Handbook of Pharmaceutical Excipients

FIFTH EDITION

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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 2004 and PhEur 2005 contain three separate monographs for the anhydrous, the dihydrate, and the dodecahydrate; the JP 2001 contains one monograph for the dodecahydrate; and the USP 28 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 and Molecular Weight

Na_2HPO_4	141.96
$Na_2HPO_4 \cdot H_2O$	159.94
$Na_2HPO_4 \cdot 2H_2O$	177.98
$Na_2HPO_4 \cdot 7H_2O$	268.03
$Na_2HPO_4 \cdot 12H_2O$	358.08

5 Structural Formula

$Na_2HPO_4 \cdot xH_2O$ where x = 0, 1, 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 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 28 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[a].

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	—
pH	9.0–9.4	—	—
Reducing substances	—	+	—
Insoluble substances	—	—	⩽0.4%
Monosodium phosphate	—	⩽0.025	—
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%

[a] PhEur 2005 (Suppl. 5.1) for the dodecahydrate.

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 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, $Na_4P_2O_7$. 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, and ciprofloxacin.[4] 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)[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.

LD_{50} (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 Guide (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/cm^3 for the anhydrous material;
0.9 g/cm^3 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).

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