
Handbook of
PHARMACEUTICAL
EXCIPIENTS

Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

Edited by
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Dibasic Sodium Phosphate

1. Nonproprietary Names

BP: Sodium phosphate

PhEur: Dinatrii phosphas dihydricus

Dinatrii phosphas dodecahydricus

USP: Dibasic sodium phosphate

Note that the BP 1993 contains one monograph, for the dodecahydrate ($12\text{H}_2\text{O}$), whilst the PhEur 1987 and PhEur 1989 contain two separate monographs for the dihydrate ($2\text{H}_2\text{O}$) and the dodecahydrate. The USP XXII contains one monograph applicable to both the heptahydrate ($7\text{H}_2\text{O}$) and the anhydrous material.

See also Section 17.

2. Synonyms

Disodium hydrogen phosphate; disodium phosphate; E339; secondary sodium phosphate; sodium orthophosphate; phosphoric acid, disodium salt.

3. Chemical Name and CAS Registry Number

Anhydrous dibasic sodium phosphate [7558-79-4]

Dibasic sodium phosphate dihydrate [10028-24-7]

Dibasic sodium phosphate heptahydrate [7782-85-6]

Dibasic sodium phosphate dodecahydrate [10039-32-4]

4. Empirical Formula Molecular Weight

Na_2HPO_4	141.96
$\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$	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 $x = 0, 2, 7$ 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 saline laxative and in the treatment of hypophosphatemia.^(1,2)

Dibasic sodium phosphate is also used in food products, e.g. as an emulsifier in processed cheese.

8. Description

Anhydrous dibasic sodium phosphate occurs as a white powder. The dihydrate is a white or almost white, odorless, crystalline material. 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

Test	PhEur*	USP XXII
Identification	+	+
Appearance of solution	+	—
Loss on drying		
(anhydrous form)	—	$\leq 5.0\%$
(dihydrate)	19.5-21.0%	—
(heptahydrate)	—	43.0-50.0%
(dodecahydrate)	57.0-61.0%	—
Insoluble substances	—	$\leq 0.4\%$
Reducing substances	+	—
Monosodium phosphate Chloride	+	—
(anhydrous form)	—	$\leq 0.06\%$
(dihydrate)	≤ 400 ppm	—
(heptahydrate)	—	$\leq 0.06\%$
(dodecahydrate)	≤ 200 ppm	—
Sulfate		
(anhydrous form)	—	$\leq 0.2\%$
(dihydrate)	$\leq 0.1\%$	—
(heptahydrate)	—	$\leq 0.2\%$
(dodecahydrate)	≤ 500 ppm	—
Arsenic		
(anhydrous form)	—	≤ 16 ppm
(dihydrate)	≤ 4 ppm	—
(heptahydrate)	—	≤ 16 ppm
(dodecahydrate)	≤ 2 ppm	—
Heavy metals	≤ 20 ppm	$\leq 0.002\%$
Iron		
(dihydrate)	≤ 40 ppm	—
(dodecahydrate)	≤ 20 ppm	—
Assay (dried basis)	98.0-101.0%	98.0-100.5%

* PhEur 1987 for the dodecahydrate and PhEur 1989 for the dihydrate.

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.

Dissociation constant:

$\text{pK}_{\text{a}1} = 2.15$ at 25°C;

$\text{pK}_{\text{a}2} = 7.20$ at 25°C.

Hygroscopicity: the anhydrous form is hygroscopic and will absorb 2-7 moles of water on exposure to air, whereas the heptahydrate is stable in air.

Osmolarity: a 2.23% w/v aqueous solution of the dihydrate is iso-osmotic with serum; a 4.45% w/v aqueous solution of the dodecahydrate is iso-osmotic 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, $\text{Na}_4\text{P}_2\text{O}_7$. 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. 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, neutralized with sodium carbonate and dibasic sodium phosphate 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 and hence deficiency, hypophosphatemia,⁽¹⁾ is 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, the remainder being excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia which may lead to hypocalcemia or other severe electrolyte imbalances.^(3,4) Adverse effects occur less frequently following oral consumption although phosphates act as mild saline laxatives when administered by this route 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. Generally 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⁽⁵⁾

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dibasic sodium phosphate may be irritant 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. Pharmacopeias

Aust, Belg, Br, Cz, Egypt, Eur, Fr, Ger, Gr, Hung, Ind, It, Jpn, Mex, Neth, Nord, Port, Rom, Swiss, US and Yug. These pharmacopeias may specify one or more states of hydration for dibasic sodium phosphate. Monographs or specifications can be found for the anhydrous form, the

dihydrate, the dodecahydrate and the heptahydrate, although not all forms may necessarily be found in any one pharmacopeia.

18. Related Substances

Dibasic potassium phosphate; Monobasic Sodium Phosphate; tribasic sodium phosphate.

Dibasic potassium phosphate: K₂HPO₄

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.

Pharmacopeias: Gr, Mex and US.

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 iso-osmotic with serum.

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

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

Tribasic sodium phosphate: Na₃PO₄·xH₂O

Molecular weight: 163.94 for the anhydrous material; 380.06 for the dodecahydrate (12H₂O).

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 12-12.2.

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, whilst the dodecahydrate is soluble 1 in 5 parts of water at 20°C.

19. Comments

Each gram of anhydrous dibasic sodium phosphate represents approximately 14.1 mmol of sodium and 7.0 mmol of phosphate. Each gram of dibasic sodium phosphate dihydrate represents approximately 11.2 mmol of sodium and 5.6 mmol of phosphate. Each gram of dibasic sodium phosphate heptahydrate represents approximately 7.5 mmol of sodium and 3.7 mmol of phosphate. Each gram of dibasic sodium phosphate dodecahydrate represents approximately 5.6 mmol of sodium and 2.8 mmol of phosphate.

20. 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. Haskell LP. Hypocalcaemic tetany induced by hypertonic phosphate enema [letter]. *Lancet* 1985; ii: 1433.
4. Martin RR, Lisehora GR, Braxton M, Barcia PJ. Fatal poisoning from sodium phosphate enema: case report and experimental study. *JAMA* 1987; 257: 2190-2192.
5. Sweet DV, editor. Registry of toxic effects of chemical substances. Cincinnati: US Department of Health, 1987.

21. General References

—

22. Authors

USA: AS Kearney.

Monobasic Sodium Phosphate

1. Nonproprietary Names

BP: Sodium acid phosphate

PhEur: Natrii dihydrogenophosphas dihydricus

USP: Monobasic sodium phosphate

Note that the BP 1993 and the PhEur 1983 contain one monograph for the dihydrate ($2\text{H}_2\text{O}$), whilst the USP XXII has a single monograph applicable to either the dihydrate, monohydrate or the anhydrous material.

See also Section 17.

2. Synonyms

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 [10028-24-7] or [13472-35-0]

4. Empirical Formula 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

$\text{NaH}_2\text{PO}_4 \cdot x\text{H}_2\text{O}$

Where $x = 0, 1$ 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.^(1,2)

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

8. Description

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

9. Pharmacopeial Specifications

Test	PhEur 1983	USP XXII (Suppl 6)
Identification	+	+
pH	4.2-4.5	4.1-4.5
Appearance of solution	+	—
Water		
(anhydrous form)	—	$\leq 2.0\%$
(monohydrate)	—	10.0-15.0%
(dihydrate)	21.5-24.0%	18.0-26.5%
Insoluble substances	—	$\leq 0.2\%$
Reducing substances	+	—
Chloride	≤ 200 ppm	$\leq 0.014\%$
Sulfate	≤ 300 ppm	$\leq 0.15\%$
Aluminum, cadmium and related elements	—	+
Arsenic	≤ 2 ppm	≤ 8 ppm
Heavy metals	≤ 10 ppm	$\leq 0.002\%$
Iron	≤ 10 ppm	—
Organic volatile impurities	—	+
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: $\text{pK}_a = 2.15$ 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, $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$, and at 250°C it leaves a final residue of sodium metaphosphate, 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.^(3,4)

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 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 and hence deficiency, hypophosphatemia,⁽¹⁾ is 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, the remainder being excreted in the feces.

Excessive administration of phosphate, particularly intravenously, rectally, or in patients with renal failure, can cause hyperphosphatemia which may lead to hypocalcemia or other severe electrolyte imbalances.⁽⁵⁻⁷⁾ Adverse effects occur less frequently following oral consumption although phosphates act as mild saline laxatives when administered by this route 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. Generally 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⁽⁸⁾

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 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. Pharmacopeias

Aust, Belg, Br, Eur, Fr, Ger, Gr, Hung, Ind, It, Mex, Neth, Nord, Port, Swiss, and Yug; also BP Vet, specify the dihydrate.

Braz, Chin and Mex specify the monohydrate.

US specifies either the dihydrate, monohydrate or anhydrous form.

18. Related Substances

Dibasic Sodium Phosphate; monobasic potassium phosphate.

Monobasic potassium phosphate: 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.

Pharmacopeias: Mex and USP NF.

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: each gram of monobasic potassium phosphate represents approximately 7.3 mmol of potassium and of phosphate.

19. Comments

Each gram of anhydrous monobasic sodium phosphate represents approximately 8.3 mmol of sodium and of phosphate. Each gram of monobasic sodium phosphate monohydrate represents approximately 7.2 mmol of sodium and of phosphate. Each gram of monobasic sodium phosphate dihydrate represents approximately 6.4 mmol of sodium and of phosphate.

20. Specific References

- Lloyd CW, Johnson CE. Management of hypophosphatemia. Clin Pharm 1988; 7: 123-128.
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22. Authors

USA: GW Radebaugh.