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Croscarmellose Sodium

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

DEFINITION

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

IDENTIFICATION

Add the following:

▲• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K. [Note—Depending on the degree of substitution, the intensity of the absorption band at about 1750 cm^{-1} may vary.]▲ (NF 1-May-2022)

Change to read:

• ▲**B.**▲ (NF 1-May-2022)

Analysis: Mix 1 g with 100 mL of methylene blue solution (1 in 250,000), stir the mixture, and allow it to settle.

Acceptance criteria: The Croscarmellose Sodium absorbs the methylene blue and settles as a blue, fibrous mass.

Delete the following:

▲• **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.▲ (NF 1-May-2022)

Change to read:

• ▲**C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Sodium***

Sample: Dissolve a portion of the residue from the *Residue on Ignition* test in 2 mL of water.

Analysis: Add 2 mL of 15% potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of potassium pyroantimonate TS, and heat to boiling. Allow to cool in ice water and, if necessary, rub the inside of the test tube with a glass rod.

Acceptance criteria: A dense precipitate is formed.▲ (NF 1-May-2022)

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.

• ◆**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

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.

Sample solution: Transfer 500 mg of croscarmellose sodium 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.

Analysis

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

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 each *Standard solution*.

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, determined from the standard curve and the absorbance of the *Sample solution* (mg)

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 hour, 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; and again weigh.

Calculate, in grams, the weight of the residue by difference, W_1.

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 of base

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⟩**

Analysis: Dry at 105° for 6 h.

Acceptance criteria: NMT 10.0%

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count is NMT 10^3 cfu/g, and the total combined molds and yeasts count is NMT 10^2 cfu/g. It meets the requirements of the test for absence of *Escherichia coli*.

• **pH ⟨791⟩**

Analysis: Mix 1 g with 100 mL of water for 5 min.

Acceptance criteria: 5.0–7.0

• **Settling Volume**

Analysis: To 75 mL of water in a 100-mL graduated cylinder, add 1.5 g of croscarmellose sodium 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

Change to read:

• ▲◆▲ (NF 1-May-2022) **Packaging and Storage:** Preserve in ▲tight▲ (NF 1-May-2022) containers.▲◆▲ (NF 1-May-2022)

Add the following:

▲• **USP Reference Standards ⟨11⟩**

USP Croscarmellose Sodium RS▲ (NF 1-May-2022)

Topic/Question	Contact	Expert Committee
CROSCARMELLOSE SODIUM	Documentary Standards Support	CE2020 Complex Excipients

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