

Handbook of Pharmaceutical Excipients

Sixth edition

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

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Pharmaceutical Press



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SIXTH EDITION

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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; tonic 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.

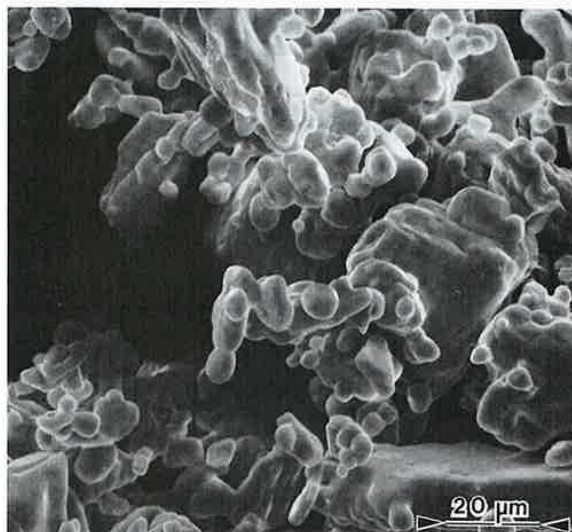
10 Typical Properties

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×.



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

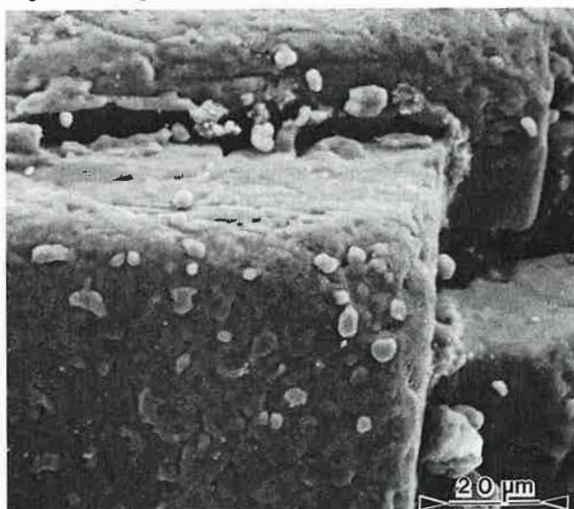


Table II: Pharmacopeial specifications for sodium chloride.

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/cm³;

1.20 g/cm³ for saturated aqueous solution.

Density (bulk) 0.93 g/cm³

Density (tapped) 1.09 g/cm³

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 W/m/K at 273 K

Specific heat capacity 854 J/kg/K

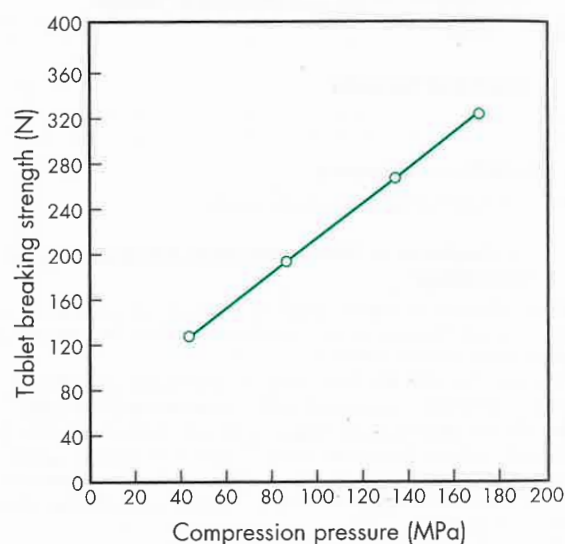


Figure 1: Compression characteristics of sodium chloride (cubic crystals).⁽³⁾ Tablet diameter = 12 mm.

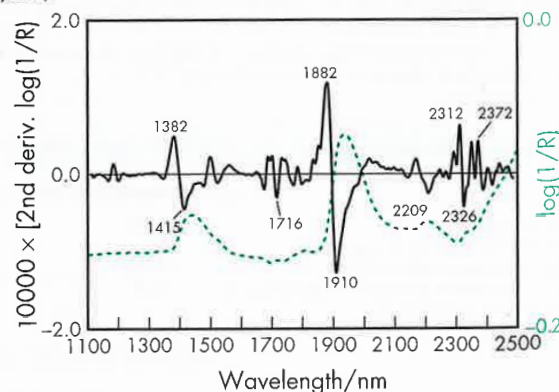


Figure 2: Near-infrared spectrum of sodium chloride measured by reflectance. Sodium chloride does not absorb in the near-infrared region; however, it will generally show some peaks due to traces of moisture (approx. 1450 nm and 1950 nm).

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.

LD₅₀ (mouse, IP): 6.61 g/kg⁽²⁵⁾

LD₅₀ (mouse, IV): 0.65 g/kg

LD₅₀ (mouse, oral): 4.0 g/kg

LD₅₀ (mouse, SC): 3.0 g/kg

LD₅₀ (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.

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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.

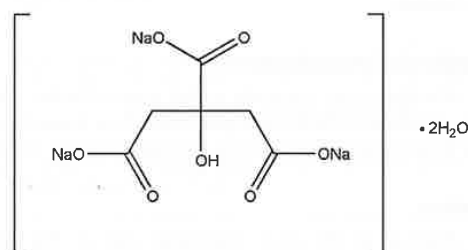
3 Chemical Name and CAS Registry Number

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.

- 19 Deziel-Evans LM, Hussey WJ. Possible sulfite sensitivity with gentamicin infusion. *DICP Ann Pharmacother* 1989; 23: 1032-1033.
- 20 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.
- 21 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3261.
- 22 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).
- 23 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 896.
- 20 General References**
- Halsby SF, Mattocks AM. Absorption of sodium bisulfite from peritoneal dialysis solutions. *J Pharm Sci* 1965; 54: 52-55.
- Wilkins JW *et al.* Toxicity of intraperitoneal bisulfite. *Clin Pharmacol Ther* 1968; 9: 328-332.
- 21 Authors**
- MA Kabir, JP Reo.
- 22 Date of Revision**
- 5 February 2009.

Sodium Phosphate, Dibasic

1 Nonproprietary Names

BP: Anhydrous Disodium Hydrogen Phosphate
Disodium Hydrogen Phosphate Dihydrate
Disodium Hydrogen Phosphate Dodecahydrate

JP: Dibasic Sodium Phosphate Hydrate

PhEur: Disodium Phosphate, Anhydrous
Disodium Phosphate Dihydrate
Disodium Phosphate Dodecahydrate

USP: Dibasic Sodium Phosphate

Note that the BP 2009 and PhEur contain three separate monographs for the anhydrous (PhEur 6.3), the dihydrate (PhEur 6.0), and the dodecahydrate (PhEur 6.1); the JP XV contains one monograph for the dodecahydrate; and the USP 32 contains one monograph that includes the anhydrous, the monohydrate, the dihydrate, the heptahydrate, and the dodecahydrate. *See also* Section 8.

2 Synonyms

Dinatrii phosphas anhydricus; dinatrii phosphas dihydricus; dinatrii phosphas dodecahydricus; disodium hydrogen phosphate; disodium phosphate; E339; phosphoric acid, disodium salt; secondary sodium phosphate; sodium orthophosphate.

3 Chemical Name and CAS Registry Number

Anhydrous dibasic sodium phosphate [7558-79-4]
Dibasic sodium phosphate dihydrate [10028-24-7]
Dibasic sodium phosphate dodecahydrate [10039-32-4]
Dibasic sodium phosphate heptahydrate [7782-85-6]
Dibasic sodium phosphate hydrate [10140-65-5]
Dibasic sodium phosphate monohydrate [118830-14-1]

4 Empirical Formula and Molecular Weight

Na ₂ HPO ₄	141.96
Na ₂ HPO ₄ ·H ₂ O	159.94
Na ₂ HPO ₄ ·2H ₂ O	177.98
Na ₂ HPO ₄ ·7H ₂ O	268.03
Na ₂ HPO ₄ ·12H ₂ O	358.08

5 Structural Formula

See Section 4.

6 Functional Category

Buffering agent; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Dibasic sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and as a sequestering agent. Therapeutically, dibasic sodium phosphate is used as a mild laxative and in the treatment of hypophosphatemia.^(1,2)

Dibasic sodium phosphate is also used in food products; for example as an emulsifier in processed cheese.

8 Description

The USP 32 states that dibasic sodium phosphate is dried or contains, 1, 2, 7, or 12 molecules of water of hydration.

Anhydrous dibasic sodium phosphate occurs as a white powder. The dihydrate occurs as white or almost white, odorless crystals. The heptahydrate occurs as colorless crystals or as a white granular or caked salt that effloresces in warm, dry air. The dodecahydrate occurs as strongly efflorescent, colorless or transparent crystals.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity pH = 9.1 for a 1% w/v aqueous solution of the anhydrous material at 25°C. A saturated aqueous solution of the dodecahydrate has a pH of about 9.5.

Ionization constants

$PK_{a1} = 2.15$ at 25°C;⁽³⁾

$PK_{a2} = 7.20$ at 25°C;

$PK_{a3} = 12.38$ at 25°C.

Moisture content The anhydrous form is hygroscopic and will absorb up to 7 moles of water on exposure to air, whereas the heptahydrate is stable in air.

NIR spectra *see* Figure 1.

Osmolarity A 2.23% w/v aqueous solution of the dihydrate is isoosmotic with serum; a 4.45% w/v aqueous solution of the dodecahydrate is isoosmotic with serum.

Solubility Very soluble in water, more so in hot or boiling water; practically insoluble in ethanol (95%). The anhydrous material

Table 1: Pharmacopeial specifications for sodium phosphate, dibasic.

Test	JP XV ^(a)	PhEur 6.0 ^(b) 6.1, ^(a) 6.3 ^(c)	USP 32
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	9.0–9.4	—	—
Reducing substances	—	+	—
Insoluble substances	—	—	≤0.4%
Monosodium phosphate	—	≤2.5%	—
Carbonate	+	—	—
Chloride	≤0.014%	+	≤0.06%
Anhydrous	—	≤200 ppm	—
Dihydrate	—	≤400 ppm	—
Dodecahydrate	—	≤200 ppm	—
Water	—	+	—
Anhydrous	—	—	—
Dihydrate	—	—	—
Dodecahydrate	—	57.0–61.0%	—
Sulfates	≤0.038%	+	≤0.2%
Anhydrous	—	≤500 ppm	—
Dihydrate	—	≤0.1%	—
Dodecahydrate	—	≤500 ppm	—
Arsenic	≤2 ppm	+	≤16 ppm
Anhydrous	—	≤2 ppm	—
Dihydrate	—	≤4 ppm	—
Dodecahydrate	—	≤2 ppm	—
Heavy metals	≤10 ppm	+	≤0.002%
Anhydrous	—	≤10 ppm	—
Dihydrate	—	≤20 ppm	—
Dodecahydrate	—	≤10 ppm	—
Iron	—	+	—
Anhydrous	—	≤20 ppm	—
Dihydrate	—	≤40 ppm	—
Dodecahydrate	—	≤20 ppm	—
Loss on drying	57.0–61.0%	+	+
Anhydrous	—	≤1.0%	≤5.0%
Monohydrate	—	—	10.3–12.0%
Dihydrate	—	19.5–21.0%	18.5–21.5%
Heptahydrate	—	—	43.0–50.0%
Dodecahydrate	—	—	55.0–64.0%
Assay (dried basis)	≥98.0%	98.0–101.0%	98.0–100.5%
		98.5–102.5% ^(a)	

(a) JP XV and PhEur 6.1 for the dodecahydrate.

(b) PhEur 6.0 for the dihydrate;

(c) PhEur 6.3 for the anhydrous.

is soluble 1 in 8 parts of water, the heptahydrate 1 in 4 parts of water, and the dodecahydrate 1 in 3 parts of water.

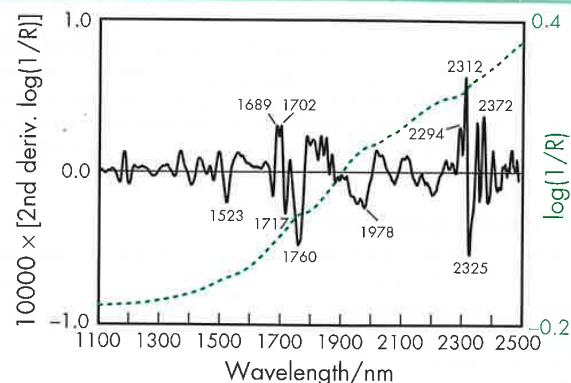
11 Stability and Storage Conditions

The anhydrous form of dibasic sodium phosphate is hygroscopic. When heated to 40°C, the dodecahydrate fuses; at 100°C it loses its water of crystallization; and at a dull-red heat (about 240°C) it is converted into the pyrophosphate, Na₄P₂O₇. Aqueous solutions of dibasic sodium phosphate are stable and may be sterilized by autoclaving.

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

12 Incompatibilities

Dibasic sodium phosphate is incompatible with alkaloids, antipyrine, chloral hydrate, lead acetate, pyrogallol, resorcinol and calcium gluconate, and ciprofloxacin.⁽⁴⁾ Interaction between

**Figure 1:** Near-infrared spectrum of dibasic sodium phosphate measured by reflectance.

calcium and phosphate, leading to the formation of insoluble calcium-phosphate precipitates, is possible in parenteral admixtures.

13 Method of Manufacture

Either bone phosphate (bone ash), obtained by heating bones to whiteness, or the mineral phosphorite is used as a source of tribasic calcium phosphate, which is the starting material in the industrial production of dibasic sodium phosphate.

Tribasic calcium phosphate is finely ground and digested with sulfuric acid. This mixture is then leached with hot water and neutralized with sodium carbonate, and dibasic sodium phosphate is crystallized from the filtrate.

14 Safety

Dibasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations.

Phosphate occurs extensively in the body and is involved in many physiological processes since it is the principal anion of intracellular fluid. Most foods contain adequate amounts of phosphate, making hypophosphatemia (phosphate deficiency)⁽¹⁾ virtually unknown except for certain disease states⁽²⁾ or in patients receiving total parenteral nutrition. Treatment is usually by the oral administration of up to 100 mmol of phosphate daily.

Approximately two-thirds of ingested phosphate is absorbed from the gastrointestinal tract, virtually all of it being excreted in the urine, and the remainder is excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia that may lead to hypocalcemia or other severe electrolyte imbalances.^(5,6) Adverse effects occur less frequently following oral consumption, although phosphates act as mild saline laxatives when administered orally or rectally. Consequently, gastrointestinal disturbances including diarrhea, nausea, and vomiting may occur following the use of dibasic sodium phosphate as an excipient in oral formulations. However, the level of dibasic sodium phosphate used as an excipient in a pharmaceutical formulation is not usually associated with adverse effects.

LD₅₀ (rat, oral): 17 g/kg⁽⁷⁾

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dibasic sodium phosphate may be irritating to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Database (injections; infusions; nasal, ophthalmic, oral, otic, 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

Dibasic potassium phosphate; sodium phosphate, monobasic; tribasic sodium phosphate.

Dibasic potassium phosphate

Empirical formula K_2HPO_4

Molecular weight 174.15

CAS number [7758-11-4]

Synonyms Dipotassium hydrogen orthophosphate; dipotassium hydrogen phosphate; dipotassium phosphate; E340; potassium phosphate.

Appearance Colorless or white, granular, hygroscopic powder.

Acidity/alkalinity pH = 8.5–9.6 for a 5% w/v aqueous solution at 25°C.

Osmolarity A 2.08% w/v aqueous solution of dibasic potassium phosphate is isoosmotic with serum.

Solubility Freely soluble in water; very slightly soluble in ethanol (95%).

Comments One gram of dibasic potassium phosphate contains approximately 11.5 mmol of potassium and 5.7 mmol of phosphate.

Tribasic sodium phosphate

Empirical formula $Na_3PO_4 \cdot xH_2O$

Molecular weight

163.94 for the anhydrous material

380.06 for the dodecahydrate ($12H_2O$)

CAS number [7601-54-9] for the anhydrous material.

Synonyms E339; trisodium orthophosphate; trisodium phosphate; TSP.

Acidity/alkalinity pH = 12.1 for a 1% w/v aqueous solution of the anhydrous material at 25°C. A 1% w/v aqueous solution of the dodecahydrate at 25°C has a pH of 12.0–12.2.

Density

1.3 g/cm³ for the anhydrous material;

0.9 g/cm³ for the dodecahydrate.

Solubility The anhydrous material is soluble 1 in 8 parts of water, while the dodecahydrate is soluble 1 in 5 parts of water at 20°C.

18 Comments

One gram of anhydrous dibasic sodium phosphate represents approximately 14.1 mmol of sodium and 7.0 mmol of phosphate.

One gram of dibasic sodium phosphate dihydrate represents approximately 11.2 mmol of sodium and 5.6 mmol of phosphate.

One gram of dibasic sodium phosphate heptahydrate represents approximately 7.5 mmol of sodium and 3.7 mmol of phosphate.

One gram of dibasic sodium phosphate dodecahydrate represents approximately 5.6 mmol of sodium and 2.8 mmol of phosphate.

A specification for sodium phosphate, dibasic is contained in the Food Chemicals Codex (FCC).⁽⁸⁾

The PubChem Compound ID (CID) for anhydrous dibasic sodium phosphate is 24203, and for dibasic sodium phosphate dodecahydrate is 61456.

19 Specific References

- 1 Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123–128.
- 2 Holland PC *et al.* Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; 335: 697–701.
- 3 Albert A, Serjeant EP. *Ionization Constants of Acids and Bases*, 2nd edn. Edinburgh: Chapman and Hall, 1971.
- 4 Benjamin BE. Ciprofloxacin and sodium phosphates not compatible during actual Y-site injection [letter]. *Am J Health Syst Pharm* 1996; 53: 1850–1851.
- 5 Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema [letter]. *Lancet* 1985; ii: 1433.
- 6 Martin RR *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *J Am Med Assoc* 1987; 257: 2190–2192.
- 7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3273.
- 8 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 900.

20 General References

Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 36th edn. London: Pharmaceutical Press, 2009; 1682.

21 Author

AS Kearney.

22 Date of Revision

12 February 2009.



Sodium Phosphate, Monobasic

1 Nonproprietary Names

BP: Anhydrous Sodium Dihydrogen Phosphate
Sodium Dihydrogen Phosphate Monohydrate
Sodium Dihydrogen Phosphate Dihydrate

PhEur: Sodium Dihydrogen Phosphate Dihydrate

USP: Monobasic Sodium Phosphate

Note that the BP 2009 contains three separate monographs for the anhydrous, the monohydrate, and the dihydrate; the PhEur 6.0 contains a single monograph for the dihydrate; and the USP 32 contains one monograph for the anhydrous, the monohydrate and the dihydrate. See also Section 8.

2 Synonyms

Acid sodium phosphate; E339; *Kalipol* 32; monosodium orthophosphate; monosodium phosphate; natrii dihydrogenophosphas dihydricus; phosphoric acid, monosodium salt; primary sodium phosphate; sodium biphosphate; sodium dihydrogen orthophosphate; sodium dihydrogen phosphate.

3 Chemical Name and CAS Registry Number

Anhydrous monobasic sodium phosphate [7558-80-7]
Monobasic sodium phosphate monohydrate [10049-21-5]
Monobasic sodium phosphate dihydrate [13472-35-0]

4 Empirical Formula and Molecular Weight

NaH_2PO_4 119.98
 $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ 137.99
 $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ 156.01

5 Structural Formula

See Section 4.

6 Functional Category

Buffering agent; emulsifying agent; sequestering agent.

7 Applications in Pharmaceutical Formulation or Technology

Monobasic sodium phosphate is used in a wide variety of pharmaceutical formulations as a buffering agent and as a sequestering agent. Therapeutically, monobasic sodium phosphate is used as a mild saline laxative and in the treatment of hypophosphatemia.⁽¹⁻³⁾

Monobasic sodium phosphate is also used in food products, for example, in baking powders, and as a dry acidulant and sequestrant.

8 Description

The USP 32 states that monobasic sodium phosphate contains one or two molecules of water of hydration or is anhydrous.

The hydrated forms of monobasic sodium phosphate occur as odorless, colorless or white, slightly deliquescent crystals. The anhydrous form occurs as a white crystalline powder or granules.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium phosphate, monobasic.

Test	PhEur 6.0	USP 32
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Aluminum, calcium and related elements	—	+
Arsenic	≤ 2 ppm	≤ 8 ppm
Chloride	≤ 200 ppm	≤ 0.014%
Insoluble substances	—	≤ 0.2%
Heavy metals	≤ 10 ppm	≤ 0.002%
Iron	≤ 10 ppm	—
pH	4.2–4.5	4.1–4.5
Reducing substances	+	—
Sulfate	≤ 300 ppm	≤ 0.15%
Water	+	+
Anhydrous	—	≤ 2.0%
Monohydrate	—	10.0–15.0%
Dihydrate	21.5–24.0%	18.0–26.5%
Assay (dried basis)	98.0–100.5%	98.0–103.0%

10 Typical Properties

Acidity/alkalinity pH = 4.1–4.5 for a 5% w/v aqueous solution of the monohydrate at 25°C.

Density 1.915 g/cm³ for the dihydrate.

Dissociation constant pK_a = 2.15 at 25°C

NIR spectra see Figures 1 and 2.

Solubility Soluble 1 in 1 of water; very slightly soluble in ethanol (95%).

11 Stability and Storage Conditions

Monobasic sodium phosphate is chemically stable, although it is slightly deliquescent. On heating at 100°C, the dihydrate loses all of its water of crystallization. On further heating, it melts with decomposition at 205°C, forming sodium hydrogen pyrophosphate, Na₂H₂P₂O₇. At 250°C it leaves a final residue of sodium metaphosphate, NaPO₃.

Aqueous solutions are stable and may be sterilized by autoclaving.

Monobasic sodium phosphate should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Monobasic sodium phosphate is an acid salt and is therefore generally incompatible with alkaline materials and carbonates; aqueous solutions of monobasic sodium phosphate are acidic and will cause carbonates to effervesce.

Monobasic sodium phosphate should not be administered concomitantly with aluminum, calcium, or magnesium salts since they bind phosphate and could impair its absorption from the gastrointestinal tract. Interaction between calcium and phosphate, leading to the formation of insoluble calcium phosphate precipitates, is possible in parenteral admixtures.⁽⁴⁻⁶⁾

13 Method of Manufacture

Monobasic sodium phosphate is prepared by adding phosphoric acid to a hot, concentrated solution of disodium phosphate until the liquid ceases to form a precipitate with barium chloride. This

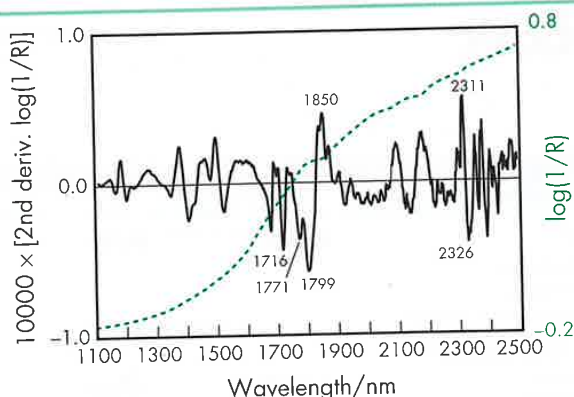


Figure 1: Near-infrared spectrum of anhydrous monobasic sodium phosphate measured by reflectance.

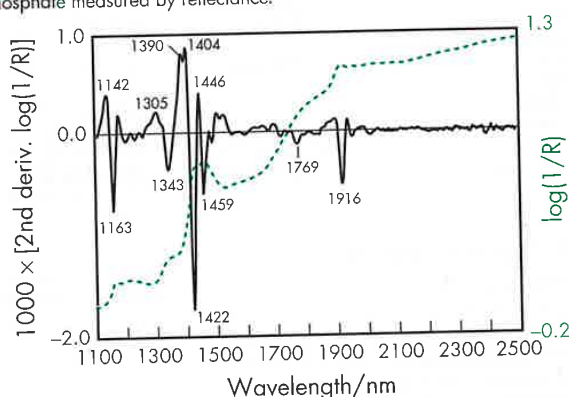


Figure 2: Near-infrared spectrum of monobasic sodium phosphate dihydrate measured by reflectance.

solution is then concentrated and the monobasic sodium phosphate is crystallized.

14 Safety

Monobasic sodium phosphate is widely used as an excipient in parenteral, oral, and topical pharmaceutical formulations.

Phosphate occurs extensively in the body and is involved in many physiological processes since it is the principal anion of intracellular fluid. Most foods contain adequate amounts of phosphate, making hypophosphatemia⁽¹⁾ virtually unknown except in certain disease states⁽²⁾ or in patients receiving total parenteral nutrition. Treatment is usually by the oral administration of up to 100 mmol of phosphate daily.

Approximately two-thirds of ingested phosphate is absorbed from the gastrointestinal tract, virtually all of it being excreted in the urine, and the remainder is excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia that may lead to hypocalcemia or other severe electrolyte imbalances.⁽⁷⁻⁹⁾ Adverse effects occur less frequently following oral consumption, although phosphates act as mild saline laxatives when administered orally or rectally (2-4 g of monobasic sodium phosphate in an aqueous solution is used as a laxative). Consequently, gastrointestinal disturbances including diarrhea, nausea, and vomiting may occur following the use of monobasic sodium phosphate as an excipient in oral formulations. However, the level of monobasic sodium phosphate used as an excipient in a

pharmaceutical formulation is not usually associated with adverse effects.

LD₅₀ (rat, IM): 0.25 g/kg⁽¹⁰⁾

LD₅₀ (rat, oral): 8.29 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Monobasic sodium phosphate may be irritant to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (injections; infusions; ophthalmic, oral, 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

Dibasic sodium phosphate; monobasic potassium phosphate.

Monobasic potassium phosphate

Empirical formula KH₂PO₄

Molecular weight 136.09

CAS number [7778-77-0]

Synonyms E340; monopotassium phosphate; potassium acid phosphate; potassium biphosphate; potassium dihydrogen orthophosphate.

Appearance Colorless crystals or a white, odorless, granular or crystalline powder.

Acidity/alkalinity pH ≈ 4.5 for a 1% w/v aqueous solution at 25°C.

Solubility Freely soluble in water; practically insoluble in ethanol (95%).

Comments 1 g of monobasic potassium phosphate represents approximately 7.3 mmol of potassium and of phosphate.

The EINECS number for monobasic potassium phosphate is 231-913-4.

18 Comments

One gram of anhydrous monobasic sodium phosphate represents approximately 8.3 mmol of sodium and of phosphate.

One gram of monobasic sodium phosphate monohydrate represents approximately 7.2 mmol of sodium and of phosphate.

One gram of monobasic sodium phosphate dihydrate represents approximately 6.4 mmol of sodium and of phosphate.

A specification for sodium phosphate monobasic is contained in the Food Chemicals Codex (FCC).⁽¹¹⁾

The EINECS number for monobasic sodium phosphate is 231-449-2. The PubChem Compound ID (CID) for monobasic sodium phosphate dihydrate is 23673460.

19 Specific References

- Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123-128.
- Holland PC *et al.* Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; 335: 697-701.
- Rosen GH *et al.* Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. *Crit Care Med* 1995; 23: 1204-1210.
- Eggert LD *et al.* Calcium and phosphorus compatibility in parenteral nutrition solutions for neonates. *Am J Hosp Pharm* 1982; 39: 49-53.
- Niemiec PW, Vanderveen TW. Compatibility considerations in parenteral nutrient solutions. *Am J Hosp Pharm* 1984; 41: 893-911.

- 6 Pereira-da-Silva L *et al.* Compatibility of calcium and phosphate in four parenteral nutrition solutions for preterm neonates. *Am J Health Syst Pharm* 2003; 60: 1041–1044.
- 7 Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema [letter]. *Lancet* 1985; ii: 1433.
- 8 Larson JE *et al.* Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; 5: 45–49.
- 9 Martin RR *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *J Am Med Assoc* 1987; 257: 2190–2192.
- 10 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3274.
- 11 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 901.

20 General References

Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 36th edn. London: Pharmaceutical Press, 2009; 1682.

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]

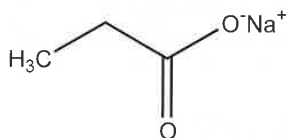
Propionic acid, sodium salt, anhydrous [137-40-6]

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-