin, and vegetable gums.[2] It has been shown to be an effective preservative for promethazine hydrochloride solutions in a concentration of 1 g/L.[3]

Sorbic acid has limited stability and activity against bacteria and is thus frequently used in combination with other antimicrobial preservatives or glycols, when synergistic effects appear to occur; *see* Section 10.

8 Description

Sorbic acid is a tasteless, white to yellow-white crystalline powder with a faint characteristic odor.

9 Pharmacopeial Specifications

See Table I.

SEM 1: Excipient: sorbic acid; manufacturer: Pfizer Ltd.; magnification: 60×.

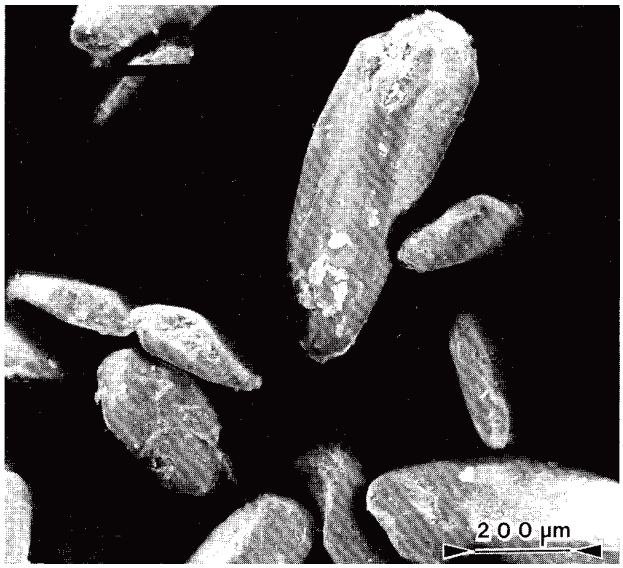


Table I: Pharmacopeial specifications for sorbic acid.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting range	132–136°C	132–135°C
Water	⩽1.0%	⩽0.5%
Residue on ignition	—	⩽0.2%
Sulfated ash	⩽0.2%	—
Heavy metals	⩽10 ppm	⩽0.001%
Aldehyde (as C_2H_4O)	⩽0.15%	—
Assay (anhydrous basis)	99.0–101.0%	99.0–101.0%

10 Typical Properties

Antimicrobial activity Sorbic acid is primarily used as an antifungal agent, although it also possesses antibacterial properties. The optimum antibacterial activity is obtained at pH 4.5; and practically no activity is observed above pH 6.[4,5] The efficacy of sorbic acid is enhanced when it is used in combination with other antimicrobial preservatives or glycols since synergistic effects occur.[6] Reported minimum inhibitory concentrations (MICs) at pH 6 are shown in Table II.[7]

Boiling point 228°C with decomposition.

Density 1.20 g/cm^3

Dissociation constant pK_a = 4.76

Table II: Minimum inhibitory concentrations (MICs) of sorbic acid at pH 6.

Microorganism	MIC (µg/mL)
Aspergillus niger	200–500
Candida albicans	25–50
Clostridium sporogenes	100–500
Escherichia coli	50–100
Klebsiella pneumoniae	50–100
Penicillium notatum	200–300
Pseudomonas aeruginosa	100–300
Pseudomonas cepacia	50–100
Pseudomonas fluorescens	100–300
Saccharomyces cerevisiae	200–500
Staphylococcus aureus	50–100

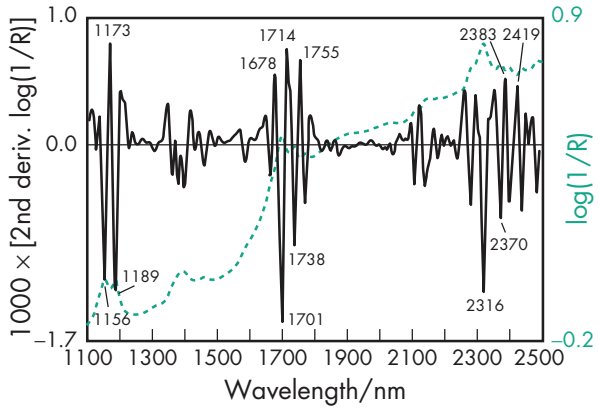


Figure 1: Near-infrared spectrum of sorbic acid measured by reflectance.

Flash point 127°C

Melting point 134.5°C

NIR spectra *see* Figure 1.

Solubility *see* Table III. In syrup, the solubility of sorbic acid decreases with increasing sugar content.

Vapor pressure <1.3 Pa (<0.01 mmHg) at 20°C

Table III: Solubility of sorbic acid.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 11
Chloroform	1 in 15
Ethanol	1 in 8
Ethanol (95%)	1 in 10
Ether	1 in 30
Glycerin	1 in 320
Methanol	1 in 8
Propylene glycol	1 in 19
Water	1 in 400 at 30°C 1 in 26 at 100°C

11 Stability and Storage Conditions

Sorbic acid is sensitive to oxidation, particularly in the presence of light; oxidation occurs more readily in aqueous solution than in the solid form. Sorbic acid may be stabilized by phenolic antioxidants such as 0.02% propyl gallate.[6]

Sorbic acid is combustible when exposed to heat or flame. When heated to decomposition, it emits acrid smoke and irritating fumes. The bulk material should be stored in a well-closed container, protected from light, at a temperature not exceeding 40°C.

12 Incompatibilities

Sorbic acid is incompatible with bases, oxidizing agents, and reducing agents. Some loss of antimicrobial activity occurs in the presence of nonionic surfactants and plastics. Oxidation is catalyzed by heavy-metal salts. Sorbic acid will also react with sulfur-containing amino acids, although this can be prevented by the addition of ascorbic acid, propyl gallate, or butylhydroxytoluene.

When stored in glass containers, the solution becomes very pH sensitive; therefore, preparations using sorbic acid as a preservative should be tested for their microbial purity after prolonged periods of storage.

Aqueous solutions of sorbic acid without the addition of antioxidants are rapidly decomposed when stored in polypropylene, polyvinylchloride, and polyethylene containers.

13 Method of Manufacture

Naturally occurring sorbic acid may be extracted as the lactone (parasorbic acid) from the berries of the mountain ash *Sorbus aucuparia* L. (Fam. Rosaceae). Synthetically, sorbic acid may be prepared by the condensation of crotonaldehyde and ketene in the presence of boron trifluoride; by the condensation of crotonaldehyde and malonic acid in pyridine solution; or from 1,1,3,5-tetraalkoxyhexane. Fermentation of sorbaldehyde or sorbitol with bacteria in a culture medium has also been used.

14 Safety

Sorbic acid is used as an antimicrobial preservative in oral and topical pharmaceutical formulations and is generally regarded as a nontoxic material. However, adverse reactions to sorbic acid and potassium sorbate, including irritant skin reactions[8–11] and allergic hypersensitivity skin reactions (which are less frequent), have been reported.[12–14]

Other adverse reactions that have been reported include exfoliative dermatitis due to ointments that contain sorbic acid,[15] and allergic conjunctivitis caused by contact lens solutions preserved with sorbic acid.[16]

No adverse reactions have been described after systemic administration of sorbic acid, and it has been reported that it can be ingested safely by patients who are allergic to sorbic acid.[17] However, perioral contact urticaria has been reported.[11]

The WHO has set an estimated total acceptable daily intake for sorbic acid, calcium sorbate, potassium sorbate, and sodium sorbate, expressed as sorbic acid, at up to 25 mg/kg bodyweight.[18,19]

Animal toxicological studies have shown no mammalian carcinogenicity or teratogenicity for sorbic acid consumed at up to 10% of the diet.[20]

LD_{50} (mouse, IP): 2.82 g/kg[21]

LD_{50} (mouse, oral): 3.20 g/kg

LD_{50} (mouse, SC): 2.82 g/kg

LD_{50} (rat, oral): 7.36 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sorbic acid can be irritant to the skin, eyes, and respiratory system. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic solutions; oral capsules, solutions, syrups, tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Calcium sorbate; potassium sorbate; sodium sorbate.

Calcium sorbate

Empirical formula $C_{12}H_{14}O_4Ca$
Synonyms E203
Molecular weight 262.33
CAS number [7492-55-9]
Appearance White, odorless, tasteless, crystalline powder.
Solubility Soluble 1 in 83 parts of water; practically insoluble in fats.
Comments The EINECS number for calcium sorbate is 231-321-6.

Sodium sorbate

Empirical formula $C_6H_7O_2Na$
Synonyms E201; sodium (*E*,*E*)-hexa-2,4-dienoate.
Molecular weight 134.12
CAS number [42788-83-0]
Appearance Light, white, crystalline powder.
Solubility Soluble 1 in 3 parts of water.
Comments The EINECS number for sodium sorbate is 231-819-3.

18 Comments

The *trans*,*trans*-isomer of sorbic acid is the commercial product. A specification for sorbic acid is contained in the Food Chemicals Codex (FCC).[22]

The EINECS number for sorbic acid is 203-768-7. The PubChem Compound ID (CID) for sorbic acid includes 643460 and 1550734.

19 Specific References

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