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20 General References

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Sendall FEJ *et al*. Effervescent tablets. *Pharm J* 1983; **230**: 289–294.
Travers DN, White RC. The mixing of micronized sodium bicarbonate with sucrose crystals. *J Pharm Pharmacol* 1971; **23**: 260S–261S.

21 Author

CG Cable.

22 Date of Revision

16 February 2009.

Sodium Borate

1 Nonproprietary Names

BP: Borax
JP: Sodium Borate
PhEur: Borax
USP-NF: Sodium Borate

2 Synonyms

Borax decahydrate; boric acid disodium salt; E285; natrii tetraboras; sodium biborate decahydrate; sodium pyroborate decahydrate; sodium tetraborate decahydrate.

3 Chemical Name and CAS Registry Number

Disodium tetraborate decahydrate [1303-96-4]

4 Empirical Formula and Molecular Weight

$Na_2B_4O_7{\cdot}10H_2O$ 381.37

5 Structural Formula

See Section 4.

6 Functional Category

Alkalizing agent; antimicrobial preservative; buffering agent; disinfectant; emulsifying agent; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium borate is used in pharmaceutical applications similarly to boric acid (*see* Boric Acid). It has been used externally as a mild astringent and as an emulsifying agent in creams.[1] It has also been used in lozenges, mouthwashes, otic preparations (0.3% w/v), and ophthalmic solutions (0.03–1.0% w/v). Sodium borate has additionally been investigated in the prevention of crystal formation in freeze-dried solutions.[2]

Preparations of sodium borate in honey have historically been used as paints for the throat, tongue, and mouth, but such use is now inadvisable because of concerns about toxicity in such applications; *see* Section 14. Sodium borate is also used in cosmetics such as moisturizers, deodorants, and shampoos.

8 Description

Sodium borate occurs as white, hard crystals, granules, or crystalline powder. It is odorless and efflorescent.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium borate.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Carbonate and bicarbonate	+	—	+
Color of solution	+	+	—
pH	9.1–9.6	9.0–9.6	—
Heavy metals	⩽20 ppm	⩽25 ppm	⩽0.002%
Arsenic	⩽5 ppm	⩽5 ppm	—
Calcium	—	⩽100 ppm	—
Ammonium	—	⩽10 ppm	—
Sulfates	—	⩽50 ppm	—
Assay	99.0–103.0%	99.0–103.0%	99.0–105.0%

10 Typical Properties

Acidity/alkalinity pH = 9.0–9.6 (4% w/v aqueous solution)
Density 1.73 g/cm^3
Melting point 75°C when rapidly heated. At 100°C it loses $5H_2O$; at 150°C it loses $9H_2O$; and at 320°C it becomes anhydrous. At about 880°C the substance melts into a glassy state: 'borax beads'.
Solubility 1 in 1 of glycerin; 1 in 1 of boiling water; 1 in 16 of water; practically insoluble in ethanol (95%), ethanol (99.5%), and diethyl ether.

11 Stability and Storage Conditions

Sodium borate should be stored in a well-closed container in a cool, dry, place. *See also* Section 18.

12 Incompatibilities

Sodium borate is incompatible with acids and with metallic and alkaloidal salts.

13 Method of Manufacture

Sodium borate can be prepared from minerals such as borosodium calcite, pandermite, or tinkal; these are natural sodium or calcium borates. Treatment of the mineral with sodium carbonate and sodium hydrogencarbonate yields the sodium borate decahydrate. In the USA, brine from salt lakes is also an important source of sodium borate.[3]

14 Safety

Sodium borate has weak bacteriostatic and astringent properties. Historically, sodium borate has been used as a disinfectant in skin lotions and eye-, nose-, and mouthwashes. However, boric acid is easily absorbed via mucous membranes and damaged skin, and severe toxicity has been observed, especially in babies and children.[4] Consequently, the use of sodium borate as a disinfectant is now considered somewhat obsolete and careful use is recommended. The toxic effects of sodium borate include vomiting, diarrhea, erythema, CNS depression, and kidney damage. The lethal oral intake is approximately 20 g in adults and 5 g in children.[5]

LD_{50} (guinea pig, oral): 5.33 g/kg[5,6]
LD_{50} (mouse, IP): 2.711 g/kg
LD_{50} (mouse, IV): 1.320 g/kg
LD_{50} (mouse, oral): 2.0 g/kg
LD_{50} (rat, oral): 2.66 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and the quantity of material handled; do not combine with acids.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (otic preparations; ophthalmic solutions and suspensions). Included in nonparenteral medicines licensed in the UK, Italy, France, Germany, and Japan. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Boric acid; sodium borate anhydrous.

Sodium borate anhydrous

Synonyms Borax glass; disodium tetraborate anhydrous; fused borax; fused sodium borate; sodium pyroborate; sodium tetraborate anhydrous.
Empirical formula $Na_2B_4O_7$
Molecular weight 201.2
CAS number [1330-43-4]
Boiling point 1575°C (decomposes)
Melting point 741°C
Solubility Slightly soluble in glycerin, and water; practically insoluble in ethanol (95%).
Specific gravity 2.367
Comments The EINECS number for sodium borate anhydrous is 215-540-4.

18 Comments

Commercially available sodium borate decahydrate is usually present as monoclinic prismatic crystals that become opaque on the surface in dry air. In addition to the decahydrate, a pentahydrate exists; this is also known as 'jeweller's borax'. The anhydrous substance is also available and is called 'pyroborax'.

The EINECS number for sodium borate is 271-536-2. The PubChem Compound ID (CID) for sodium borate is 11954323.

19 Specific References

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5 Lewis RJ. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3234.
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20 General References

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21 Author

HJ de Jong.

22 Date of Revision

3 February 2009.

Sodium Carbonate

1 Nonproprietary Names

BP: Anhydrous Sodium Carbonate
JP: Dried Sodium Carbonate
PhEur: Sodium Carbonate, Anhydrous
USP-NF: Sodium Carbonate

2 Synonyms

Bisodium carbonate; calcined soda; carbonic acid disodium salt; cenzias de soda; crystol carbonate; disodium carbonate; E500; natrii carbonas anhydricus; soda ash; soda calcined.

3 Chemical Name and CAS Registry Number

Sodium carbonate anhydrous [497-19-8]
Sodium carbonate monohydrate [5968-11-6]
Sodium carbonate decahydrate [6132-02-1]

4 Empirical Formula and Molecular Weight

Na_2CO_3	105.99
$Na_2CO_3·H_2O$	124.0
$Na_2CO_3·10H_2O$	286.1

5 Structural Formula

See Section 4.

6 Functional Category

Alkalizing agent; buffering agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium carbonate is used as an alkalizing agent in injectable, ophthalmic, oral, and rectal formulations.

In effervescent tablets or granules, sodium carbonate is used in combination with an acid, typically citric acid or tartaric acid.[1] When the tablets or granules come into contact with water, an acid–base reaction occurs in which carbon dioxide gas is produced and the product disintegrates.[2] Raw materials with low moisture contents are required to prevent the early triggering of the effervescent reaction.[2]

As an alkalizing agent, concentrations of sodium carbonate between 2% and 5% w/w are used in compressed tablet formulations.[1,3] As an effervescent agent, concentrations of sodium carbonate up to 10% w/w can be used.[2]

Therapeutically, sodium carbonate is also used as an oral antacid.[4]

8 Description

Sodium carbonate is a white, almost white, or colorless inorganic salt, produced as crystalline powder or granules. It is hygroscopic and odorless with an alkaline taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium carbonate.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Alkali hydroxides and bicarbonates	—	+	—
Chlorides	⩽0.071%	⩽125 ppm	—
Sulfates	—	⩽250 ppm	—
Arsenic	⩽3.1 ppm	⩽5 ppm	—
Iron	—	⩽50 ppm	—
Heavy metals	⩽20 ppm	⩽50 ppm	⩽0.001%
Loss on drying	⩽2.0%	⩽1.0%	—
Water	—	—	⩽0.5%
Assay (dried basis)	>99.0%	99.5–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity Strongly alkaline; pH = 11.4 (1% w/v aqueous solution at 25°C).[5]

Hygroscopicity One mole of sodium carbonate will gradually absorb 1 mole of water (approximately 15%) on exposure to air.

Melting point 851°C

Refractive index n_D^{20} = 1.3352 at 1.0% w/w solution; 1.3440 at 5.0% w/w solution; 1.3547 for 10.0% w/w solution.[6]

Solubility Freely soluble in water, with solubility initially increasing with temperature and then settling at 30.8% w/w above 80°C[5] (*see* Figure 1). Soluble in glycerin; practically insoluble in ethanol (95%).

Specific gravity 2.53

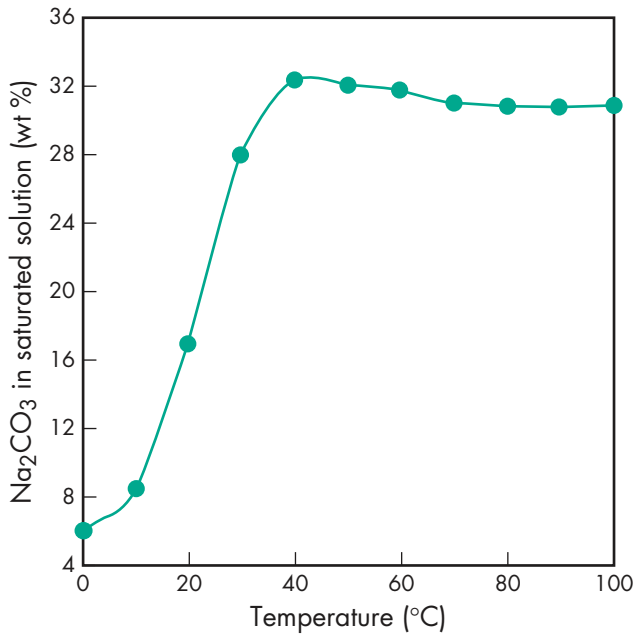

Figure 1: Solubility of sodium carbonate in water.[5] Adapted with permission.

11 Stability and Storage Conditions

Sodium carbonate converts to the monohydrate form when in contact with water and produces heat. It begins to lose carbon dioxide at temperatures above 400°C[7] and decomposes before boiling. Store in airtight containers.

12 Incompatibilities

Sodium carbonate decomposes when in contact with acids in the presence of water to produce carbon dioxide and effervescence. It may react violently with aluminum, phosphorous pentoxide, sulfuric acid, fluorine, and lithium.

13 Method of Manufacture

Sodium carbonate is produced by the ammonia-soda process, also known as the Solvay process.[7]

14 Safety

Sodium carbonate is used in injectable, oral, and rectal pharmaceutical formulations. The pure form of sodium carbonate is mildly toxic by ingestion, moderately toxic by inhalation and SC routes, and very toxic by the IP route. It is irritating to the skin and eyes. Dust and vapors of sodium carbonate may irritate mucous membranes, causing coughing and shortness of breath. It also has experimental reproductive effects.

Sodium carbonate can migrate to food from packaging materials. When used as an excipient or antacid, sodium carbonate is generally regarded as a nontoxic and nonirritating material.

LD_{50} (mouse, IP): 0.12 g/kg[8]
LD_{50} (mouse, SC): 2.21 g/kg
LD_{50} (rat, oral): 4.09 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. When heated to decomposition it emits toxic fumes of sodium oxide. Eye protection and gloves are recommended. Respiratory protection is also recommended if inhalable dust is present.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (injections; ophthalmic solution; oral capsules and tablets; rectal suspensions). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in parenteral (powder for solution for injection) and nonparenteral medicines (oral effervescent tablets, soluble tablets, granules, lozenges, chewing gums) licensed in the UK.

USP32–NF27 allows either the anhydrous or the monohydrate form.

17 Related Substances

Sodium bicarbonate; sodium carbonate decahydrate; sodium carbonate monohydrate.

Sodium carbonate decahydrate

Empirical formula $Na_2CO_3 \cdot 10H_2O$
Molecular weight 286.1
CAS number [6132-02-1]
Description Colorless, transparent, or white crystals or powder.
Solubility Freely soluble in water; practically insoluble in ethanol (95%).
Comments Listed in PhEur 6.0 and JP XV. Used in alkaline baths.[4]

Sodium carbonate monohydrate

Empirical formula $Na_2CO_3 \cdot H_2O$
Molecular weight 124.0
CAS number [5968-11-6]
Description Colorless or white crystals or granules.
Solubility Soluble in 3 parts water, 1.8 parts boiling water, or 7 parts glycerin. Practically insoluble in ethanol (95%). Dries out in warm dry air or above 50°C, and converts to anhydrous form above 100°C.
Comments Listed in PhEur 6.0 and USP32–NF27. Commonly used in antacid preparations and as a reagent.[4]

18 Comments

Sodium carbonate is more stable in effervescent formulations than sodium bicarbonate,[3] but is less effective as an effervescent agent and therefore sodium bicarbonate is most commonly used in effervescent formulations.[2] Sodium carbonate can be added to these formulations as a stabilizing agent (up to 10% w/w) as it absorbs moisture, preventing early effervescent reactions.[2] This effect is exploited in *Effer-Soda*, in which a sodium bicarbonate core is protected by a surface layer of sodium carbonate, equivalent to 8–12% w/w.[9]

The technical grade of sodium carbonate anhydrous (approximately 99% purity) is known as soda ash.

A specification for sodium carbonate is contained in the Food Chemicals Codex (FCC).[10]

The EINECS number for sodium carbonate is 207-838-8. The PubChem Compound ID (CID) for sodium carbonate is 10340.

19 Specific References

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5 Eggeman T. Sodium carbonate.*Kirk-Othmer Encyclopedia of Chemical Technology*, 5th edn, vol. **22**: New York: Wiley, 2001; 787–797.
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8 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Chemicals*, 11th edn. New York: Wiley, 2004; 3236.
9 SPI Pharma. Technical Bulletin No. 117/0300: *Effer-Soda*, 2007.
10 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 878.

20 General References

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21 Author

KP Hapgood.

22 Date of Revision

3 March 2009.

Sodium Chloride

1 Nonproprietary Names

BP: Sodium Chloride
JP: Sodium Chloride
PhEur: Sodium Chloride
USP: Sodium Chloride

2 Synonyms

Alberger; chlorure de sodium; common salt; hopper salt; natrii chloridum; natural halite; rock salt; saline; salt; sea salt; table salt.

3 Chemical Name and CAS Registry Number

Sodium chloride [7647-14-5]

4 Empirical Formula and Molecular Weight

NaCl 58.44

5 Structural Formula

See Section 4.

6 Functional Category

Tablet and capsule diluent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

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

Sodium chloride has been used as a lubricant and diluent in capsules and direct-compression tablet formulations in the past,[1–5] although this practice is no longer common. Sodium chloride has also been used as a channeling agent[6,7] and as an osmotic agent[8,9] in the cores of controlled-release tablets. It has been used as a porosity modifier in tablet coatings,[10] and to control drug release from microcapsules.[11,12]

The addition of sodium chloride to aqueous spray-coating solutions containing hydroxypropyl cellulose or hypromellose suppresses the agglomeration of crystalline cellulose particles.[13] Sodium chloride can also be used to modify drug release from gels[14] and from emulsions.[15] It can be used to control micelle size,[16–18] and to adjust the viscosity of polymer dispersions by altering the ionic character of a formulation.[19,20]

See Table I.

Table I: Uses of sodium chloride.

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

8 Description

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

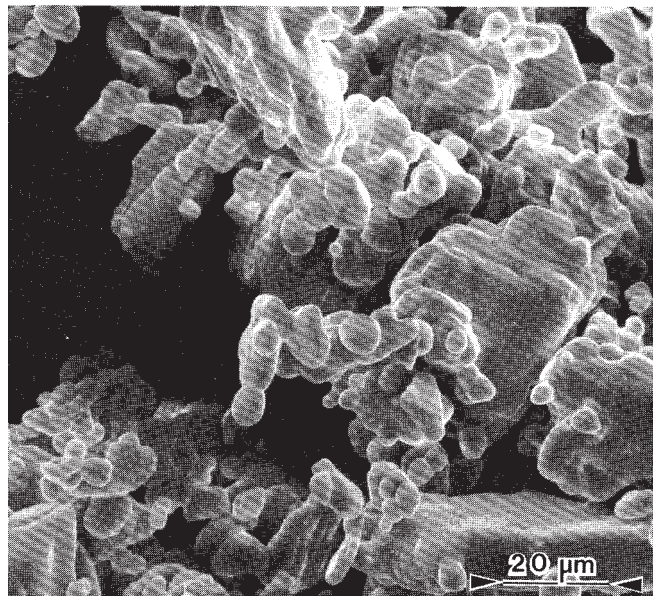
9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

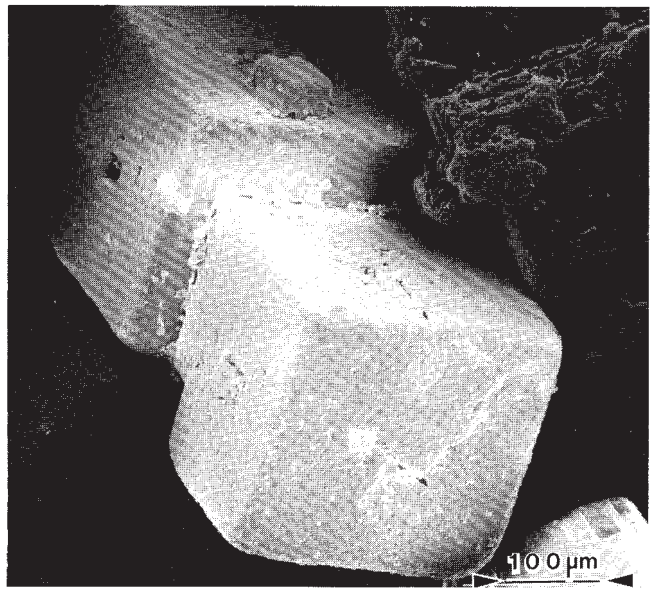
10 Typical Properties

Acidity/alkalinity pH = 6.7–7.3 (saturated aqueous solution)
Angle of repose 38° for cubic crystals
Boiling point 1413°C

SEM 1: Excipient: sodium chloride, powder; manufacturer: Mallinckrodt Speciality Chemicals Co.; magnification: 600×.



SEM 2: Excipient: sodium chloride, granular; manufacturer: Van Waters & Rogers, Inc.; magnification: 120×.



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SEM 3: Excipient: sodium chloride, granular; manufacturer: Van Waters & Rogers, Inc.; magnification: 600×.

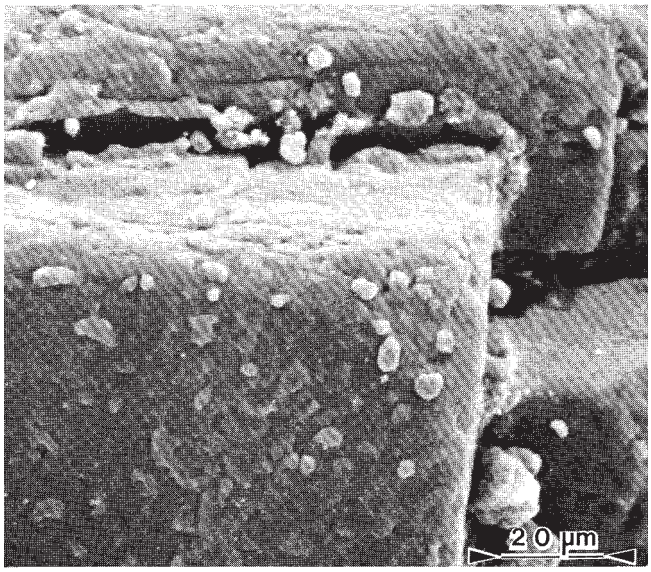

Table II: Pharmacopeial specifications for sodium chloride.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	+
Acidity or alkalinity	+	+	+
Loss on drying	⩽0.5%	⩽0.5%	⩽0.5%
Arsenic	⩽2 ppm	⩽1 ppm	⩽1 µg/g
Bromides	+	⩽100 ppm	⩽0.01%
Chloride	—	—	+
Barium	+	+	+
Nitrites	—	+	+
Aluminum	—	⩽0.2 ppm[a]	⩽0.2 µg/g[a]
Magnesium and alkaline earth metals	+	⩽100 ppm	⩽0.01%
Iodide	+	+	+
Iron	+	⩽2 ppm	⩽2 µg/g
Sulfate	+	⩽200 ppm	⩽0.02%
Ferrocyanides	+	+	+
Heavy metals	⩽3 ppm	⩽5 ppm	⩽5 ppm
Phosphate	+	⩽25 ppm	⩽0.0025%
Potassium	—	⩽500 ppm[a] [b]	⩽0.05%[a] [b]
Sterility	—	—	+
Bacterial endotoxins	—	⩽5 IU/g[b]	+
Assay (dried basis)	99.0–100.5%	99.0–100.5%	99.0–100.5%

(a) If for use in peritoneal dialysis, hemodialysis or hemofiltration solutions.
(b) If for parenteral use.

Compressibility With sodium chloride powder of less than 30 µm particle size, tablets are formed by plastic deformation; above this size, both plastic deformation and fracture occur.[1,3,4] *See also* Figure 1.

Density

2.17 g/cm^3;

1.20 g/cm^3 for saturated aqueous solution.

Density (bulk) 0.93 g/cm^3

Density (tapped) 1.09 g/cm^3

Dielectric constant 5.9 at 1 MHz

Freezing point depression *see* Table III.

Table III: Freezing point depression values of aqueous sodium chloride.

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

Hardness (Mohs) 2–2.5

Hygroscopicity Hygroscopic above 75% relative humidity.

Melting point 804°C

NIR spectra *see* Figure 2.

Osmolarity A 0.9% w/v aqueous solution is iso-osmotic with serum.

Refractive index n_D^{20} = 1.343 for a 1 M aqueous solution.

Solubility *see* Table IV.

Thermal conductivity 1.15 Wm/K at 273 K

Specific heat capacity 854 J/kg/K

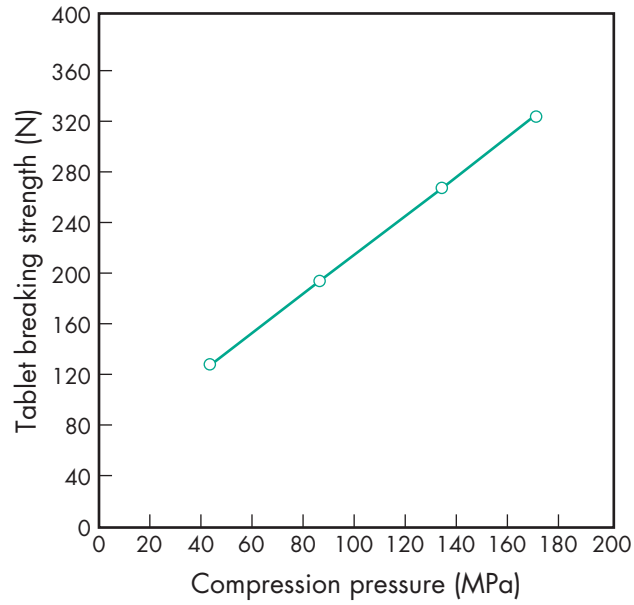

Figure 1: Compression characteristics of sodium chloride (cubic crystals).[3] Tablet diameter = 12 mm.

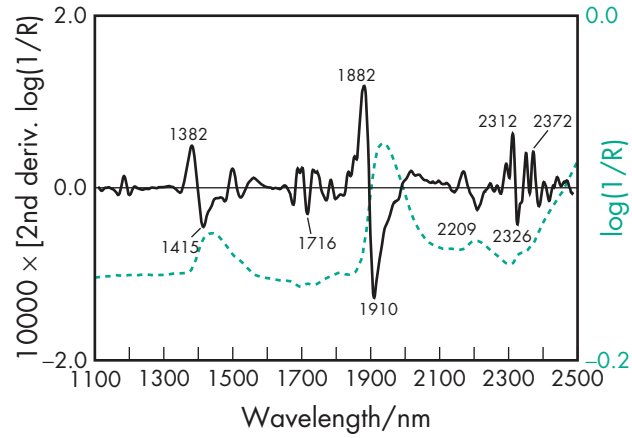

Figure 2: Near-infrared spectrum of sodium chloride measured by reflectance. Sodium chloride does not absorb in the near-infrared region; however, it will generally show some peaks due to traces of moisture (approx. 1450 nm and 1950 nm).

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Table IV: Solubility of sodium chloride.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	Slightly soluble
Ethanol (95%)	1 in 250
Glycerin	1 in 10
Water	1 in 2.8
	1 in 2.6 at 100°C

Vapor pressure

133.3 Pa at 865°C for solid;

1759.6 Pa at 20°C for a saturated aqueous solution (equivalent to 75.3% relative humidity).

Viscosity A 10% w/v solution has a viscosity of 1.19 mPa s (1.19 cP).

11 Stability and Storage Conditions

Aqueous sodium chloride solutions are stable but may cause the separation of glass particles from certain types of glass containers. Aqueous solutions may be sterilized by autoclaving or filtration. The solid material is stable and should be stored in a well-closed container, in a cool, dry place.

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

12 Incompatibilities

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

13 Method of Manufacture

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

14 Safety

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

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

LD_{50} (mouse, IP): 6.61 g/kg[25]

LD_{50} (mouse, IV): 0.65 g/kg

LD_{50} (mouse, oral): 4.0 g/kg

LD_{50} (mouse, SC): 3.0 g/kg

LD_{50} (rat, oral): 3.0 g/kg

15 Handling Precautions

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

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (injections; inhalations; nasal, ophthalmic, oral, otic, rectal, and topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Potassium chloride.

18 Comments

Sodium chloride 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.

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

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

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

A saturated solution of sodium chloride can be used as a constant-humidity solution; at 25°C, a relative humidity of 75% is produced. A specification for sodium chloride is contained in the Food Chemicals Codex (FCC).[26]

The EINECS number for sodium chloride is 231-598-3. The PubChem Compound ID (CID) for sodium chloride is 5234.

19 Specific References

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21 Author

JS Maximilien.

22 Date of Revision

3 February 2009.

Sodium Citrate Dihydrate

1 Nonproprietary Names

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

2 Synonyms

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

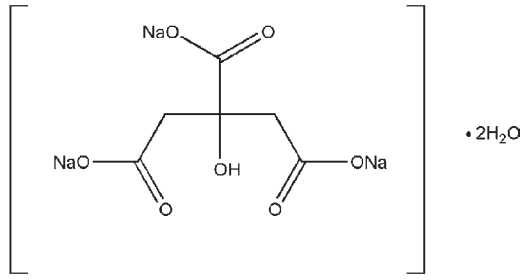
3 Chemical Name and CAS Registry Number

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; emulsifying agent; sequestering 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 used in food products, primarily to adjust the pH of solutions. It is also used as a sequestering agent. The anhydrous material is used in effervescent tablet formulations.[1] Sodium citrate is additionally used as a blood anticoagulant either alone or in combination with other citrates such as disodium hydrogen 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.

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
Sequestering 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 32 states that sodium citrate may be either the dihydrate or anhydrous material.

9 Pharmacopeial Specifications

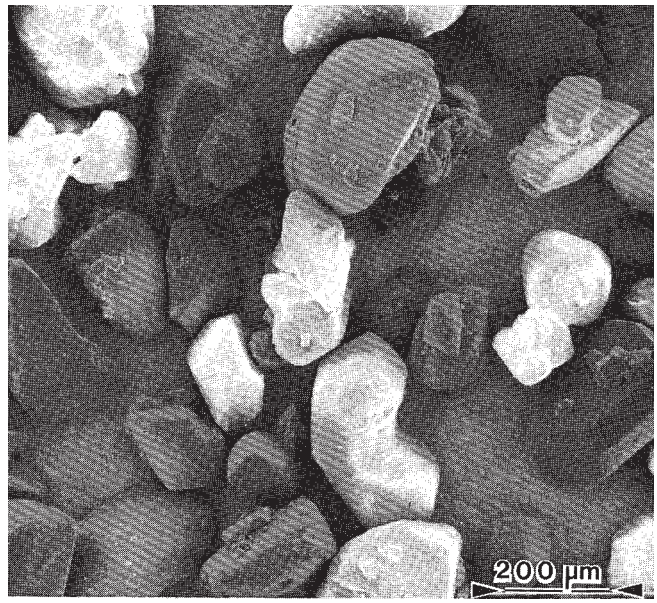
See Table II.

Table II: Pharmacopeial specifications for sodium citrate dihydrate.

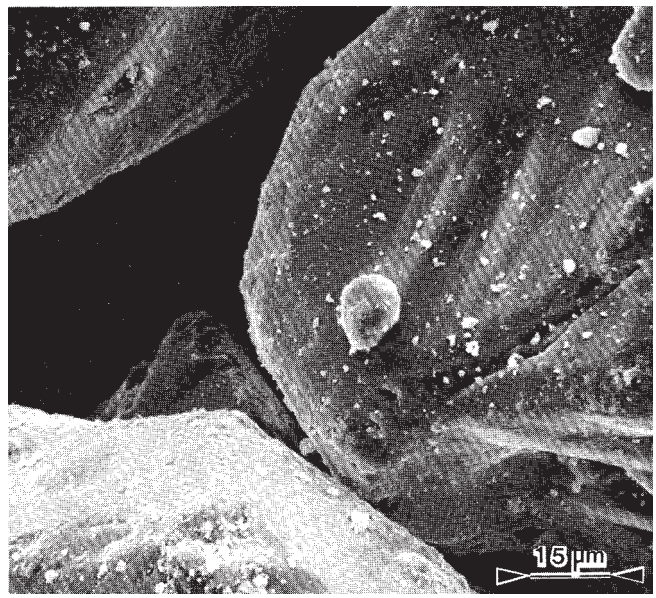
Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	—	+	—
pH	7.5–8.5	—	—
Appearance of solution	+	+	—
Acidity or alkalinity	—	+	+
Loss on drying	10.0–13.0%	—	—
Water	—	11.0–13.0%	10.0–13.0%
Oxalate	+	⩽300 ppm	—
Sulfate	⩽0.048%	⩽150 ppm	—
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Arsenic	⩽2 ppm	—	—
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.

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



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



10 Typical Properties

Acidity/alkalinity pH = 7.0–9.0 (5% w/v aqueous solution)
Density (bulk) 1.12 g/cm^3
Density (tapped) 0.99 g/cm^3
Density (true) 1.19 g/cm^3
Melting point Converts to the anhydrous form at 150°C.
NIR spectra *see* Figure 1.
Osmolarity A 3.02% w/v aqueous solution is iso-osmotic with serum.
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%).

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.

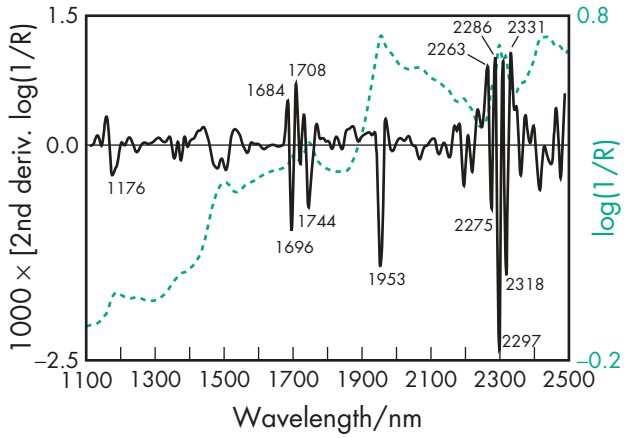


Figure 1: Near-infrared spectrum of sodium citrate dihydrate measured by reflectance.

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.

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 List of Acceptable Non-medicinal Ingredients.

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

LD_{50} (mouse, IP): 1.36 g/kg[3]
LD_{50} (mouse, IV): 0.17 g/kg
LD_{50} (rabbit, IV): 0.45 g/kg
LD_{50} (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.

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

19 Specific References

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20 General References

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21 Author

GE Amidon.

22 Date of Revision

6 February 2009.

Sodium Cyclamate

1 Nonproprietary Names

BP: Sodium Cyclamate

PhEur: Sodium Cyclamate

2 Synonyms

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

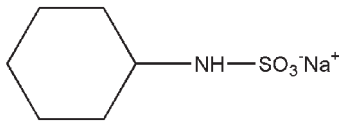
3 Chemical Name and CAS Registry Number

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, foods, beverages, and table-top sweeteners. 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. Sodium cyclamate enhances flavor systems and can be used to mask some unpleasant taste characteristics. In most applications, sodium cyclamate is used in combination with saccharin, often in a ratio of 10 : 1.[1]

8 Description

Sodium cyclamate occurs as white, odorless or almost odorless crystals, or as a crystalline powder with an intensely sweet taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium cyclamate.

Test	PhEur 6.0
Identification	+
Characters	+
Appearance of solution	+
pH (10% w/v aqueous solution)	5.5–7.5
Absorbance at 270 nm	≤0.10
Sulfamic acid	+
Aniline	≤1 ppm
Cyclohexylamine	≤10 ppm
Dicyclohexylamine	≤1 ppm
Sulfates	≤0.1%
Heavy metals	≤10 ppm
Loss on drying	≤1.0%
Assay (dried basis)	98.5–101.0%

10 Typical Properties

Acidity/alkalinity pH = 5.5–7.5 for a 10% w/v aqueous solution.

NIR spectra *see* Figure 1.

Solubility *see* Table II.

Table II: Solubility of sodium cyclamate.

Solvent	Solubility at 20°C unless otherwise stated
Benzene	Practically insoluble
Chloroform	Practically insoluble
Ethanol (95%)	1 in 250
Ether	Practically insoluble
Propylene glycol	1 in 25
Water	1 in 5 1 in 2 at 45°C

11 Stability and Storage Conditions

Sodium cyclamate is hydrolyzed by sulfuric acid and cyclohexylamine at a very slow rate that is proportional to the hydrogen ion concentration. Therefore, for all practical considerations, it can be regarded as stable. Solutions are also stable to heat, light, and air over a wide pH range.

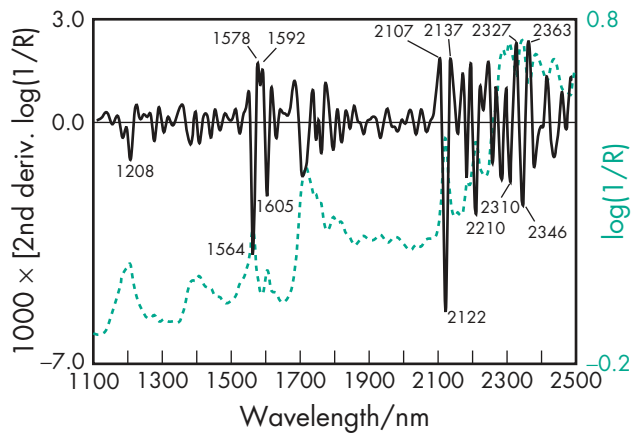


Figure 1: Near-infrared spectrum of sodium cyclamate measured by reflectance.

Samples of tablets containing sodium cyclamate and saccharin have shown no loss in sweetening power following storage for up to 20 years.

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

12 Incompatibilities

—

13 Method of Manufacture

Cyclamates are prepared by the sulfonation of cyclohexylamine in the presence of a base. Commercially, the sulfonation can involve sulfamic acid, a sulfate salt, or sulfur trioxide. Tertiary bases such as triethylamine or trimethylamine may be used as the condensing agent. The amine salts of cyclamate that are produced are converted to the sodium, calcium, potassium, or magnesium salt by treatment with the appropriate metal oxide.

14 Safety

There has been considerable controversy concerning the safety of cyclamate following the FDA decision in 1970 to ban its use in the USA.[2–4] This decision resulted from a feeding study in rats that suggested that cyclamate could cause an unusual form of bladder cancer. However, that study has been criticized because it involved very high doses of cyclamate administered with saccharin, which has itself been the subject of controversy concerning its safety; *see* Saccharin. Although excreted almost entirely unchanged in the urine, a potentially harmful metabolite of sodium cyclamate, cyclohexylamine, has been detected in humans.[5] In addition, there is evidence to suggest cyclamate is metabolized to cyclohexylamine by the microflora in the large intestine of some individuals (approximately 25% of the population with higher precedence in Japanese than Europeans or North Americans). Cyclohexylamine, following absorption, is metabolized to an extent of 1-2% to cyclohexanol and cyclohexane-1,2-diol. Established no-observed-effect level (NOEL) and acceptable daily intake (ADI) values are based on cyclohexylamine levels of high cyclamate converters.[6,7]

Extensive long-term animal feeding studies and epidemiological studies in humans have failed to show any evidence that cyclamate is carcinogenic or mutagenic.[8,9] As a result, sodium cyclamate is now accepted in many countries for use in foods and pharmaceutical formulations. *See also* Section 16.

Few adverse reactions to cyclamate have been reported, although its use has been associated with instances of photosensitive dermatitis.[10]

The WHO has set an estimated acceptable daily intake for sodium and calcium cyclamate, expressed as cyclamic acid, at up to 11 mg/kg body-weight.[11] In Europe, a temporary acceptable daily intake for sodium and calcium cyclamate, expressed as cyclamic acid, has been set at up to 1.5 mg/kg body-weight.

LD_{50} (mouse, IP): 1.15 g/kg[12]
LD_{50} (mouse, IV): 4.8 g/kg
LD_{50} (mouse, oral): 17 g/kg
LD_{50} (rat, IP): 1.35 g/kg
LD_{50} (rat, IV): 3.5 g/kg
LD_{50} (rat, oral): 15.25 g/kg

15 Handling Precautions

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

16 Regulatory Status

The use of cyclamates as artificial sweetners in food, soft drinks, and artificial sweetening tablets was at one time prohibited in the UK and some other countries owing to concern about the metabolite cyclohexylamine. However, this is no longer the case, and cyclamates are now permitted for use as a food additive in Europe.

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

17 Related Substances

Alitame; calcium cyclamate; cyclamic acid.

Calcium cyclamate

Empirical formula $C_{12}H_{24}CaN_2O_6S_2{\cdot}2H_2O$
Molecular weight 432.57
CAS number

[5897-16-5] for the dihydrate;

[139-06-0] for the anhydrous form.

Synonyms Calcium *N*-cyclohexylsulfamate dihydrate; *Cyclan*; cyclohexanesulfamic acid calcium salt; cyclohexylsulfamic acid calcium salt; E952; *Sucaryl calcium*.
Appearance White, odorless or almost odorless crystals or a crystalline powder with an intensely sweet taste.
Acidity/alkalinity pH = 5.5–7.5 for a 10% w/v aqueous solution.
Solubility Freely soluble in water; practically insoluble in benzene, chloroform, ethanol (95%), and ether.

Cyclamic acid

Empirical formula $C_6H_{13}NO_3S$
Molecular weight 179.23
CAS number [100-88-9]
Synonyms Cyclamate; cyclohexanesulfamic acid; *N*-cyclohexylsulfamic acid; E952; hexamic acid; *Sucaryl*.
Appearance White, odorless or almost odorless crystals or a crystalline powder with an intensely sweet taste.
Melting point 169–170°C
Solubility Slightly soluble in water.

18 Comments

The perceived intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace the bulk, textural, or preservative characteristics of sucrose if sucrose is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g. sodium cyclamate with saccharin sodium or acesulfame potassium.

Sodium cyclamate has also been used to increase the solubility of neohesperidin dihydrochalcone in sweetener blends.[13]

The PubChem Compound ID (CID) for sodium cyclamate is 23665706.

19 Specific References

1 Bernryma GH *et al*. A case for safety of cyclamate and cyclamate-saccharin combinations. *Am J Clin Nutr* 1968; **21**(6): 673–687.
2 Nabors LO, Miller WT. Cyclamate: a toxicological review. *Commen Toxicol* 1989; **3**(4): 307–315.
3 Lecos C. The sweet and sour history of saccharin, cyclamate and aspartame. *FDA Consumer* 1981; **15**(7): 8–11.
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12 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3243.
13 Benavente-Garcia O *et al*. Improved water solubility of neohesperidin dihydrochalcone in sweetener blends. *J Agric Food Chem* 2001; **49**(1): 189–191.

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Anonymous. Saccharin is safe. *Chem Br* 2001; **37**(4): 18.
Schiffman SS *et al*. Effect of temperature, pH, and ions on sweet taste. *Physiol Behav* 2000; **68**(4): 469–481.

21 Author

PL Goggin.

22 Date of Revision

12 December 2008.

Sodium Formaldehyde Sulfoxylate

1 Nonproprietary Names

USP-NF: Sodium Formaldehyde Sulfoxylate

2 Synonyms

Formaldehyde hydrosulfite; formaldehyde sodium sulfoxylate; formaldehydesulfoxylic acid sodium salt; methanesulfinic acid, hydroxy-, monosodium salt; monosodium hydroxymethane sulfinate; *Rongalite*; sodium hydroxymethane sulfinate; sodium hydroxymethylsulfinate; sodium methanalsulfoxylate; sodium sulfinomethanolate.

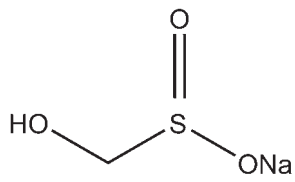
3 Chemical Name and CAS Registry Number

Sodium formaldehyde sulfoxylate [149-44-0]
Sodium formaldehyde sulfoxylate dihydrate [6035-47-8]

4 Empirical Formula and Molecular Weight

CH_3NaO_3S 118.09
$CH_3NaO_3S{\cdot}2H_2O$ 154.11

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium formaldehyde sulfoxylate is a water-soluble antioxidant and is generally used as the dihydrate. It is used in the formulation of injection products at a level of up to 0.1% w/v in the final preparation administered to the patient.

8 Description

When freshly prepared, sodium formaldehyde sulfoxylate occurs as white, odorless crystals, which quickly develop a characteristic garlic odor on standing.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium formaldehyde sulfoxylate.

Test	USP32–NF27
Identification	+
Clarity and color of solution	+
Alkalinity	+
pH (1 in 50 solution)	9.5–10.5
Loss on drying	⩽27.0%
Sulfide	+
Iron	+
Sodium sulfite	⩽5.0%
Assay (as sulfur dioxide)	45.5–54.5%

Note: USP32–NF27 also states that sodium formaldehyde sulfoxylate may contain a suitable stabilizer such as sodium carbonate.

10 Typical Properties

Acidity/alkalinity pH = 9.5–10.5 (2% w/v aqueous solution)
Melting point 64–68°C (dihydrate)
Solubility Freely soluble in water; slightly soluble in ethanol, chloroform, ether and benzene.

11 Stability and Storage Conditions

Store in well-closed, light-resistant containers at controlled room temperature (15–30°C).

12 Incompatibilities

Sodium formaldehyde sulfoxylate is incompatible with strong oxidizing agents; it is decomposed by dilute acid.

13 Method of Manufacture

Sodium formaldehyde sulfoxylate is manufactured from sodium dithionate and formaldehyde in water.

14 Safety

The toxicological properties of sodium formaldehyde sulfoxylate have not been fully investigated. However, it is used in the formulation of injection products at a level to 0.1% w/v in the final preparation administered to the patient.

Sodium formaldehyde sulfoxylate is moderately toxic by ingestion, and when heated to decomposition it emits toxic fumes of sulfur dioxide and sodium oxide.[1]

LD_{50} (mouse, oral): 4 g/kg[1,2]
LD_{50} (rat, IP): >2 g/kg[2]
LD_{50} (rat, oral): >2 g/kg[2]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. May cause irritation of the eyes, skin, respiratory tract and digestive tract; the use of eye protection, a respirator and gloves is strongly recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (parenteral products up to 0.1% via the IM, IV, and SC routes). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Zinc formaldehyde sulfoxylate.

Zinc formaldehyde sulfoxylate
Empirical formula $C_2H_6O_6S_2Zn$
Molecular weight 256.5
CAS number [24887-06-7]

Comments Used as an additive in polymers and textiles. The EINECS number is 246-515-6.

18 Comments

Sodium formaldehyde sulfoxylate has been investigated as an antidote to mercury poisoning, but is considered less effective than dimercaprol (British anti-lewisite (BAL)) and other treatments.[3,4] It is also used as an industrial bleach. It is used in chemical synthesis as a nucleophilic agent in the preparation of sulfones. The empirical formula and molecular weight are also given as CH_4O_3SNa and 119.1, respectively.[1]

The EINECS number for sodium formaldehyde sulfoxylate is 205-739-4. The PubChem Compound ID for sodium formaldehyde sulfoxylate is 23725019.

19 Specific References

1 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 1815.
2 Sigma-Aldrich. Material safety data sheet: Sodium formaldehyde sulfoxylate, Australia, 2004.
3 Stocken LA. British anti-lewisite as an antidote for acute mercury poisoning. *Biochem J* 1947; **41**: 358–360.
4 Lehotzky K. Protection by spironolactone and different antidotes against acute organic mercury poisoning of rats. *Int Arch Occup Environ Health* 1974; **33**: 329–334.

20 General References

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21 Author

RC Moreton.

22 Date of Revision

3 March 2009.

S

Sodium Hyaluronate

1 Nonproprietary Names

BP: Sodium Hyaluronate
PhEur: Sodium Hyaluronate

2 Synonyms

Hyaluronan; hyaluronate sodium; natrii hyaluronas; *RITA HA C-1-C*.

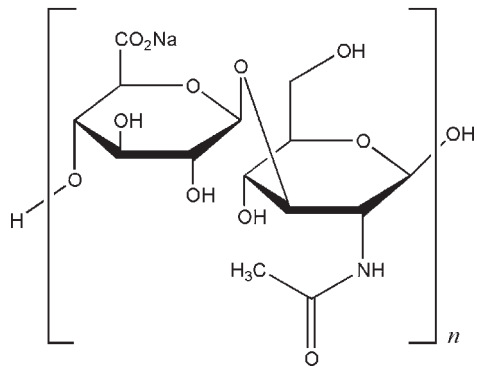
3 Chemical Name and CAS Registry Number

Sodium hyaluronate [9067-32-7]

4 Empirical Formula and Molecular Weight

$(C_{14}H_{20}NO_{11}Na)_n$ $(401.3)_n$

5 Structural Formula



6 Functional Category

Humectant; lubricant; sustained-release agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium hyaluronate is the predominant form of hyaluronic acid at physiological pH. The name hyaluronan is used when the polysaccharide is mentioned in general terms, and in the literature the terms hyaluronic acid and sodium hyaluronate are used interchangeably.

Hyaluronan is used therapeutically to treat osteoarthritis in the knee, and is an effective treatment for arthritic pain.[1] Crosslinked hyaluronan gels are used as drug delivery systems.[2]

Hyaluronan is the most common negatively charged glycosaminoglycan in the human vitreous humor, and is known to interact with polymeric and liposomal DNA complexes,[3] where hyaluronan solutions have been shown to decrease the cellular uptake of complexes.[4] This is useful for enhancing the availability and retention time of drugs administered to the eye. It is immunoneutral, which makes it useful for the attachment of biomaterials for use in tissue engineering and drug delivery systems;[5] it also has important applications in the fields of vascosurgery and vascosupplementation.[6]

8 Description

The PhEur 6.3 describes sodium hyaluronate as the sodium salt of hyaluronic acid, a glycosaminoglycan consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide units.

Sodium hyaluronate occurs as white to off-white powder or granules. It is very hygroscopic.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specification for sodium hyaluronate.

Test	PhEur 6.3
Characters	+
Identification	+
Appearance of solution	+
pH	5.0–8.5
Intrinsic viscosity	+
Sulfated glycosaminoglycans	⩽1%
Nucleic acids	⩽0.5
Protein	⩽0.3%[a]
Chlorides	⩽0.5%
Iron	⩽80 ppm
Heavy metals	⩽20 ppm[b]
Loss on drying	⩽20.0%
Microbial contamination	⩽10^2 cfu/g
Bacterial endotoxins	<0.5 IU/mg[c]
Assay	95.0–105.0%

(a) <0.1% for parenteral dosage forms.
(b) ⩽10 ppm for parenteral preparations.
(c) ⩽0.5 IU/mg for parenteral dosage forms.

10 Typical Properties

Acidity/alkalinity pH = 5.0–8.5 (0.5% w/v aqueous solution)

Solubility Soluble in water, although speed of dissolution depends upon molecular weight (higher molecular weights are slower to dissolve, although this process can be increased by gentle agitation). Slightly soluble in mixtures of organic solvents with water.[7]

11 Stability and Storage Conditions

Sodium hyaluronate should be stored in a cool, dry place in tightly sealed containers. The powder is stable for 3 years if stored in unopened containers.

12 Incompatibilities

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13 Method of Manufacture

Sodium hyaluronate occurs naturally in vitreous humor, serum, chicken combs, shark skin, and whale cartilage; it is usually extracted and purified from chicken combs. It may also be manufactured by fermentation of selected *Streptococcus zooepidemicus* bacterial strains; sodium hyaluronate is removed from the fermentation medium by filtration and purified by ultrafiltration. It is then precipitated with an organic solvent and dried.

14 Safety

Sodium hyaluronate is used in cosmetics and in topical, parenteral, and ophthalmic pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material. Sodium hyaluronate has been reported to be an experimental teratogen.[8]

LD_{50} (mouse, IP): 1.5 g/kg[8]
LD_{50} (rabbit, IP): 1.82 g/kg
LD_{50} (rat, IP): 1.77 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, sodium hyaluronate emits toxic fumes of Na_2O.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (topical gel preparation).

17 Related Substances

Hyaluronic acid.

Hyaluronic acid

Molecular weight Hyaluronic acid molecules have a molecular weight of 300–2000 kDa as the number of repeating disaccharide units in each molecule is variable. In its natural form, hyaluronic acid exists as a high-molecular-weight polymer of 10^6–10^7 Da.

CAS number [9067-32-7]

Appearance Hyaluronic acid appears as a white to off-white powder or granules.

Comments Hyaluronic acid is used as an adjuvant for ophthalmic drug delivery,[9] and has been found to enhance the absorption of drugs and proteins via mucosal tissue.[10] It has also been used experimentally in controlled-release films that are suitable for application to surgical sites for the prevention of adhesion formation,[11] and in matrix formulations used in gene delivery systems.[12] The EINECS number for hyaluronic acid is 232-678-0.

18 Comments

Microspheres prepared from hyaluronan esters have been evaluated for the vaginal administration of calcitonin in the treatment of postmenopausal osteoporosis.[13] Microspheres prepared from hyaluronan esters have also been used experimentally as delivery devices for nerve growth factors,[14] and as a nasal delivery system for insulin.[15]

An *N*-(2-hydroxypropyl)methacrylamide (HPMA)–hyaluronan polymeric drug delivery system has been used for the targeted delivery of doxorubicin to cancer cells. This copolymer exhibited increased toxicity due to hyaluronan receptor-mediated uptake of the macromolecular drug.[16]

The EINECS number for sodium hyaluronate is232-678-0. The PubChem Compound ID (CID) for sodium hyaluronate is 3084049.

19 Specific References

1 Castellacci E, Polieri T. Antalgesic effect and clinical tolerability of hyaluronic acid in patients with degenerative diseases of knee cartilage: an outpatient treatment survey. *Drugs Exp Clin Res* 2004; **30**(2): 67–73.
2 Dehayza P, Cheng L. Sodium hyaluronate microspheres. US Patent No. 2,004,127,459; 2004.
3 Pitkänen L *et al*. Vitreous is a barrier in nonviral gene transfer by cationic lipids and polymers. *Pharm Res* 2003; **20**(4): 576–583.
4 Ruponen M *et al*. Interactions of polymeric and liposomal gene delivery systems with extracellular glycosaminoglycans: physicochemical and transfection studies. *Biochim Biophys Acta* 1999; **1415**: 331–341.
5 Vercruysse KP, Prestwich GD. Hyaluronate derivatives in drug delivery. *Crit Rev Ther Carrier Syst* 1998; **15**: 513–555.
6 Balazs EA. *et al* Clinical uses of hyaluronan. Evered D, Whelan J, eds. *The Biology of Hyaluronan*. Chichester: Wiley, 1989; 265–280.
7 Contipro C a.s. *Sodium hyaluronate*. http://www.contipro.cz (accessed 7 January 2009).
8 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 1970.
9 Saettone MF *et al*. Mucoadhesive ophthalmic vehicles: evaluation of polymeric low-viscosity formulations. *J Ocul Pharm* 1994; **10**: 83–92.
10 Cho KY *et al*. Release of ciprofloxacin from polymer-graft-hyaluronic acid hydrogels *in vitro*. *Int J Pharm* 2003; **260**(1): 83–91.
11 Jackson JK *et al*. Paclitaxel-loaded crosslinked hyaluronic acid films for the prevention of postsurgical adhesions. *Pharm Res* 2002; **19**(4): 411–417.
12 Kim A *et al*. Characterization of DNA-hyaluronan matrix for sustained gene transfer. *J Control Release* 2003; **90**(1): 81–75.
13 Rochira M *et al*. Novel vaginal delivery systems for calcitonin II. Preparation and characterisation of HYAFF microspheres containing calcitonin. *Int J Pharm* 1996; **144**: 19–26.
14 Ghezzo E *et al*. Hyaluronan derivative microspheres as NGF delivery devices: preparation methods and *in vitro* release characterization. *Int J Pharm* 1992; **29**: 133–141.
15 Illum L *et al*. Hyaluronic acid ester microspheres as a nasal delivery system for insulin. *J Control Release* 1994; **29**: 133–141.
16 Luo Y *et al*. Targetted delivery of doxorubicin by HPMA copolymer–hyaluronan bioconjugates. *Pharm Res* 2002; **19**(4): 396–402.

20 General References

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21 Authors

ME Quinn, PJ Sheskey.

22 Date of Revision

7 January 2009.

Sodium Hydroxide

1 Nonproprietary Names

BP: Sodium Hydroxide
JP: Sodium Hydroxide
PhEur: Sodium Hydroxide
USP-NF: Sodium Hydroxide

S

2 Synonyms

Caustic soda; E524; lye; natrii hydroxidum; soda lye; sodium hydrate.

3 Chemical Name and CAS Registry Number

Sodium hydroxide [1310-73-2]

4 Empirical Formula and Molecular Weight

NaOH 40.00

5 Structural Formula

See Section 4.

6 Functional Category

Alkalizing agent; buffering agent.

7 Applications in Pharmaceutical Formulation or Technology

Sodium hydroxide is widely used in pharmaceutical formulations to adjust the pH of solutions.[1] It can also be used to react with weak acids to form salts.

8 Description

Sodium hydroxide occurs as a white or nearly white fused mass. It is available in small pellets, flakes, sticks, and other shapes or forms. It is hard and brittle and shows a crystalline fracture. Sodium hydroxide is very deliquescent and on exposure to air it rapidly absorbs carbon dioxide and water.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium hydroxide.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
Insoluble substances and organic matter	—	—	+
Sodium carbonate	⩽2.0%	⩽2.0%	—
Sulfates	—	⩽50 ppm	—
Chlorides	⩽0.05%	⩽50 ppm	—
Iron	—	⩽10 ppm	—
Mercury	+	—	—
Heavy metals	⩽30 ppm	⩽20 ppm	⩽0.003%
Potassium	+	—	+
Assay (total alkali calculated as NaOH)	⩾95.0%	97.0–100.5%	95.0–100.5%

10 Typical Properties

Acidity/alkalinity

pH ≈ 12 (0.05% w/w aqueous solution);

pH ≈ 13 (0.5% w/w aqueous solution);

pH ≈ 14 (5% w/w aqueous solution).

Melting point 318°C

Solubility *see* Table II.

Table II: Solubility of sodium hydroxide.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	1 in 7.2
Ether	Practically insoluble
Glycerin	Soluble
Methanol	1 in 4.2
Water	1 in 0.9
	1 in 0.3 at 100°C

11 Stability and Storage Conditions

Sodium hydroxide should be stored in an airtight nonmetallic container in a cool, dry place. When exposed to air, sodium hydroxide rapidly absorbs moisture and liquefies, but subsequently becomes solid again owing to absorption of carbon dioxide and formation of sodium carbonate.

12 Incompatibilities

Sodium hydroxide is a strong base and is incompatible with any compound that readily undergoes hydrolysis or oxidation. It will react with acids, esters, and ethers, especially in aqueous solution.

13 Method of Manufacture

Sodium hydroxide is manufactured by electrolysis of brine using inert electrodes. Chlorine is evolved as a gas at the anode and hydrogen is evolved as a gas at the cathode. The removal of chloride and hydrogen ions leaves sodium and hydroxide ions in solution. The solution is dried to produce the solid sodium hydroxide.

A second method uses the Kellner–Solvay cell. Saturated sodium chloride solution is electrolyzed between a carbon anode and a flowing mercury cathode. In this case the sodium is produced at the cathode rather than the hydrogen because of the readiness of sodium to dissolve in the mercury. The sodium–mercury amalgam is then exposed to water and a sodium hydroxide solution is produced.

14 Safety

Sodium hydroxide is widely used in the pharmaceutical and food industries and is generally regarded as a nontoxic material at low concentrations. At high concentrations it is a corrosive irritant to the skin, eyes, and mucous membranes.

LD_{50} (mouse, IP): 0.04 g/kg[2]

LD_{50} (rabbit, oral): 0.5 g/kg

15 Handling Precautions

Observe normal handling precautions appropriate to the quantity and concentration of material handled. Gloves, eye protection, a respirator, and other protective clothing should be worn.

Sodium hydroxide is a corrosive irritant to the skin, eyes, and mucous membranes. The solid and solutions cause burns, often with deep ulceration. It is moderately toxic on ingestion and harmful on inhalation.

In the UK, the workplace exposure limit for sodium hydroxide has been set at 2 mg/m^3 short-term.[3]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (dental preparations; injections; inhalations; nasal, ophthalmic, oral, otic, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Potassium hydroxide.

18 Comments

Sodium hydroxide is most commonly used in solutions of fixed concentration. Sodium hydroxide has some antibacterial and antiviral properties and is used as a disinfectant in some applications.[4–6]

A specification for sodium hydroxide is contained in the Food Chemicals Codex (FCC).[7]

The EINECS number for sodium hydroxide is 215-185-5. The PubChem Compound ID (CID) for sodium hydroxide is 14798.

19 Specific References

1 Zhan X *et al*. Improved stability of 25% vitamin C parenteral formulation. *Int J Pharm* 1998; **173**: 43–49.

2 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3254–3255.

3 Health and Safety Executive. *EH40/2005: Workplace Exposure Limits*. Sudbury: HSE Books, 2005 (updated 2007). http://www.hse.gov.uk/coshh/table1.pdf (accessed 5 February 2009).

4 Brown P *et al*. Sodium hydroxide decontamination of Creutzfeldt–Jakob disease virus. *N Engl J Med* 1984; **320**: 727.

5 Gasser G. Creutzfeldt–Jakob disease [letter]. *Br Med J* 1990; **300**: 1523.

6 Perkowski CA. Operational aspects of bioreactor contamination control. *J Parenter Sci Technol* 1990; **44**: 113–117.

7 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 888.

20 General References

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21 Author

AH Kibbe.

22 Date of Revision

5 February 2009.

Sodium Lactate

1 Nonproprietary Names

BP: Sodium Lactate Solution
PhEur: Sodium Lactate Solution
USP: Sodium Lactate Solution

2 Synonyms

E325; 2-hydroxypropanoic acid monosodium salt; *Lacolin*; lactic acid monosodium salt; lactic acid sodium salt; natrii lactatis solutio; *Patlac*; *Purasal*; *Ritalac NAL*; sodium α-hydroxypropionate.

3 Chemical Name and CAS Registry Number

Sodium lactate [72-17-3]

4 Empirical Formula and Molecular Weight

$C_3H_5NaO_3$ 112.06

5 Structural Formula

The PhEur 6.0 and USP 32 describe sodium lactate solution as a mixture of the enantiomers of sodium 2-hydroxypropanoate in approximately equal proportions.

6 Functional Category

Antimicrobial preservative; buffering agent; emulsifying agent; flavoring agent; humectant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium lactate is widely used in cosmetics,[1,2] food products and pharmaceutical applications including parenteral and topical formulations.

Therapeutically, sodium lactate is used in infusions as a component of Ringer-lactate solution; as an alternative for sodium hydrogencarbonate in light acidosis; as a rehydrating agent; and as a carrier for electrolyte concentrates or medicines in perfusion/infusion solutions.

8 Description

Sodium lactate occurs as a clear, colorless, slightly syrupy liquid. It is odorless, or has a slight odor with a characteristic saline taste. It is hygroscopic.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium lactate.

Test	PhEur 6.0	USP 32
Characters	+	–
Identification	+	+
Appearance of solution	+	–
pH	6.5–9.0	5.0–9.0
Reducing sugars and sucrose	+	+
Methanol	⩽50 ppm[a]	+
Chlorides	⩽50 ppm	⩽0.05%
Oxalates and phosphates	+	+
Sulfates	⩽100 ppm	+
Aluminum	⩽0.1 ppm[a]	–
Barium	+	–
Iron	⩽10 ppm	–
Heavy metals	⩽10 ppm	⩽0.001%
Bacterial endotoxins	+[b]	–
Assay	96.0–104.0%	98.0–102.0%

(a) If intended for use in the manufacture of parenteral dosage forms, hemodialysis, or hemofiltration solutions.
(b) If intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

10 Typical Properties

Acidity/alkalinity pH = 7 for an aqueous solution.
Boiling point 112°C
Hygroscopicity Very hygroscopic.
Melting point 17°C with decomposition at 140°C.
Solubility Miscible with ethanol (95%), and with water.
Specific gravity 1.31–1.34

11 Stability and Storage Conditions

Sodium lactate should be stored in a well-closed container in a cool, dry, place. Sodium lactate is combustible and decomposes upon heating.

12 Incompatibilities

See Lactic Acid.

13 Method of Manufacture

See Lactic Acid.

14 Safety

Sodium lactate occurs naturally in the body and is involved in physiological processes. It is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient. Low concentrations are well tolerated by skin and eye mucosa, although higher concentrations should be avoided.

LD_{50} (rat, IP): 2 g/kg[3]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium lactate may cause eye irritation. When heated to decomposition, sodium lactate emits toxic fumes of Na_2O.[3]

16 Regulatory Status

GRAS listed (not for infant formulas). Included in the FDA Inactive Ingredient Database (epidural, IM, IV, and SC injections; oral suspensions; topical gels and solutions). Included in nonparenteral