BRIEFING

**Croscarmellose Sodium**, *NF 20* page 2536 and page 4007 of *PF 23(3)* [May–June 1997]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for the *Croscarmellose Sodium* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The revisions presented in this proposal, which represents the *Adoption Stage 6* draft, are based on comments received in response to the Official Inquiry Stage 4 draft, which appeared in *Pharmacopeial Previews* on page 4007 of *PF 23(3)* [May–June 1997].

Differences between this Adoption Stage 6 document and the current *NF* monograph include the following:

1. **Definition**—Revisions are made to make the definition more specific.
2. **Packaging and storage**—The container type is changed from tight to well-closed.
3. **Identification**—No change.
4. **Microbial limits**—This section is added to strengthen the monograph. The proposed limits are consistent with those proposed for oral solids.
5. **pH**—The volume of water used is changed to 100 mL, and the mixing time is changed from 1 hour to 5 minutes, based on comments received.
6. **Loss on drying**—The drying time is changed to 6 hours, based on data indicating that an equilibrium loss on drying value is obtained after 6 hours.
7. **Sodium chloride and sodium glycolate**—No change.
8. **Residue on ignition**—This section is added as a test separate from **Degree of substitution**.
9. **Heavy metals**—No change.
10. **Degree of substitution**—The **Residue on ignition** test is deleted, having become a separate test.
11. **Content of water-soluble material**—No change.
12. **Settling volume**—No change.
13. **Organic volatile impurities**—No change.

(EMC: J. Lane) RTS—37582-4

**Change to read:**

- **Croscarmellose Sodium**

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

**Packaging and storage**—Preserve in well-closed containers.

**Identification**—
A: Mix 1 g of it 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 of it 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 it with water, prepared as directed in Identification test B, responds to the flame test for Sodium (191).

Microbial limits (61) — 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.

pH (791) — Mix 1 g of it with 100 mL of water for 5 minutes: the pH of the dispersion is between 5.0 and 7.0.

Loss on drying (731) — Dry it at 105º for 6 hours: it loses not more than 10.0% of its weight.

Sodium chloride and sodium glycolate —

SODIUM CHLORIDE — Weigh accurately about 5 g of it into 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 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 by the formula:

$$\frac{584.4V}{bW},$$

in which \(V\) and \(N\) represent the volume, in mL, and the normality, respectively, of the silver nitrate; \(b\) is the percentage of Loss on drying, determined separately; \(W\) is the weight, in g, of the specimen; and 584.4 is the equivalence factor for sodium chloride.

SODIUM GLYCOLATE — Transfer about 500 mg of it, accurately weighed, into 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 minutes). Slowly add 50 mL of acetone, with stirring, then add 1 g of sodium chloride, and stir for several minutes 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.

Prepare a series of standard solutions as follows. Transfer 100 mg of glycolic acid, previously dried in a desiccator at room temperature overnight and accurately weighed, to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Use this solution within 30 days. Transfer 1.0-mL, 2.0-mL, 3.0-mL, and 4.0-mL portions of the solution, respectively, to separate 100-mL volumetric flasks, add water to each flask to make 5 mL, then add 5 mL of glacial acetic acid, dilute with acetone to volume, and mix.

Transfer 2.0 mL of the test 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 minutes, accurately timed, 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 minutes, 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. From the standard curve and the absorbance of the test specimen, determine the weight \((w)\), in mg, of glycolic acid in the specimen, and calculate the percentage of sodium glycolate in the specimen taken by the formula:

\[
12.9w \div [(100 - b)W],
\]

in which 12.9 is a factor converting glycolic acid to sodium glycolate; \(b\) is the percentage of 
loss on drying, determined separately; and \(W\) is the weight, in g, of the specimen. The sum of the percentages of sodium chloride and sodium glycolate is not more than 0.5%.

Residue on ignition (281) : between 14.0% and 28.0%, calculated on the dried basis, about 1.0 g being used for the test, using 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. Ignition temperature 600 ± 50°.

Heavy metals, Method II (231) : 0.001%.

Degree of substitution — Transfer about 1 g of it, accurately weighed, 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 minutes with intermittent shaking. Add 5 drops of \(m\)-cresol purple TS, and from a buret add about 15 mL of 0.1 N hydrochloric acid VS. Insert the stopper in the flask, and shake. If the solution is purple, 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 purple 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, \(A\), by the formula:

\[
1150M/(7102 - 412M - 80C),
\]

where \(C\) is the percentage of residue on ignition of the Croscarmellose Sodium as determined in the test for Residue on ignition (281).

Calculate the degree of sodium carboxymethyl substitution, \(S\), by the formula:

\[
(162 + 58A)C/(7102 - 80C).
\]

The degree of substitution is the sum of \(A + S\). It is between 0.60 and 0.85, calculated on the dried basis.

Content of water-soluble material — Disperse about 10 g, accurately weighed, in 800 mL of water, accurately measured, and stir for 1 minute every 10 minutes during the first 30 minutes. Allow to stand for an additional hour, or centrifuge, if necessary. Decant about 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 accurately, 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 hours, 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 by the formula:

$$100 \frac{W_1(800 + W_2)}{W_2 W(1 - 0.01b)},$$

in which $W_2$ is the weight, in g, of the specimen taken; and $b$ is the percentage Loss on drying of the specimen taken: not more than 10.0% is found.

**Settling volume** — 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 hours. Note the volume of the settled mass. It is between 10.0 and 30.0 mL.

**Organic volatile impurities, Method IV (467)**: meets the requirements.

**Auxiliary Information**—Staff Liaison: Catherine Sheehan, Senior Scientific Associate

Expert Committee: (EMC) Excipients: Monograph Content

Phone Number: 1-301-816-8262