Carboxymethylcellulose Sodium

Stage 2, ver. 1

DEFINITION

Cellulose, polycarboxymethyl ether, sodium salt
Carboxymethylcellulose Sodium
Sodium salt of partly *O*-carboxymethylated cellulose
[9004-32-4]

Carboxymethylcellulose Sodium is the sodium salt of a carboxymethyl ether of cellulose. It contains not less than 6.0 percent and not more than 12.0 percent of sodium (Na) on the dried basis, corresponding to 0.53 -1.45 degree of substitution.

Identification

A. Infrared absorption spectrophotometry – KBr or ATR
   Record the infrared absorption spectrum of *Carboxymethylcellulose Sodium* and compare with the reference spectrum (obtained by KBr) or the spectrum obtained with the Reference Standard (by either KBr or ATR): the transmission minima or absorption maxima correspond in position and relative size.
B. Dissolve 1 g of powdered Carboxymethylcellulose Sodium to 50 mL of water, while stirring to produce a uniform dispersion. Continue the stirring, and a clear viscous solution is produced.
C. To 2 mL of the solution prepared in Identification B, 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. A dense precipitate is formed.

D. It meets the requirement of the test for Assay.

Loss on drying — Dry it at 105º for 4 hours: it loses not more than 10.0% of its weight.

***pH* :** between 6.0 and 8.5 in a solution prepared in carbon dioxide-free water (1 in 100).

Sodium Chloride—

Transfer about 5 g of Carboxymethylcellulose Sodium, accurately weighed, 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 minutes, stirring occasionally to ensure hydration. Cool, add 100 mL of water and 10 mL of nitric acid, and titrate, while stirring constantly, with 0.05 N silver nitrate, determining the endpoint potentiometrically. Calculate the percentage of sodium chloride (NaCl) in the Carboxymethylcellulose Sodium taken by the formula:

$$584.4VN/[(100 - b)W],$$

in which 584.4 is the equivalence factor for sodium chloride; V is the volume, in mL, of silver nitrate; N is the normality of silver nitrate; b is the percentage obtained from the *Loss on drying* test, determined separately; and W is the weight, in g, of the Carboxymethylcellulose Sodium taken. Sodium chloride is not more than 0.5% on the dried basis.

Sodium glycolate—

Blank – Prepare a solution containing 5% (v/v) of glacial acetic acid and 5% (v/v) water in Acetone

Test solution— Transfer about 500 mg of Carboxymethylcellulose Sodium, accurately weighed, to a 100-mL beaker, moisten thoroughly with 5 mL of glacial acetic acid, add 5 mL of water, and stir with a glass rod to ensure complete hydration (about 15 minutes). Slowly add 50 mL of acetone while stirring, add 1 g

of sodium chloride, and stir for several minutes to ensure the complete precipitation of Carboxymethylcellulose. Filter through a fast filter paper, previously wetted with a small amount of acetone, collect the filtrate in a 100-mL volumetric flask, and use an additional 30 mL of acetone to facilitate the transfer of solids and to wash the filter cake. Dilute the filtrate with acetone to volume, and mix. Allow to stand for 24 h without shaking. Use the clear supernatant as the test solution.

Standard solutions— Transfer 100 mg of glycolic acid, previously dried overnight in a desiccator at room temperature and accurately weighed, to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Use this stock solution within 30 days. Transfer 1.0-mL, 2.0-mL, 3.0-mL, and 4.0-mL portions of the stock solution, respectively, to separate 100-mL volumetric flasks. To each flask, add water to make 5 mL, add 5 mL of glacial acetic acid, dilute with acetone to volume, and mix. These solutions will contain 0.01, 0.02, 0.03, and 0.04 mg/mL of glycolic acid.

Procedure— Transfer 2.0 mL of the *Blank,* 2.0 mL of *Test solution* and 2.0 mL of each *Standard solution* to separate 25-mL volumetric flasks. Place the uncovered flasks in a boiling water bath for 20 minutes, accurately timed, to remove the acetone, remove from the bath, and cool. To each flask, add 5.0 mL of 2,7-dihydroxynaphthalene TS, mix, add an additional 15.0 mL of 2,7-dihydroxynaphthalene TS, and mix again. Cover the mouth of each flask with a small piece of aluminum foil, place the flasks upright in a boiling water bath for 20 minutes, 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 water, and prepare a standard curve using the absorbances obtained from the *Blank* and the *Standard solutions*. From the standard curve and the absorbance of the test solution, determine the concentration (*c*), in mg/mL, of glycolic acid in the *Test solution*, and calculate the percentage of sodium glycolate in the sample taken by the formula:

$$\% \text{ sodium glycolate} = (98.03/76.05)(cV)/[W(100-\%LOD)/100]x100$$

98.03 = formula weight for sodium glycolate
76.05= formula weight for glycolic acid
c= concentration of glycolic acid in the *Test solution* from the standard curve (mg/mL)
V= volume of Test solution (100 mL)
W= weight of sample (mg)
%LOD = %Loss on Drying
The amount of sodium glycolate is no more than 0.5%, on the dried basis.

Sodium sulfate—
[Note: This test is only necessary if sulfuric acid is utilized in the manufacturing process, as indicated on the Labeling.]
Test solution— Dissolve 0.5 g of Carboxymethylcellulose Sodium, accurately weighed, in 50 mL of water. To 10 mL of this solution, add 1 mL of hydrochloric acid, shake well, heat to produce a flocculent precipitate, cool, and centrifuge. Separate the supernatant, and wash the precipitate with three 10-mL portions of water, centrifuging each time and combining the washings with the supernatant. Dilute with water to 50 mL, transfer 10 mL to a Nessler tube, and dilute with water to 50 mL.
Control solution— Transfer 0.40 mL of 0.01 N sulfuric acid to a second Nessler tube, add 1 mL of dilute hydrochloric acid, and add water to make 50 mL.
Procedure— If the *Test solution* is not perfectly clear after acidification, filter the *Test solution* and the *Control solution* through a filter paper that gives a negative test for sulfate. Add 2 mL of barium chloride TS to each solution, mix well, and allow to stand for 10 minutes. Compare the white turbidity produced by viewing downward or transversely against a black background. The *Test solution* shows no more turbidity than the *Control solution*. Sodium sulfate is not more than 1.0%.

Assay —

Titrimetric system:

Mode: Direct titration

Titrant: 0.1 N perchloric acid in glacial acetic acid VS

Accurately weigh about 200 mg of Carboxymethylcellulose Sodium, previously dried at 105º for 4 hours, into a 100mL screw-neck bottle, add 75 mL of glacial acetic acid, insert a magnetic stirring bar and close the bottle tightly with the screw cap. Put the bottle into the preheated stirring block thermostat and heat to refluxing temperature for at least 2 hours under vigorous stirring. Allow to cool to room temperature, carefully open the screw and titrate the *Sample solution* with 0.1 N perchloric acid in glacial acetic acid VS, while stirring with a magnetic stirrer, and determine the endpoint potentiometrically.

Each mL of 0.1 N perchloric acid is equivalent to 2.299 mg of Total Na (m).

Calculate the percentage of sodium by the formula:

$$100(22.99)\,VN/W$$

in which V is the volume, in mL, of the perchloric acid consumed, N is the normality of the perchloric acid, and W is the weight, in mg, of the Carmellose Sodium on the dried basis taken for the Assay.

Viscosity—

Using undried Carboxymethylcellulose Sodium, weigh the amount that, on the dried basis, will provide 350 g of solution of the appropriate concentration (0.5%, 1%, 2% or 4% (w/w) as described in the labeling).

Add the substance in small amounts to 300 mL of stirred water contained in a tared, wide-mouth bottle, continue stirring rapidly until the powder is well wetted, add sufficient water to make the mixture weigh 350 g.

Stir for 90 – 150 min with an appropriate stirrer indicated on the labeling using a constant rotating speed of approximately 1000-2000 rpm until the substance is completely dissolved. Allow to stand for 30 min, while cooling the solution to 25 °C (water bath).

Determine the viscosity of the Carboxymethylcellulose Sodium sample solution using the viscometer, spindle, and speed indicated on the *Labeling*.

Follow the instrument manufacturer's directions to measure the apparent viscosity.

Determine the factor for calculating the mass with reference to the dried substance using the following expression:

$$F_{TV} = \frac{100 - b}{100}$$

Where:

b = loss on drying (%)

F_{TV} = factor for calculating the mass with reference to the dried substance

Calculate the mass (m) of Carboxymethylcellulose Sodium required to prepare different concentration of 350 g solution using the following formula:

$$\frac{C \times 350}{F_{TV} \times 100}$$

Where:

C = % (w/w) of Carboxymethylcellulose Sodium in the solution

Acceptance criteria: Viscosity falls within the viscosity range indicated by the *Labeling* (including certificate of analysis, package label, package insert, etc.).

Labeling— Label to indicate the viscosity test result and the acceptable viscosity range, giving the viscosity measurement parameters, concentration of the solution, and the type of equipment (apparatus, stirrer, etc.) used. Label to indicate if sulfuric acid is utilized in the manufacturing process.

Microbial limits <*61*>— If intended for use in the manufacture of ophthalmic solution, the total aerobic microbial count does not exceed 1000 per g, the total combined molds and yeasts count does not exceed 100 per g, and it meets the requirements of the tests for absence of *Escherichia coli*.

Reagents and solutions:

Potassium pyroantimonate TS:

Dissolve 2 g of potassium pyroantimonate in 85 mL of hot water. Cool quickly, and add 50 mL of a solution containing 50 mg/mL of potassium hydroxide in water and 1 mL of sodium hydroxide solution (8.5 in 100). Allow to stand for 24 h, filter, and dilute with water to 150 mL.

2,7-dihydroxynaphthalene TS

Dissolve 100 mg of 2,7-dihydroxynaphthalene in 1000 mL of sulfuric acid, and allow the solution to stand until the yellow color disappears. If the solution is very dark, discard it and prepare a new solution from a different supply of sulfuric acid. This solution is stable for approximately 1 month if stored in a dark bottle.

0.1 N Perchloric Acid in Glacial Acetic Acid VS:

$HClO_4$, **100.46**

10.05 g in 1000 mL

Mix 8.5 mL of perchloric acid with 500 mL of glacial acetic acid and 21 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL. Alternatively, the solution may be prepared as follows. Mix 11 mL of 60% perchloric acid with 500 mL of glacial acetic acid and 30 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL.

Allow the prepared solution to stand for 1 day for the excess acetic anhydride to be combined, and determine the water content by *Method I* (see *Water Determination* ⟨921⟩), except to use a test specimen of about 5 g of the 0.1 N perchloric acid that is expected to contain approximately 1 mg of water and the *Reagent* (see *Reagent* in *Water Determination* ⟨921⟩*, Method Ia*) diluted such that 1 mL is equivalent to about 1–2 mg of water. If the water content exceeds 0.5%, add more acetic anhydride. If the solution contains no titratable water, add sufficient water to obtain a content of between 0.02% and 0.5% of water. Allow the solution to stand for 1 day, and again titrate the water content. The solution so obtained contains between 0.02% and 0.5% of water, indicating freedom from acetic anhydride.

STANDARDIZATION: Accurately weigh about 700 mg of potassium biphthalate, previously crushed lightly and dried at 120° for 2 h, and dissolve it in 50 mL of glacial acetic acid in a 250-mL flask. Add 2 drops of crystal violet TS, and titrate with the perchloric acid solution until the violet color changes to blue-green. Deduct the volume of the perchloric acid consumed by 50 mL of the glacial acetic acid. Each 20.422 mg of potassium biphthalate is equivalent to 1 mL of 0.1 N perchloric acid.

$$N = \frac{\text{g } KHC_8H_4O_4}{0.20422 \times \text{mL } HClO_4 \text{ (corrected for the blank)}}$$

NOTE—If this volumetric solution is used in a qualitative application such as pH adjustment, dissolution medium, or diluent, its standardization is not required.