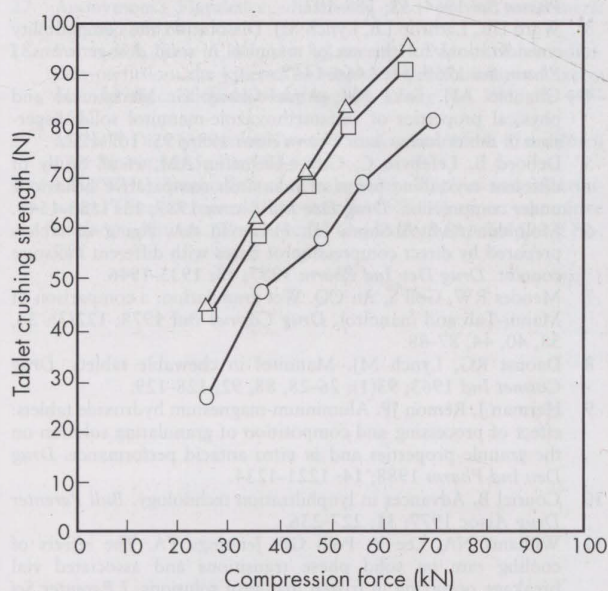


**Table II:** Solubility of mannitol.

Solvent	Solubility at 20°C
Alkalis	Soluble
Ethanol (95%)	1 in 83
Ether	Practically insoluble
Glycerin	1 in 18
Propan-2-ol	1 in 100
Water	1 in 5.5



**Figure 1:** Compression characteristics of granular mannitol (Pearlitol, Roquette Frères).  
 ○: Pearlitol 300DC  
 □: Pearlitol 400DC  
 △: Pearlitol 500DC  
 Tablet diameter: 20 mm  
 Lubricant: magnesium stearate 0.7% w/w for Pearlitol 400DC and Pearlitol 500DC; magnesium stearate 1% w/w for Pearlitol 300DC.

### 11 Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects.<sup>(22)</sup> In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions.

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

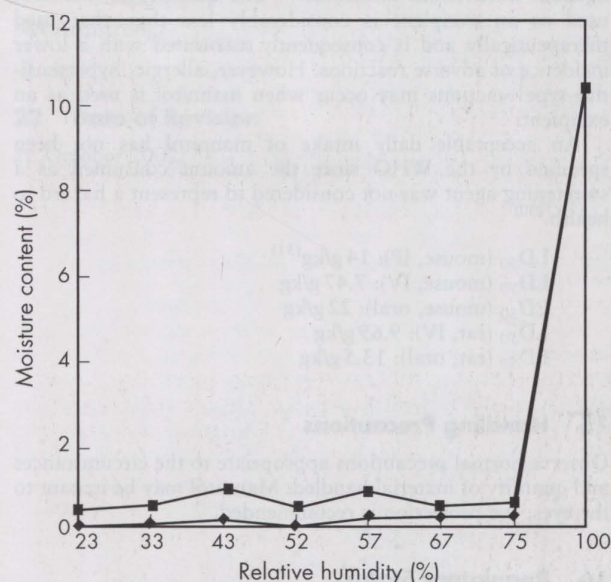
### 12 Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.<sup>(23)</sup> Precipitation has been reported to occur when a 2.5% w/v mannitol solution was allowed to contact plastic.<sup>(24)</sup> Sodium cephalixin at 2 mg/mL and 30 mg/mL is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol and may form complexes with some metals such as aluminum,

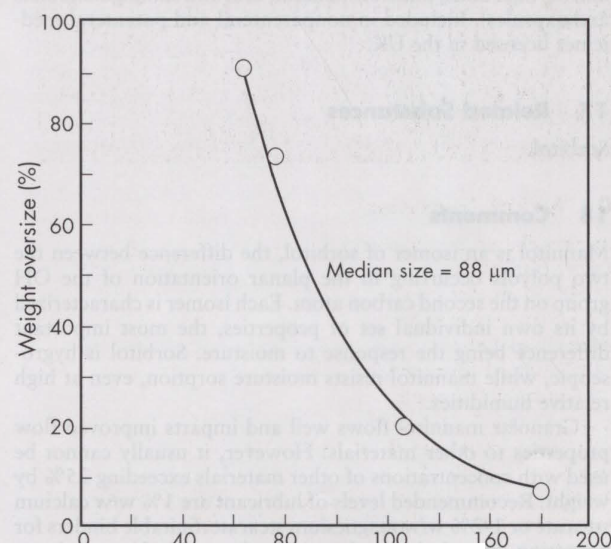
copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formulation.<sup>(25)</sup> Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.<sup>(26)</sup>

### 13 Method of Manufacture

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.



**Figure 2:** Sorption-desorption isotherm for mannitol.  
 ◆: Sorption equilibrium moisture  
 ■: Desorption equilibrium moisture



**Figure 3:** Particle size distribution of mannitol powder.

## 14 Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities.<sup>(27)</sup> If it is used in foods as a bulking agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement 'excessive consumption may have a laxative effect'. After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.<sup>(28)</sup>

A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions.<sup>(29)</sup> The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitivity-type reactions may occur when mannitol is used as an excipient.

An acceptable daily intake of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health.<sup>(30)</sup>

LD<sub>50</sub> (mouse, IP): 14 g/kg<sup>(31)</sup>

LD<sub>50</sub> (mouse, IV): 7.47 g/kg

LD<sub>50</sub> (mouse, oral): 22 g/kg

LD<sub>50</sub> (rat, IV): 9.69 g/kg

LD<sub>50</sub> (rat, oral): 13.5 g/kg

## 15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended.

## 16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IP, IM, IV, and SC injections; infusions; buccal, oral and sublingual tablets and capsules). Included in nonparenteral and parenteral medicines licensed in the UK.

## 17 Related Substances

Sorbitol.

## 18 Comments

Mannitol is an isomer of sorbitol, the difference between the two polyols occurring in the planar orientation of the OH group on the second carbon atom. Each isomer is characterized by its own individual set of properties, the most important difference being the response to moisture. Sorbitol is hygroscopic, while mannitol resists moisture sorption, even at high relative humidities.

Granular mannitol flows well and imparts improved flow properties to other materials. However, it usually cannot be used with concentrations of other materials exceeding 25% by weight. Recommended levels of lubricant are 1% w/w calcium stearate or 1–2% w/w magnesium stearate. Suitable binders for preparing granulations of powdered mannitol are methylcellulose 400, starch paste, povidone, and so on. Usually, 3–6 times as much magnesium stearate or 1.5–3

times as much calcium stearate is needed for lubrication of mannitol granulations than is needed for other excipients.

Mannitol has been reported to sublime at 130°C.<sup>(32)</sup>

The EINECS number for mannitol is 200-711-8.

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NA Armstrong.

## 22 Date of Revision

22 October 2002.

# Propylene Glycol

## 1 Nonproprietary Names

BP: Propylene glycol  
JP: Propylene glycol  
PhEur: Propylenglycolum  
USP: Propylene glycol

## 2 Synonyms

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

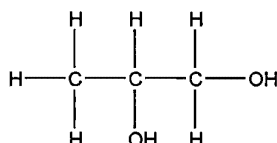
## 3 Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]  
(-)-1,2-Propanediol [4254-14-2]  
(+)-1,2-Propanediol [4254-15-3]

## 4 Empirical Formula Molecular Weight

C<sub>3</sub>H<sub>8</sub>O<sub>2</sub> 76.09

## 5 Structural Formula



## 6 Functional Category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible cosolvent.

## 7 Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics.

As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.

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

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

Table I: Uses of propylene glycol.

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

## 8 Description

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

## 9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for propylene glycol.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Appearance	—	+	—
Specific gravity	1.035–1.040	1.035–1.040	1.035–1.037
Acidity	+	+	+
Water	≤ 0.5%	≤ 0.2%	≤ 0.2%
Residue on ignition	≤ 0.005%	—	≤ 0.007%
Sulfated ash	—	≤ 0.01%	—
Chloride	≤ 0.007%	—	≤ 0.007%
Sulfate	≤ 0.002%	—	≤ 0.006%
Heavy metals	≤ 5 ppm	≤ 5 ppm	≤ 5 ppm
Organic volatile impurities	—	—	+
Refractive index	—	1.431–1.433	—
Oxidizing substances	—	+	—
Reducing substances	—	+	—
Arsenic	≤ 2 ppm	—	—
Glycerin	+	—	—
Distilling range	184–189 °C	—	—
Assay	—	—	≥ 99.5%

## 10 Typical Properties

Autoignition temperature: 371 °C

Boiling point: 188 °C

Density: 1.038 g/cm<sup>3</sup> at 20 °C

Flammability: upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.

Flash point: 99 °C (open cup)

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

Heat of vaporization: 705.4 J/g (168.6 cal/g) at b.p.

Melting point: –59 °C

Osmolarity: a 2.0% v/v aqueous solution is iso-osmotic with



Refractive index:  $n_D^{20} = 1.4324$

Specific rotation  $[\alpha]_D^{20}$ :

–15.0° (neat) for (R)-form

+15.8° (neat) for (S)-form

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

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

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

**Vapor density (relative):** 2.62 (air = 1)

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

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

## 11 Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving.

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

## 12 Incompatibilities

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

## 13 Method of Manufacture

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

## 14 Safety

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material. It is also used extensively in foods and cosmetics. Probably as a consequence of its metabolism and excretion, propylene glycol is less toxic than other glycols. Propylene glycol is rapidly absorbed from the gastrointestinal tract; there is also evidence that it is absorbed topically when applied to damaged skin. It is extensively metabolized in the liver, mainly to lactic and pyruvic acids and is also excreted unchanged in the urine.<sup>(1,2)</sup>

In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin. Some local irritation is produced upon application to mucous membranes or when it is used under occlusive conditions.<sup>(3)</sup> Parenteral administration may cause pain or irritation when used in high concentration.

Propylene glycol is estimated to be one-third as intoxicating as ethanol, with administration of large volumes being associated with adverse effects most commonly on the central nervous system, especially in neonates and children.<sup>(4-6)</sup> Other adverse reactions reported, though generally isolated, include: ototoxicity;<sup>(7)</sup> cardiovascular effects; seizures; and hyperosmolarity<sup>(8)</sup> and lactic acidosis, both of which most frequently in patients with renal impairment. effects are more likely to occur following consumption of large

quantities of propylene glycol or on administration to neonates, children under 4 years of age, pregnant women, and patients with hepatic or renal failure. Adverse events may also occur in patients treated with disulfiram or metronidazole.<sup>(9)</sup>

On the basis of metabolic and toxicological data, the WHO has set an acceptable daily intake of propylene glycol at up to 25 mg/kg body-weight.<sup>(10)</sup> Formulations containing 35% propylene glycol can cause hemolysis in humans.

In animal studies, there has been no evidence that propylene glycol is teratogenic or mutagenic. Rats can tolerate a repeated oral daily dose of up to 30 mL/kg in the diet over 6 months, while the dog is unaffected by a repeated oral daily dose of 2 g/kg in the diet for 2 years.<sup>(11)</sup>

LD<sub>50</sub> (mouse, IP): 9.72 g/kg<sup>(12)</sup>

LD<sub>50</sub> (mouse, IV): 6.63 g/kg

LD<sub>50</sub> (mouse, oral): 22.0 g/kg

LD<sub>50</sub> (mouse, SC): 17.34 g/kg

LD<sub>50</sub> (rat, IM): 0.01 g/kg

LD<sub>50</sub> (rat, IP): 6.66 g/kg

LD<sub>50</sub> (rat, IV): 6.42 g/kg

LD<sub>50</sub> (rat, oral): 0.02 g/kg

LD<sub>50</sub> (rat, SC): 22.5 g/kg

## 15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylene glycol should be handled in a well-ventilated environment; eye protection is recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for propylene glycol vapor and particulates is 474 mg/m<sup>3</sup> (150 ppm) and 10 mg/m<sup>3</sup> for particulates.<sup>(13)</sup>

## 16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, inhalations, ophthalmic, oral, otic, percutaneous, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

## 17 Related Substances

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## 18 Comments

In addition to its uses as an excipient, propylene glycol is used in veterinary medicine as an oral glucogenic in ruminants.<sup>(14)</sup> The EINECS number for propylene glycol is 200-338-0.

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PJ Weller.

## 22 Date of Revision

3 May 2002.

# Sodium Phosphate, Dibasic

## 1 Nonproprietary Names

BP: Anhydrous disodium hydrogen phosphate  
Disodium hydrogen phosphate  
Disodium hydrogen phosphate dodecahydrate  
JP: Dibasic sodium phosphate  
PhEur: Dinatrii phosphas anhydricus  
Dinatrii phosphas dihydricus  
Dinatrii phosphas dodecahydricus  
USP: Dibasic sodium phosphate

Note that the BP 2001 and PhEur 2002 contain three separate monographs for the anhydrous, the dihydrate, and the dodecahydrate; the JP 2001 contains one monograph for the dodecahydrate; and the USP 25 contains one monograph for the anhydrous, the monohydrate, the dihydrate, the heptahydrate, and the dodecahydrate. See also Section 8.

## 2 Synonyms

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 Molecular Weight

$\text{Na}_2\text{HPO}_4$	141.96
$\text{Na}_2\text{HPO}_4 \cdot \text{H}_2\text{O}$	159.94
$\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$	177.98
$\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$	268.03
$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$	358.08

## 5 Structural Formula

$\text{Na}_2\text{HPO}_4 \cdot x\text{H}_2\text{O}$  where  $x = 0, 1, 2, 7, \text{ or } 12$ .

## 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.<sup>(1,2)</sup>

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

## 8 Description

The USP 25 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.

**Table I:** Pharmacopeial specifications for sodium phosphate, dibasic.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	9.0–9.4	—	—
Reducing substances	—	+	—
Monosodium phosphate	—	≤0.025%	—
Carbonate	+	—	—
Chloride	≤0.014%	+	≤0.06%
Dihydrate	—	≤400 ppm	—
Dodecahydrate	—	≤200 ppm	—
Water	—	+	—
Dihydrate	—	—	—
Dodecahydrate	—	57.0–61.0%	—
Sulfates	≤0.038%	—	≤0.2%
Dihydrate	—	≤0.1%	—
Dodecahydrate	—	≤500 ppm	—
Arsenic	≤2 ppm	+	≤16 ppm
Dihydrate	—	≤4 ppm	—
Dodecahydrate	—	≤2 ppm	—
Heavy metals	≤10 ppm	+	≤0.002%
Dihydrate	—	≤20 ppm	—
Dodecahydrate	—	≤10 ppm	—
Iron	—	+	—
Dihydrate	—	≤40 ppm	—
Dodecahydrate	—	≤20 ppm	—
Loss on drying	57.0–61.0%	+	+
Anhydrous	—	—	≤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%

## 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:**<sup>(3)</sup>pK<sub>a1</sub> = 2.15 at 25°CpK<sub>a2</sub> = 7.20 at 25°CpK<sub>a3</sub> = 12.38 at 25°C

**Moisture content:** the anhydrous form is hygroscopic and will absorb water on exposure to air, whereas the heptahydrate is stable in air.

**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 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, Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub>. 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.<sup>(4)</sup> Interaction between 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)<sup>(1)</sup> virtually unknown except for certain disease states<sup>(2)</sup> 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.<sup>(5,6)</sup> 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.

LD<sub>50</sub> (rat, oral): 17 g/kg<sup>(7)</sup>

**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 as a food additive. Included in the FDA Inactive Ingredients Guide (injections; infusions; nasal, ophthalmic, oral, otic, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

**17 Related Substances**

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

**Dibasic potassium phosphate**

Empirical formula: K<sub>2</sub>HPO<sub>4</sub>

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<sub>3</sub>PO<sub>4</sub>·xH<sub>2</sub>O

Molecular weight:

163.94 for the anhydrous material

380.06 for the dodecahydrate (12H<sub>2</sub>O)

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/cm<sup>3</sup> for the anhydrous material

0.9 g/cm<sup>3</sup> 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.

## 19 Specific References

- 1 Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123-128.
- 2 Holland PC, Wilkinson AR, Diez J, Lindsell DRM. 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, Lisehora GR, Braxton M, Barcia PJ. 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*, 10th edn. New York: Wiley, 2000: 3273.

## 20 General References

- Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 33rd edn. London: Pharmaceutical Press, 2002: 1193-1194.

## 21 Author

AS Kearney.

## 22 Date of Revision

23 October 2002.



# Sodium Phosphate, Monobasic

## 1 Nonproprietary Names

BP: Anhydrous sodium dihydrogen phosphate  
Sodium dihydrogen phosphate monohydrate  
Sodium dihydrogen phosphate dihydrate  
PhEur: Natrii dihydrogenophosphas dihydricus  
USP: Monobasic sodium phosphate

Note that the BP 2001 contains three separate monographs for the anhydrous, the monohydrate, and the dihydrate; the PhEur 2002 contains a single monograph for the dihydrate; and the USP 25 contains one monograph for the anhydrous, the monohydrate and the dihydrate. *See also* Section 8.

## 2 Synonyms

Acid sodium phosphate; E339; monosodium orthophosphate; monosodium phosphate; 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 Molecular Weight

$\text{NaH}_2\text{PO}_4$	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

$\text{NaH}_2\text{PO}_4 \cdot x\text{H}_2\text{O}$  where  $x = 0, 1, \text{ or } 2$ .

## 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.<sup>(1,2)</sup>

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 25 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 2002	USP 25
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Aluminum, cadmium and related elements	—	+
Arsenic	≤ 2 ppm	≤ 8 ppm
Chloride	≤ 200 ppm	≤ 0.014%
Heavy metals	≤ 10 ppm	≤ 0.002%
Insoluble substances	—	≤ 0.2%
Iron	≤ 10 ppm	—
Organic volatile impurities	—	+
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/cm<sup>3</sup> for the dihydrate.

Dissociation constant:  $\text{p}K_a = 2.15$  at 25°C

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,  $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ . At 250°C it leaves a final residue of sodium metaphosphate,  $\text{NaPO}_3$ .

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.<sup>(3,4)</sup>

### 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 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<sup>(1)</sup> virtually unknown except for in certain disease states<sup>(2)</sup> 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.<sup>(5-7)</sup> 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.

LD<sub>50</sub> (rat, IM): 0.25 g/kg<sup>(8)</sup>

LD<sub>50</sub> (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 as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections; infusions; ophthalmic, oral, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

### 17 Related Substances

Dibasic sodium phosphate; monobasic potassium phosphate.

### Monobasic potassium phosphate

Empirical formula: KH<sub>2</sub>PO<sub>4</sub>

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.

The EINECS number for monobasic sodium phosphate is 231-449-2.

### 19 Specific References

- Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123-128.
- Holland PC, Wilkinson AR, Diez J, Lindsell DRM. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet* 1990; 335: 697-701.
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- Haskell LP. Hypocalcaemic tetany induced by hypertonic phosphate enema [letter]. *Lancet* 1985; ii: 1433.
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### 21 Authors

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### 22 Date of Revision

23 October 2002.