

BRIEFING

Dibasic Calcium Phosphate Dihydrate, *USP 29* page 359. The Japanese Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Dibasic Calcium Phosphate Dihydrate* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, is based on the corresponding monograph for Dibasic Calcium Phosphate Dihydrate that was prepared by the Japanese Pharmacopoeia. The Japanese Pharmacopoeia draft was based in part on comments from the European Pharmacopoeia and the United States Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the Japanese Pharmacopoeia.

Differences between the Japanese Pharmacopoeia Adoption Stage 6 document and the current *USP* monograph for Dibasic Calcium Phosphate include the following:

1. *Definition*—The current Dibasic Calcium Phosphate monograph is proposed to be split into two separate monographs: Anhydrous Dibasic Calcium Phosphate and Dibasic Calcium Phosphate Dihydrate.
2. *Packaging and storage*—Retained as a nonharmonized attribute.
3. *Labeling*—Statement removed as it is no longer necessary with two monographs for the anhydrous and the dihydrate forms of Dibasic Calcium Phosphate.
4. *USP Reference standards*—No change.
5. *Identification*—Changed test *A* by increasing the volume of hydrochloric acid to assist in sample dissolution. Changed test *B* by decreasing the sample size and volume of nitric acid, and providing temperature and time for warming of sample.
6. *Loss on ignition*—Removed specification pertaining to anhydrous material.
7. *Carbonate*—Added statement to require carbon dioxide-free water in sample preparation.
8. *Chloride*—Changed sample size and volume of diluent to allow for complete dissolution of the sample.
9. *Sulfate*—Decreased sample size.
10. *Arsenic*—Retained as a nonharmonized attribute.
11. *Barium*—Added statement “heat to boiling”.
12. *Heavy metals*—Retained as a nonharmonized attribute.
13. *Limit of acid-insoluble substances*—Added statement to indicate “heat to boiling” in preparation step. Added step to incinerate residue at 600°.
14. *Limit of fluoride*—Retained as a nonharmonized attribute.
15. *Organic volatile impurities*—Test removed from harmonization draft.
16. *Residual solvents*—Test removed from harmonization draft.
17. *Assay*—Replaced existing method with new titration assay to be consistent with JP standards.

(DSN: K. Moore) RTS—C44231

Change to read:

~~Dibasic Calcium Phosphate~~

■ Dibasic Calcium Phosphate Dihydrate ■ 2S (*USP30*)

Add the following:

■

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) ■2S (USP30)

Delete the following:

■CaHPO₄ 436.06

~~Phosphoric acid, calcium salt (1:1).~~

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

~~Dihydrate 472.09 [7789-77-7].~~

■2S (USP30)

Add the following:

■CaHPO₄·2H₂O

Phosphoric acid, calcium salt (1:1).

Calcium phosphate, Dihydrate (1:1) [7789-77-7].

■2S (USP30)

Delete the following:

~~» Dibasic Calcium Phosphate is anhydrous or contains two molecules of water of hydration. It contains not less than 98.0 percent and not more than 105.0 percent of anhydrous dibasic calcium phosphate (CaHPO_4) or of dibasic calcium phosphate dihydrate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$).~~

Add the following:

» Dibasic Calcium Phosphate Dihydrate contains two molecules of water of hydration. It contains not less than 98.0 percent and not more than 105.0 percent of dibasic calcium phosphate dihydrate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$).

Delete the following:

~~■ **Packaging and storage**—Preserve in well-closed containers. ■2S (USP30)~~

Add the following:

■ **Packaging and storage**—Preserve in well-closed containers. No storage requirements specified. ■2S (USP30)

Delete the following:

~~■ **Labeling**—Label it to indicate whether it is anhydrous or the dihydrate. ■2S (USP30)~~

USP Reference standards $\langle 11 \rangle$ —USP Sodium Fluoride RS.

Delete the following:

~~■ **Identification**—~~

~~**A:** Dissolve about 100 mg by warming with a mixture of 5 mL of 3 N hydrochloric acid and 5 mL of water, add 2.5 mL of 6 N ammonium hydroxide dropwise, with shaking, and then add 5 mL of ammonium oxalate TS: a white precipitate is formed.~~

~~**B:** To 10 mL of a warm solution (1 in 100) in a slight excess of nitric acid add 10 mL of ammonium molybdate TS: a yellow precipitate of ammonium phosphomolybdate is formed. ■2S (USP30)~~

Add the following:

■ **Identification**—

A: Dissolve about 100 mg 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: a white precipitate is formed.

B:

Ammonium molybdate solution—Dissolve 21.2 g of ammonium molybdate in water to make 200 mL of solution (10%). Prepare before use.

Dissolve about 100 mg of sample in 5 mL of diluted nitric acid. Warm the solution to 70° , and add 2 mL of *Ammonium molybdate solution*: a yellow precipitate of ammonium phosphomolybdate is formed.

■2S (USP30)

Delete the following:

~~■ **Loss on ignition** 〈 733 〉 —Ignite it at 800 ° to 825 ° to constant weight: anhydrous Dibasic Calcium Phosphate loses between 6.6% and 8.5% of its weight, and the dihydrate form of Dibasic Calcium Phosphate loses between 24.5% and 26.5% of its weight. ■ 2S (USP30)~~

Add the following:

■ **Loss on ignition** 〈 733 〉 —Ignite about 1 g at 800 ° to 825 ° to constant weight: the material loses between 24.5% and 26.5% of its weight. ■ 2S (USP30)

Delete the following:

~~■ **Carbonate** —Mix 1.0 g with 5 mL of water, and add 2 mL of hydrochloric acid: no effervescence occurs. ■ 2S (USP30)~~

Add the following:

■ **Carbonate** —Mix 1.0 g with 5 mL of carbon dioxide-free water, and immediately add 2 mL of hydrochloric acid: no effervescence occurs. ■ 2S (USP30)

Delete the following:

~~■ **Chloride** 〈 221 〉 —To 0.30 g add 10 mL of water and 2 mL of nitric acid, and warm gently, if necessary, until no more dissolves. Dilute to 25 mL, filter, if necessary, and add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 1.0 mL of 0.020 N hydrochloric acid (0.25%). ■ 2S (USP30)~~

Add the following:

■ **Chloride** 〈 221 〉 —To 0.20 g add 20 mL of water and 13 mL of diluted nitric acid, and warm gently, if necessary, until no more dissolves. Dilute to 100 mL, and filter, if necessary. To 50 mL of this solution add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 0.70 mL of 0.010 N hydrochloric acid (0.25%). ■ 2S (USP30)

Delete the following:

~~■ **Sulfate** 〈 221 〉 —Dissolve 1.0 g in the smallest possible amount of 3 N hydrochloric acid, dilute with water to 100 mL, and filter, if necessary. To 20 mL of the filtrate add 1 mL of barium chloride TS: the turbidity does not exceed that produced by 1.0 mL of 0.020 N sulfuric acid (0.5%). ■ 2S (USP30)~~

Add the following:

■ **Sulfate** 〈 221 〉 —Dissolve 0.5 g in 5 mL of water and 5 mL of diluted hydrochloric acid, 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: the turbidity does not exceed that produced by 1.0 mL of 0.010 N sulfuric acid (0.5%). ■ 2S (USP30)

Arsenic, Method I 〈 211 〉 —Prepare the *Test Preparation* by dissolving 1.0 g in 25 mL of 3 N hydrochloric acid, and diluting with water to 55 mL: the resulting solution meets the requirements of the test, the addition of 20 mL of 7 N sulfuric acid specified under *Procedure* being omitted. The limit is 3 µg per g.

Delete the following:

~~■ **Barium** —Heat 0.50 g with 10 mL of water, and add hydrochloric acid dropwise, stirring after each addition, until no more dissolves. Filter, and to the filtrate add 2 mL of potassium sulfate TS: no turbidity is produced within 10 minutes. ■ 2S (USP30)~~

Add the following:

■ **Barium**—Heat to boiling 0.50 g with 10 mL of water, and add 1 mL of hydrochloric acid dropwise, stirring after each addition. Allow to cool, and filter, if necessary, and to the filtrate add 2 mL of potassium sulfate TS: no turbidity is produced within 10 minutes. ■2S (USP30)

Heavy metals, Method I 〈 231 〉—Warm 1.3 g with 3 mL of 3 N hydrochloric acid until no more dissolves, dilute with water to 50 mL, and filter: the limit is 0.003%.

Delete the following:

■ ~~**Limit of acid-insoluble substances**~~—Heat 5.0 g with a mixture of 40 mL of water and 10 mL of hydrochloric acid until no more dissolves, and dilute with water to 400 mL. If an insoluble residue remains, filter, wash with hot water until the last washing does not give a reaction for chloride, and dry the residue at 105 ° for 1 hour. The weight of the residue does not exceed 10 mg: not more than 0.2% of acid-insoluble substances is found. ■2S (USP30)

Add the following:

■ **Limit of acid-insoluble substances**—Dissolve 5.0 g with a mixture of 40 mL of water and 10 mL of hydrochloric acid by boiling gently for 5 minutes. 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 incinerate completely the residue and ashless filter paper for assay at $600 \pm 50^{\circ}$. The weight of the residue does not exceed 10 mg: not more than 0.2% of acid-insoluble substances is found. ■2S (USP30)

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

Buffer solution—Dissolve 73.5 g of sodium citrate dihydrate in water to make 250 mL of solution.

Standard solution—Dissolve an accurately weighed quantity of *USP Sodium Fluoride RS* quantitatively in water to obtain a solution containing 1.1052 mg per mL. Transfer 20.0 mL of the resulting solution to a 100-mL volumetric flask containing 50 mL of *Buffer solution*, dilute with water to volume, and mix. Each mL of this solution contains 100 µg of fluoride ion.

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 〉).

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 minutes, and read the potential, in mV. Continue stirring, and at 5-minute intervals add 100 µL, 100 µL, 300 µL, and 500 µL of *Standard solution*, reading the potential 5 minutes after each addition. Plot the logarithms of the cumulative fluoride ion concentrations (0.1 µg per mL, 0.2 µg per mL, 0.5 µg per mL, and 1.0 µg per mL) versus potential, in mV.

Procedure—Transfer 2.0 g of the specimen under test 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 of test solution. Rinse and dry the electrodes, insert them into the test solution, stir for 5 minutes, and read the potential, in mV. From the measured potential and the *Standard response line* determine the concentration, *C*, in µg per mL, of fluoride ion in the test solution. Calculate the percentage of fluoride in the specimen taken by multiplying *C* by 0.005: the limit is 0.005%.

Delete the following:

■ ~~**Organic volatile impurities, Method IV**~~ 〈 467 〉: meets the requirements. ■2S (USP30)

Delete the following:

■ ~~Residual solvents~~ ~~(467)~~: meets the requirements.

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■ 2S (USP30)

Delete the following:

■ ~~Assay~~—Dissolve about 250 mg of Dibasic Calcium Phosphate, accurately weighed, with the aid of gentle heat if necessary, in a mixture of hydrochloric acid and water (5:3) contained in a 250 mL beaker equipped with a magnetic stirrer, and cautiously add 125 mL of water. With constant stirring, add, in the order named, 0.5 mL of triethanolamine, 300 mg of hydroxy naphthol blue, and, from a 50 mL buret, about 23 mL of 0.05 M edetate disodium VS. Add sodium hydroxide solution (45 in 400) until the initial red color changes to clear blue. Continue to add it dropwise until the color changes to violet, and add an additional 0.5 mL. The pH is between 12.3 and 12.5. Continue the titration dropwise with the 0.05 M edetate disodium VS to the appearance of a clear blue endpoint that persists for not less than 60 seconds. Each mL of 0.05 M edetate disodium is equivalent to 6.903 mg of CaHPO_4 or to 8.604 mg of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$. ■ 2S (USP30)

Add the following:

■ **Assay—**

Ammonia–ammonium chloride buffer, pH 10.7—Dissolve 53.5 g of ammonium chloride in water. Add 570 mL of ammonia water, stronger. Dilute with water to make 1000 mL.

Transfer about 400 mg of Dibasic Calcium Phosphate Dihydrate, accurately weighed, into 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. Transfer 20.0 mL of this solution to a solution containing 25.0 mL of 0.02 M edetate disodium VS, 50 mL of water, and 5 mL of *Ammonia–ammonium chloride buffer, pH 10.7*. Add 25 mg of eriochrome black T–sodium chloride, and titrate the excess edetate disodium with 0.02 M zinc sulfate VS. Perform a blank determination in the same manner. Each mL of 0.02 M edetate disodium is equivalent to 3.442 mg of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$. ■ 2S (USP30)

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Expert Committee : (DSN05) Dietary Supplements - Non-Botanicals

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