• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Creatinine RS

Cresol

C_7H_8O 108.14
Phenol, methyl-;
Cresol [1319-77-3].

DEFINITION
Cresol is a mixture of isomeric cresols obtained from coal tar or from petroleum.

IDENTIFICATION
• **A**.
Sample solution: A saturated solution
Analysis: To the *Sample solution* add a few drops of ferric chloride TS.
Acceptance criteria: A bluish-violet color is produced.

IMPURITIES
• **LIMIT OF PHENOL**
Solution A: Bubble air through nitric acid until the acid is colorless, then mix 1 volume of the acid with 4 volumes of water.
Standard solution: Dissolve 1 g of phenol in 100 mL of water, and determine the actual C_6H_6O concentration as follows. Pipet 4 mL of the solution into an iodine flask, add 30.0 mL of 0.1 N bromine VS, then add 5 mL of hydrochloric acid, and immediately insert the stopper. Shake the flask repeatedly for 30 min, and allow to stand for 15 min. Add quickly 5 mL of a 200-mg/mL potassium iodide solution, taking precautions to prevent the escape of bromine vapor, and at once insert the stopper into the flask. Shake thoroughly, remove the stopper, and rinse it and the neck of the flask with a small quantity of water so that the washings flow into the flask. Add 1 mL of chloroform, shake the mixture, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination. Each mL of 0.1 N bromine is equivalent to 1.569 mg of C_6H_6O. Dilute a suitable volume of the solution with water to obtain a concentration of 250 µg/mL of C_6H_6O.
Sample solution: Place 2.5 g of Cresol in a 250-mL volumetric flask, add 10 mL of sodium hydroxide solution (100 mg/mL), and dilute with water to volume. Pipet 5 mL of this solution into a 200-mL volumetric flask, add 45 mL of water and 1 drop of methyl orange TS, neutralize with *Solution A* added dropwise, and then dilute with water to volume.
Analysis: Pipet 5.0 mL of the neutralized *Sample solution* into each of two 20- × 180-mm test tubes, graduated at the 25-mL mark, and pipet 5.0 mL of the *Standard solution* into each of two similar test tubes. To the contents of each tube add 5 mL of Millon's Reagent, allowing it to flow down the inner wall of the tube. Place the tubes simultaneously in a boiling water bath provided with a rack so that the tubes do not touch the bottom of the bath, and maintain the bath at boiling temperature for 30 min, accurately timed. At once remove the tubes from the bath, cool them immediately and thoroughly by placing them in a bath of cold water for NLT 10 min, and add 5 mL of *Solution A* to each tube. Add 3 mL of a 2% formaldehyde solution to one of each pair of tubes, add water to fill all tubes to volume, shake thoroughly, and allow to stand for 16 h, during which time the added formaldehyde imparts a yellow color while the contents of the other two tubes acquire an orange-red color.
Pipet 20 mL from each of the two tubes containing the *Standard solution* into separate 100-mL volumetric flasks, add 5 mL of *Solution A*, and then add water to volume. Transfer the solutions to burets marked *B1* and *B2*, representing, respectively, the solution not treated and the solution treated with formaldehyde.
Pipet 10 mL from each of the two tubes containing the *Sample solution* into separate 50-mL color-comparison tubes marked *N1* and *N2*, representing, respectively, the solution treated with formaldehyde and the solution not treated with formaldehyde.
Add to tube *N1* the orange-red colored solution from buret *B1*, and add to tube *N2* an equal volume of the yellow-colored solution from buret *B2*, until the colors in tubes *N1* and *N2* match when observed in a colorimeter.
Calculate the percentage of phenol (C_6H_6O) in the portion of the sample taken:

$$\text{Result} = V/W \times 5$$

V = volume of the *Standard solution* taken from buret *B1* (mL)
W = weight of Cresol taken (g)
Acceptance criteria: NMT 5.0%

SPECIFIC TESTS
• **SPECIFIC GRAVITY** ⟨**841**⟩**:** 1.030–1.038
• **DISTILLING RANGE,** *Method II* ⟨**721**⟩**:** NLT 90% distills between 195° and 205°.
• **HYDROCARBONS**
Sample solution: 1 in 60
Standard solution: To 58 mL of water add 1.5 mL of 0.02 N sulfuric acid and 1 mL of barium chloride solution (100 mg/mL).
Analysis: Compare the turbidity of the *Sample solution* against the *Standard solution* after the *Standard solution* has been shaken and allowed to stand for 5 min.
Acceptance criteria: The *Sample solution* shows no more turbidity than the *Standard solution*.

ADDITIONAL REQUIREMENTS
• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Croscarmellose Sodium

DEFINITION
Croscarmellose Sodium is the sodium salt of a cross-linked, partly *O*-(carboxymethylated) cellulose.

IDENTIFICATION
• **A**. Mix 1 g with 100 mL of methylene blue solution (1 in 250,000), stir the mixture, and allow it to settle. The Croscarmellose Sodium absorbs the methylene blue and settles as a blue, fibrous mass.
• **B**. Mix 1 g with 50 mL of water. Transfer 1 mL of the mixture to a small test tube, and add 1 mL of water and 5 drops of 1-naphthol TS. Incline the test tube, and carefully add 2 mL of sulfuric acid down the side so that it forms a lower layer: a reddish-violet color develops at the interface.
• **C**. A portion of the mixture of Croscarmellose Sodium with water, prepared as directed in *Identification* test *B*, meets the requirements of the flame test for *Identification Tests—General* ⟨191⟩*, Sodium*.

IMPURITIES
Inorganic Impurities
• **RESIDUE ON IGNITION** ⟨**281**⟩**:** 14.0%–28.0%, calculated on the dried basis. Use 1.0 g for the test, and use sufficient sulfuric acid to moisten the entire residue after the initial charring step, and additional sulfuric acid if an excessive

amount of carbonaceous material remains after the initial complete volatilization of white fumes.

Delete the following:

•• **HEAVY METALS,** *Method II* ⟨**231**⟩**:** 10 ppm• (Official 1-Jan-2018)

• **SODIUM CHLORIDE** and **SODIUM GLYCOLATE**

Sodium chloride

Sample: 5 g of Croscarmellose Sodium

Analysis: Transfer the *Sample* to a 250-mL beaker. Add 50 mL of water and 5 mL of 30% hydrogen peroxide, and heat on a steam bath for 20 min, stirring occasionally to ensure hydration. Cool, and add 100 mL of water and 10 mL of nitric acid. Titrate with 0.05 N silver nitrate VS, determining the endpoint potentiometrically, using a silver-based indicator electrode and a double-junction reference electrode containing 10% potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket, and stirring constantly (see *Titrimetry* ⟨541⟩).

Calculate the percentage of sodium chloride in the specimen taken:

$$\text{Result} = (F \times V \times N)/[(100 - b) \times W]$$

F = equivalence factor for sodium chloride, 584.4
V = volume of the silver nitrate (mL)
N = normality of the silver nitrate
b = percentage of *Loss on Drying*, determined separately
W = weight of the specimen (g)

Sodium glycolate

Sample solution: Transfer 500 mg to a 100-mL beaker. Moisten thoroughly with 5 mL of glacial acetic acid, followed by 5 mL of water, and stir with a glass rod to ensure proper hydration (usually about 15 min). Slowly add 50 mL of acetone while stirring, then add 1 g of sodium chloride, and stir for several min to ensure complete precipitation of the carboxymethylcellulose. Filter through a soft, open-textured paper, previously wetted with a small amount of acetone, and collect the filtrate in a 100-mL volumetric flask. Use an additional 30 mL of acetone to facilitate the transfer of the solids and to wash the filter cake, then dilute with acetone to volume, and mix.

Standard stock solution: Transfer 100 mg of glycolic acid, previously dried in a desiccator at room temperature overnight, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Use this solution within 30 days.]

Standard solution A: Transfer 1.0 mL of the *Standard stock solution* to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Standard solution B: Transfer 2.0 mL of the *Standard stock solution* to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Standard solution C: Transfer 3.0 mL of the *Standard stock solution* to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Standard solution D: Transfer 4.0 mL of the *Standard stock solution* to a 100-mL volumetric flask. Add water to make 5 mL, then add 5 mL of glacial acetic acid. Dilute with acetone to volume, and mix.

Analysis

Samples: *Sample solution*, *Standard solution A*, *Standard solution B*, *Standard solution C*, and *Standard solution D*

Transfer 2.0 mL of the *Sample solution* and 2.0 mL of each *Standard solution* to separate 25-mL volumetric flasks, and prepare a blank flask containing 2.0 mL of a solution containing 5% each of glacial acetic acid and water in acetone. Place the uncovered flasks in a boiling water bath for 20 min to remove the acetone. Remove from the bath, and cool. Add to each flask 5.0 mL of 2,7-dihydroxynaphthalene TS, mix, add an additional 15 mL, and again mix. Cover the mouth of each flask with a small piece of aluminum foil. Place the flasks upright in a boiling water bath for 20 min, then remove from the bath, cool, dilute with sulfuric acid to volume, and mix.

Determine the absorbance of each solution at 540 nm, with a suitable spectrophotometer, against the blank, and prepare a standard curve using the absorbances obtained from the *Standard solutions.*

Calculate the percentage of sodium glycolate in the specimen taken:

$$\text{Result} = (F \times W_1)/[(100 - b) \times W_2]$$

F = factor converting glycolic acid to sodium glycolate, 12.9
W_1 = weight of glycolic acid in the specimen (mg), determined from the standard curve and the absorbance of the *Sample solution*
b = percentage of *Loss on Drying*, determined separately
W_2 = weight of the specimen taken (g)

Acceptance criteria: The sum of the percentages of sodium chloride and sodium glycolate is NMT 0.5%.

SPECIFIC TESTS

• **CONTENT OF WATER-SOLUBLE MATERIAL**

Analysis: Disperse 10 g in 800 mL of water, and stir for 1 min every 10 min during the first 30 min. Allow to stand for an additional h, or centrifuge, if necessary. Decant 200 mL of the aqueous slurry onto a rapid-filtering filter paper in a vacuum filtration funnel, apply vacuum, and collect about 150 mL of the filtrate. Pour the filtrate into a tared 250-mL beaker, weigh, and calculate the weight, in g, of the filtrate, W_3, by difference. Concentrate on a hot plate to a small volume, but not to dryness; dry at 105° for 4 h; again weigh; and calculate the weight, in g, of residue W_1, by difference.

Calculate the percentage of water-soluble material in the specimen, on the dried basis, taken:

$$\text{Result} = [100 \times W_1 \times (800 + W_2)]/\{W_2 \times W_3 \times [1 - (0.01 \times b)]\}$$

W_1 = weight of residue by difference (g)
W_2 = weight of the specimen taken (g)
W_3 = weight of the filtrate by difference (g)
b = percentage *Loss on Drying* of the specimen taken

Acceptance criteria: NMT 10.0%

• **DEGREE OF SUBSTITUTION**

Sample: 1 g

Analysis: Transfer the *Sample* to a glass-stoppered, 500-mL conical flask. Add 300 mL of sodium chloride solution (1 in 10), then add 25.0 mL of 0.1 N sodium hydroxide VS. Insert the stopper, and allow to stand for 5 min with intermittent shaking. Add 5 drops of *m*-cresol purple TS, and from a buret add 15 mL of 0.1 N hydrochloric acid VS. Insert the stopper in the flask, and shake. If the solution is violet, add 0.1 N hydrochloric acid VS in 1-mL portions until the solution becomes yellow, shaking after each addition. Titrate with 0.1 N sodium hydroxide VS to a violet endpoint. Calculate the net number of milliequivalents, M, of base required for the neutralization of 1 g of Croscarmellose Sodium, on the dried basis.

Calculate the degree of acid carboxymethyl substitution, A:

$$\text{Result} = 1150 \times M/[7102 - (412 \times M) - (80 \times C)]$$

M = milliequivalents

NF Monographs

C = percentage of *Residue on Ignition* of the Croscarmellose Sodium as determined in the test for *Residue on Ignition*

Calculate the degree of sodium carboxymethyl substitution, S:

$$\text{Result} = [162 + (58 \times A)] \times C/[7102 - (80 \times C)]$$

A = degree of acid carboxymethyl substitution, as determined above

C = percentage of *Residue on Ignition* of the Croscarmellose Sodium as determined in the test for *Residue on Ignition*

The degree of substitution is the sum of A + S.

Acceptance criteria: The degree of substitution is 0.60–0.85, on the dried basis

- **LOSS ON DRYING ⟨731⟩:** Dry a sample at 105° for 6 h: it loses NMT 10.0% of its weight.
- **MICROBIAL ENUMERATION TESTS ⟨61⟩** and **TESTS FOR SPECIFIED MICROORGANISMS ⟨62⟩:** The total aerobic microbial count does not exceed 1000 cfu/g, and the total combined molds and yeasts count does not exceed 100 cfu/g. It meets the requirements of the tests for absence of *Escherichia coli*.
- **pH ⟨791⟩:** The pH of the dispersion is 5.0–7.0. Mix 1 g with 100 mL of water for 5 min.
- **SETTLING VOLUME**

  Analysis: To 75 mL of water in a 100-mL graduated cylinder, add 1.5 g of it in 0.5-g portions, shaking vigorously after each addition. Add water to make 100 mL, shake again until all of the powder is homogeneously distributed, and allow to stand for 4 h. Note the volume of the settled mass.

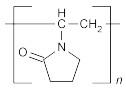
  Acceptance criteria: The volume of the settled mass is 10.0–30.0 mL

ADDITIONAL REQUIREMENTS

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

Crospovidone

Portions of the monograph text that are national *USP* text, and are not part of the harmonized text, are marked with symbols (◆◆) to specify this fact.



$(C_6H_9NO)_n$

1-Ethenyl-2-pyrrolidinone homopolymer;
1-Vinyl-2-pyrrolidinone homopolymer [9003-39-8].

DEFINITION

Crospovidone is a water-insoluble synthetic cross-linked homopolymer of *N*-vinyl-2-pyrrolidinone. It contains NLT 11.0% and NMT 12.8% of nitrogen (N), calculated on the dried basis. Two types of Crospovidone are available, depending on the particle size: Type A and Type B.

IDENTIFICATION

- **◆A. INFRARED ABSORPTION ⟨197K⟩:** Previously dried in a vacuum at 105° for 1 h◆
- **B.**

  Sample: 1 g

  Analysis: Suspend the *Sample* in 10 mL of water, add 0.1 mL of 0.1 N iodine, and shake for 30 s. Add 1 mL of starch TS, and shake.

  Acceptance criteria: No blue color develops.
- **C.** To 10 mL of water add 0.1 g and shake. A suspension is formed, and no clear solution is obtained within 15 min.
- **D.**

  Sample: 20 g of the dried substance

  Analysis: Clean and dry the analytical sieves used in the analysis by washing the sieves in hot water. Allow to dry overnight in a drying cabinet at 105°. Place the *Sample* in a 1000-mL conical flask, add 500 mL of water, and shake the suspension for 30 min. Pour the suspension through a 63-µm analytical sieve, previously tared, and rinse the sieve with water until the filtrate is clear. Dry the sieve and sample residue at 105° for 5 h in a drying cabinet without circulating air. Cool in a desiccator for 30 min, and weigh.

  Calculate the percentage sieving residue fraction of sample particles having a diameter of more than 63 µm:

$$\text{Result} = [(m_1 - m_3) \times 100]/m_2$$

  m_1 = mass of the sieve and sample residue, after drying for 5 h (g)

  m_3 = mass of the sieve (g)

  m_2 = initial mass of the sample, calculated on a dried basis (g)

  Acceptance criteria: If the sieving residue fraction is more than 15%, the substance is classified as Type A; if the sieving residue fraction is NMT 15%, the substance is classified as Type B.

ASSAY

- **NITROGEN DETERMINATION,** *Method II* ⟨461⟩

  Sample: 0.1 g

  Analysis: Proceed as directed, using the *Sample*. In the *Procedure*, omit the use of hydrogen peroxide, and use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33:1:1), instead of potassium sulfate and cupric sulfate (10:1). Heat until a clear, light green solution is obtained. Heat for an additional 45 min, and proceed as directed for *Procedure*, beginning with "Cautiously add to the digestion mixture 70 mL of water".

  Acceptance criteria: 11.0%–12.8% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%, determined on 1.0 g

Delete the following:

- **◆HEAVY METALS,** *Method II* ⟨231⟩: NMT 10 ppm◆ (Official 1-Jan-2018)
- **PEROXIDES**

  Sample suspension A: [NOTE—Use for Type A.] 40 mg/mL in water. To 25 mL of this suspension add 2 mL of titanium trichloride–sulfuric acid TS. Allow to stand for 30 min, and filter.

  Sample suspension B: [NOTE—Use for Type B.] 16 mg/mL in water. To 25 mL of this suspension add 2 mL of titanium trichloride–sulfuric acid TS. Allow to stand for 30 min, and filter.

  Compensation liquid A: [NOTE—Use for Type A.] 40 mg/mL in water. Filter, take 25 mL, and add 2 mL of a 13% solution of sulfuric acid.

  Compensation liquid B: [NOTE—Use for Type B.] 16 mg/mL in water. Filter, take 25 mL, and add 2 mL of a 13% solution of sulfuric acid.

  Analysis: Measure the absorbance of the filtrate at 405 nm against the appropriate compensation liquid.

  Acceptance criteria: NMT 0.35. For Type A, this corresponds to NMT 400 ppm expressed as H_2O_2; for Type B, this corresponds to NMT 1000 ppm expressed as H_2O_2.