

- **USP REFERENCE STANDARDS** (11)
USP Calcium Pantothenate RS

Dibasic Calcium Phosphate Dihydrate

Pharmacopeial Discussion Group Sign-Off Document

Attribute	JP	EP	USP
Definition	+	+	+
Identification A	+	+	+
Identification B	+	+	+
Acid-Insoluble Substances	+	+	+
Chloride	+	+	+
Sulfate	+	+	+
Carbonate	+	+	+
Barium	+	+	+
Loss on Ignition	+	+	+
Assay	+	+	+

Legend: +, will adopt and implement; –, will not stipulate.

Nonharmonized attributes: *Packaging and Storage, Heavy Metals, Limit of Fluoride, Iron*

Specific local attributes: Identification C (EP), Lead (USP), Description (JP)

CaHPO₄ · 2H₂O 172.09
Phosphoric acid, calcium salt (1:1);
Calcium phosphate, dihydrate (1:1) [7789-77-7].

DEFINITION

Dibasic Calcium Phosphate Dihydrate contains two molecules of water of hydration. It contains NL T 98.0% and NMT 105.0% of dibasic calcium phosphate dihydrate (CaHPO₄ · 2H₂O).

IDENTIFICATION

- **A.**
Sample: 0.1 g of Dibasic Calcium Phosphate Dihydrate
Analysis: Dissolve the *Sample* by warming in 10 mL of 2 N hydrochloric acid. Add 2.5 mL of ammonia TS dropwise, with shaking, and then add 5 mL of ammonium oxalate TS.
Acceptance criteria: A white precipitate is formed.
- **B.**
Sample: 0.1 g of Dibasic Calcium Phosphate Dihydrate
Analysis: Dissolve the *Sample* in 5 mL of diluted nitric acid. Warm the solution to 70 °, and add 2 mL of 10% ammonium molybdate solution (freshly prepared).
Acceptance criteria: A yellow precipitate of ammonium phosphomolybdate is formed.

ASSAY

- **PROCEDURE**
Buffer: Dissolve 53.5 g of ammonium chloride with sufficient water in a 1000-mL volumetric flask. Add 570 mL of ammonia water, stronger, and dilute with water to volume. The pH of this solution is 10.7.
Sample solution: Transfer 400 mg of Dibasic Calcium Phosphate Dihydrate to a 200-mL volumetric flask. Dissolve in 12 mL of diluted hydrochloric acid with the aid of gentle heat, if necessary, and dilute with water to volume.
Blank: 20 mL of water containing 1.2 mL of diluted hydrochloric acid
Titrimetric system
(See *Titrimetry* (541).)
Mode: Residual titration
Titrant: 0.02 M edetate disodium VS
Back-titrant: 0.02 M zinc sulfate VS
Endpoint detection: Visual
Analysis: To 20.0 mL of the *Sample solution* add 25.0 mL of *Titrant*, 50 mL of water, and 5 mL of *Buffer*. Add 25 mg of

eriochrome black T–sodium chloride indicator. T itrate the excess *Titrant* with the *Back-titrant*. Perform a *Blank* determination in the same manner.
Calculate the percentage of dibasic calcium phosphate dihydrate (CaHPO₄ · 2H₂O) in the sample taken:

$$\text{Result} = \{[(V_B - V_S) \times M \times F/W] \times 100\}$$

V_B = *Back-titrant* volume consumed by the *Blank* (mL)
 V_S = *Back-titrant* volume consumed by the *Sample* (mL)
 M = actual molarity of the *Back-titrant* (mM/mL)
 F = equivalency factor, 172.1 mg/mM
 W = *Sample* weight (mg)

Acceptance criteria: 98.0%–105.0%

IMPURITIES

- **CARBONATE**
Sample: 1.0 g of Dibasic Calcium Phosphate Dihydrate
Analysis: Mix the *Sample* with 5 mL of carbon dioxide-free water, and immediately add 2 mL of hydrochloric acid.
Acceptance criteria: No effervescence occurs.
- **CHLORIDE AND SULFATE, Chloride (221)**
Standard: 0.70 mL of 0.010 N hydrochloric acid
Sample: 0.2 g of Dibasic Calcium Phosphate Dihydrate
Analysis: To the *Sample* add 20 mL of water and 13 mL of diluted nitric acid, and warm gently, if necessary, to completely dissolve. Dilute with water to 100 mL, and filter if necessary. To 50 mL of the filtrate add 1 mL of silver nitrate TS.
Acceptance criteria: The turbidity of the *Sample* does not exceed that of the *Standard* (NMT 0.25%).
- **CHLORIDE AND SULFATE, Sulfate (221)**
Standard: 1.0 mL of 0.010 N sulfuric acid
Sample: 0.5 g of Dibasic Calcium Phosphate Dihydrate
Analysis: To the *Sample* add 5 mL of water and 5 mL of diluted hydrochloric acid, and warm gently, if necessary, to completely dissolve. Dilute with water to 100 mL, and filter if necessary. To 20 mL of the filtrate add 1 mL of diluted hydrochloric acid, and dilute with water to 50 mL. Add 1 mL of barium chloride TS.
Acceptance criteria: The turbidity of the *Sample* does not exceed that of the *Standard* (NMT 0.5%).
- **ARSENIC, Method I (211)**
Test preparation: 1.0 g in 25 mL of 3 N hydrochloric acid, diluted with water to 55 mL. Omit the addition of 20 mL of 7 N sulfuric acid specified in *Procedure*.
Acceptance criteria: NMT 3 µg/g
- **BARIUM**
Sample: 0.5 g Dibasic Calcium Phosphate Dihydrate
Analysis: Heat the *Sample* to boiling with 10 mL of water, and add 1 mL of hydrochloric acid dropwise, stirring after each addition. Allow to cool, and filter, if necessary. To the filtrate add 2 mL of potassium sulfate TS.
Acceptance criteria: No turbidity is produced within 10 min.
- **HEAVY METALS, Method I (231)**
Test preparation: Warm 1.3 g with 3 mL of 3 N hydrochloric acid to completely dissolve. Cool, dilute with water to 50 mL, and filter.
Acceptance criteria: NMT 30 ppm
- **LIMIT OF ACID-INSOLUBLE SUBSTANCES**
Sample solution: Dissolve 5.0 g in a mixture of 40 mL of water and 10 mL of hydrochloric acid by boiling gently for 5 min.
Analysis: After cooling, collect the insoluble substance on ashless filter paper, and wash with water until the last washing does not give a reaction for chloride (no turbidity results from the addition of silver nitrate TS). Ignite to completely incinerate the residue and the ashless filter paper at 600 ± 50°.
Acceptance criteria: The weight of the residue does not exceed 10 mg (NMT 0.2%).

• **LIMIT OF FLUORIDE**

[NOTE—Prepare and store all solutions in plastic containers.]

Buffer solution: 294 mg/mL of sodium citrate dihydrate in water

Standard stock solution: 1.1052 mg/mL of USP Sodium Fluoride RS in water

Standard solution: Transfer 20.0 mL of *Standard stock solution* to a 100-mL volumetric flask containing 50.0 mL of *Buffer solution*, dilute with water to volume, and mix. Each mL of this solution contains 100 µg of fluoride ion.

Sample solution: Transfer 2.0 g of Dibasic Calcium Phosphate dihydrate to a beaker containing a plastic-coated stirring bar. Add 20 mL of water and 2.0 mL of hydrochloric acid, and stir until dissolved. Add 50.0 mL of *Buffer solution* and sufficient water to make 100 mL.

Electrode system: Use a fluoride-specific ion-indicating electrode and a silver-silver chloride reference electrode connected to a pH meter capable of measuring potentials with a minimum reproducibility of ±0.2 mV (see *pH* <791>).

Analysis

Samples: *Standard solution* and *Sample solution*

Standard response line: Transfer 50.0 mL of *Buffer solution* and 2.0 mL of hydrochloric acid to a beaker, and add water to make 100 mL. Add a plastic-coated stirring bar, insert the electrodes into the solution, stir for 15 min, and read the potential in mV. Continue stirring, and at 5-min intervals add 100, 100, 300, and 500 µL of *Standard solution*, reading the potential 5 min after each addition. Plot the logarithms of the cumulative fluoride ion concentrations (0.1, 0.2, 0.5, and 1.0 µg/mL) versus potential in mV.

Rinse and dry the electrodes, insert them into the *Sample solution*, stir for 5 min, and read the potential in mV. From the measured potential and the *Standard response line* determine the concentration, *C* (in µg/mL), of fluoride ion in the *Sample solution*.

Calculate the content of fluoride (ppm) in the portion of Dibasic Calcium Phosphate Dihydrate taken:

$$\text{Result} = (V \times C) / W$$

V = *Sample solution* volume (mL)

C = concentration of fluoride ion, determined from the *Standard response line*, in the *Sample solution* (µg/mL)

W = weight of Dibasic Calcium Phosphate Dihydrate taken to prepare the *Sample solution* (g)

Acceptance criteria: NMT 50 ppm

SPECIFIC TESTS

• **LOSS ON IGNITION** (733)

Sample: 1 g of Dibasic Calcium Phosphate Dihydrate

Analysis: Ignite the *Sample* at 800°–825° to constant weight.

Acceptance criteria: 24.5%–26.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. No storage requirements specified.

• **USP REFERENCE STANDARDS** <11>

USP Sodium Fluoride RS

Pharmacopeial Discussion Group Sign-Off Document (Continued)

Attribute	JP	EP	USP
Chloride	+	+	+
Sulfate	+	+	+
Carbonate	+	+	+
Barium	+	+	+
Loss on ignition	+	+	+
Assay	+	+	+

Legend: + will adopt and implement; - will not stipulate.

Nonharmonized attributes: *Packaging and storage, Heavy metals, Limit of fluoride, Iron*

Specific local attributes: Identification C (EP), Lead (USP), Description (JP)

CaHPO₄

136.06

Phosphoric acid, calcium salt (1:1);

Calcium phosphate (1:1) [7757-93-9].

DEFINITION

Anhydrous Dibasic Calcium Phosphate contains NLT 98.0% and NMT 103.0% of anhydrous dibasic calcium phosphate (CaHPO₄).

IDENTIFICATION

• **A.**

Sample: 0.1 g of Anhydrous Dibasic Calcium Phosphate

Analysis: Dissolve the *Sample* by warming in 10 mL of 2 N hydrochloric acid. Add 2.5 mL of ammonia TS dropwise, with shaking, and then add 5 mL of ammonium oxalate TS.

Acceptance criteria: A white precipitate is formed.

• **B.**

Sample: 0.1 g of Anhydrous Dibasic Calcium Phosphate

Analysis: Dissolve the *Sample* in 5 mL of diluted nitric acid. Warm the solution to 70 °, and add 2 mL of 10% ammonium molybdate solution (freshly prepared).

Acceptance criteria: A yellow precipitate of ammonium phosphomolybdate is formed.

ASSAY

• **PROCEDURE**

Buffer: Dissolve 53.5 g of ammonium chloride with sufficient water in a 1000-mL volumetric flask. Add 570 mL of ammonia water, stronger, and dilute with water to volume. The pH of this solution is 10.7.

Sample solution: Transfer 400 mg of Anhydrous Dibasic Calcium Phosphate to a 200-mL volumetric flask. Dissolve in 12 mL of diluted hydrochloric acid with the aid of gentle heat, if necessary, and dilute with water to volume.

Blank: 20 mL of water containing 1.2 mL of diluted hydrochloric acid

Titrimetric system

(See *Titrimetry* <541>.)

Mode: Residual titration

Titrant: 0.02 M edetate disodium VS

Back-titrant: 0.02 M zinc sulfate VS

Endpoint detection: Visual

Analysis: To 20.0 mL of the *Sample solution* add 25.0 mL of *Titrant*, 50 mL of water, and 5 mL of *Buffer*. Add 25 mg of eriochrome black T–sodium chloride indicator. Titrate the excess *Titrant* with the *Back-titrant*. Perform a *Blank* determination in the same manner.

Calculate the percentage of anhydrous dibasic calcium phosphate (CaHPO₄) in the sample taken:

$$\text{Result} = \{[(V_B - V_S) \times M \times F] / W\} \times 100$$

V_B = *Back-titrant* volume consumed by the *Blank* (mL)

V_S = *Back-titrant* volume consumed by the *Sample* (mL)

M = actual molarity of the *Back-titrant* (mM/mL)

F = equivalency factor, 136.06 mg/mM

W = *Sample* weight (mg)

Anhydrous Dibasic Calcium Phosphate

Pharmacopeial Discussion Group Sign-Off Document

Attribute	JP	EP	USP
Definition	+	+	+
Identification A	+	+	+
Identification B	+	+	+
Acid-insoluble substances	+	+	+