Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-Jan-2018
Document Type: USP Monographs
DocId: GUID-AB046BE8-F655-4E3D-9966-EC57527190A7_3_en-US
DOI: https://doi.org/10.31003/USPNF_M38380_03_01
DOI Ref: e9018

Hydrocortisone Sodium Phosphate

$C_{21}H_{29}Na_2O_8P$ 486.40

Pregn-4-ene-3,20-dione, 11,17-dihydroxy-21-(phosphono oxy)-, disodium salt, (11β)-.

Cortisol 21-(disodium phosphate) CAS RN®: 6000-74-4; UNII: 0388G963HY.

» Hydrocortisone Sodium Phosphate contains not less than 96.0 percent and not more than 102.0 percent of $C_{21}H_{29}Na_2O_8P$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—

USP Hydrocortisone RS

USP Hydrocortisone Phosphate Triethylamine RS $C_{21}H_{31}O_8P \cdot C_6H_{15}N$ 543.64

Identification—

A: Evaporate 15 mL of a methylene chloride solution of it, prepared as directed under *Procedure* in the *Assay*, on a steam bath to dryness, and dissolve the residue in 1 mL of methylene chloride. Proceed as directed in *Identification* test *B* under *Hydrocortisone Sodium Phosphate Injection*, beginning with "Apply 5 µL of this solution."

B: The residue from the ignition of about 20 mg of it responds to the tests for *Phosphate ⟨191⟩* and for *Sodium ⟨191⟩*.

Phosphate ions—

Standard phosphate solution—Dissolve 143.3 mg of dried monobasic potassium phosphate, KH_2PO_4, in water to make 1000.0 mL. This solution contains the equivalent of 0.10 mg of phosphate (PO_4) in each mL.

Phosphate reagent A—Dissolve 5 g of ammonium molybdate in 1 N sulfuric acid to make 100 mL.

Phosphate reagent B—Dissolve 350 mg of *p*-methylaminophenol sulfate in 50 mL of water, add 20 g of sodium bisulfite, mix to dissolve, and dilute with water to 100 mL.

Procedure—Dissolve about 50 mg of Hydrocortisone Sodium Phosphate, accurately weighed, in a mixture of 10 mL of water and 5 mL of 2 N sulfuric acid contained in a 25-mL volumetric flask, by warming if necessary. Add 1 mL each of *Phosphate reagent A* and *Phosphate reagent B*, dilute with water to 25 mL, mix, and allow to stand at room temperature for 30 minutes. Similarly and concomitantly, prepare a standard solution, using 5.0 mL of *Standard phosphate solution* instead of the 50 mg of the substance under test. Concomitantly determine the absorbances of both solutions in 1-cm cells at 730 nm, with a suitable spectrophotometer, using water as the blank. The absorbance of the test solution is not more than that of the standard solution. The limit is 1.0% of phosphate (PO_4).

Chloride (as NaCl)—Dissolve about 3 g, accurately weighed, in 75 mL of water, add 1 mL of nitric acid, and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically, using a glass silver-silver chloride electrode system. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of NaCl. Not more than 1.00% of NaCl is found.

Specific rotation, pH, and free hydrocortisone—Place about 2.5 g in a tared 50-mL flask, and weigh accurately (W_U). Add 25 mL of carbon dioxide-free water, and again weigh (W_S). Calculate the quantity, in mg, of anhydrous hydrocortisone sodium phosphate in each g of solution taken by the formula:

$$1000W_U(1 - L/100)/W_S$$

in which W_U is the weight of Hydrocortisone Sodium Phosphate taken, L is the average percentage of *Loss on drying*, and W_S is the weight of the solution in carbon dioxide-free water. Use this as the *Test preparation* for the following tests.

Specific rotation ⟨781S⟩: between +121° and +129°, determined in a solution prepared by weighing accurately 5.0 mL of *Test preparation* and diluting with pH 7.0 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*) to 50.0 mL.

pH ⟨791⟩: between 7.5 and 10.5, in a solution prepared by diluting a portion of *Test preparation* with 9 volumes of carbon dioxide-free water.

Free hydrocortisone—Dilute 1 mL of *Test preparation* with carbon dioxide-free water to 100 mL. Pipet 5 mL of this solution into a glass-stoppered, 50-mL tube, add 25.0 mL of methylene chloride, insert the stopper, and mix by gentle shaking. Prepare a 1 in 500,000 solution of USP Hydrocortisone RS in methylene chloride. Similarly, shake 25 mL of this solution with 5 mL of water. Allow to stand until the methylene

chloride layers are clear (about 5 minutes). Determine the absorbances of the methylene chloride solutions in 1-cm cells at 239 nm, with a suitable spectrophotometer, using methylene chloride as the blank. The absorbance of the *Test preparation* does not exceed that of the Standard solution (1.0%).

Loss on drying ⟨731⟩—Dry it in vacuum at 80° for 5 hours: the average percentage weight loss for two determinations (*L*) does not exceed 5.0%.

Assay—

pH 9 buffer with magnesium—Mix 3.1 g of boric acid and 500 mL of water in a 1-liter volumetric flask, add 21 mL of 1 N sodium hydroxide and 10 mL of 0.1 M magnesium chloride, dilute with water to volume, and mix.

Alkaline phosphatase solution—Transfer 250 mg of alkaline phosphatase enzyme to a 25-mL volumetric flask, and dissolve by diluting with *pH 9 buffer with magnesium* to volume. Prepare this solution fresh daily.

Standard preparation—Dissolve about 50 mg of USP Hydrocortisone Phosphate Triethylamine RS, accurately weighed, in carbon dioxide-free water to make 25.0 mL.

Assay preparation—Weigh accurately, in g, 2.0 mL of the *Test preparation*, prepared as directed under *Specific rotation, pH, and Free hydrocortisone*, into a tared 100-mL volumetric flask, and dilute with carbon dioxide-free water that has been saturated with methylene chloride to volume. Pipet 10 mL of this solution into a 125-mL separator, and extract with two 25-mL portions of water-washed methylene chloride, discarding the washings.

Procedure—Weigh accurately 1.0 mL each of the *Standard preparation* (W_S) and the *Assay preparation* (W_A) into separate tared 100-mL volumetric flasks. To each flask, and to a similar flask containing 1.0 mL of water to provide a blank, add 1.0 mL of *Alkaline phosphatase solution* and then 50 mL of methylene chloride, and insert the stopper. Allow the flasks to stand at room temperature (not below 25°) for 2 hours with gentle mixing about every 15 minutes. Add 1 mL of dilute hydrochloric acid (1 in 10) to each flask, and mix gently. Add methylene chloride to each flask until the interfaces are at the 100-mL marks, and mix gently. Remove the aqueous layers by aspiration. Determine the absorbances of the methylene chloride solutions obtained from the *Standard preparation* and the *Assay preparation* at 239 nm, with a suitable spectrophotometer, using the methylene chloride solution blank to set the instrument. Calculate the percentage of $C_{21}H_{29}Na_2O_8P$, on the dried basis, taken by the formula:

$$100(A_U/A_S)(C_S/C_A)0.895(W_S/W_A)$$

in which A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively; C_A and C_S are the corresponding concentrations, in mg per mL, of those preparations; and 0.895 is the ratio of the molecular weight of hydrocortisone sodium phosphate to that of hydrocortisone phosphate triethylamine.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
HYDROCORTISONE SODIUM PHOSPHATE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 45(6)

Current DocID: GUID-AB046BE8-F655-4E3D-9966-EC57527190A7_3_en-US
Previous DocID: GUID-AB046BE8-F655-4E3D-9966-EC57527190A7_1_en-US
DOI: https://doi.org/10.31003/USPNF_M38380_03_01
DOI ref: e9018