BRIEFING

Sodium Starch Glycolate, NF 22 page 2933 and page 3202 of PF 22(6) [Nov.–Dec. 1996]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Sodium Starch Glycolate monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopoeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Sodium Starch Glycolate that was prepared by the U.S. Pharmacopeia. This draft was based in part on comments from the European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5A and 5B drafts.

Pharmacopeial Discussion Group Sign-Off Document

<table>
<thead>
<tr>
<th>Attributes</th>
<th>EP</th>
<th>JP</th>
<th>USP</th>
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</thead>
<tbody>
<tr>
<td>Definition</td>
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<td>+</td>
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<tr>
<td>Identification A</td>
<td>+</td>
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<tr>
<td>Identification B</td>
<td>+</td>
<td>+</td>
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<tr>
<td>pH</td>
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<tr>
<td>Loss on drying</td>
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<td>+</td>
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<td>Limit of iron</td>
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<td>Limit of sodium chloride</td>
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<tr>
<td>Limit of sodium glycolate</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Assay</td>
<td>+</td>
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</tbody>
</table>

Legend: + will adopt and implement; − will not stipulate.

Nonharmonized attributes: Characters, Packaging and storage, Labeling, Microbial limits, Heavy metals, Identification by IR absorption.


Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

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

1. Definition — Modified to be more specific in terms of Type A and Type B.
2. Packaging and storage— No change.
3. **Labeling**— Requirements to label indicating Type A or Type B, the botanical source of the starch from which it was derived, and the cross-linking agent are added.

4. **USP Reference standards**— Reference standards for sodium starch glycolate Type A and Type B are added for use with *Identification* test A.

5. **Identification**— An IR absorption test and a test for sodium are added.

6. **Microbial limits**— No change.

7. **pH**— Clarification of the requirements for Type A and Type B is added.

8. **Loss on drying**— No change.

9. **Limit of iron**— The test from the EP is adopted.

10. **Heavy metals**— No change.

11. **Limit of sodium chloride**— A simpler procedure using a silver nitrate titration is adopted.

12. **Limit of sodium glycolate**— This test is added to comply with EP standards.

13. **Assay**— No change.

(EMC: J. Lane) RTS—41235-1

**Change to read:**

**Sodium-Starch-Glycolate**

Starch carboxymethyl ether, sodium salt.

→ Sodium Starch Glycolate is the sodium salt of a carboxymethyl ether of starch. It contains not less than 2.8 percent and not more than 4.2 percent of sodium (Na) on the dried, alcohol-washed basis. It may contain not more than 7.0 percent of Sodium Chloride.

**Packaging and storage**— Preserve in well-closed containers, preferably protected from wide variations in temperature and humidity, which may cause caking.

**Labeling**— The labeling indicates the pH range.

**Identification**— A slightly acidified solution of it is colored blue by iodine and potassium iodide TS.

**Microbial limits** (61)— It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

**pH** (791)— Disperse 1 g in 30 mL of water; the pH of the resulting suspension is either between 3.0 and 5.0 or between 5.5 and 7.5.

**Loss on drying** (731)— Dry it at 130° for 90 minutes; it loses not more than 10.0% of its weight.

**Iron** (241): 0.002%, the *Test-preparation* being prepared as directed for *Test-preparation* under *Heavy-metals*, *Method III* (231), a 0.5-g test specimen being used and the final solution being diluted with water to 47 mL.

**Heavy-metals, Method II** (231): 0.002%.
**Sodium chloride**—Weigh accurately about 1 g, transfer to a conical flask, add 20 mL of 80% alcohol, 0.1 mL of phenolphthalein TS, and 1 N sodium hydroxide solution until the suspension becomes faintly pink, stir for 10 minutes, and filter. Repeat the extraction until chloride has been completely extracted, as shown by a test with silver nitrate TS. Dry the insoluble portion at 105° to constant weight (A mg), and reserve it for the Assay. Evaporate the combined filtrates, and dry the residue at 105° to constant weight. The weight of the dried-residue is not greater than 15% of the weight of Sodium Starch Glycolate taken. If the weight of the dried-residue is not more than 7.0% of the weight of Sodium Starch Glycolate taken, the requirement is met. If the weight is greater than 7.0% of the weight of Sodium Starch Glycolate taken, transfer it with the aid of water to a 200-mL volumetric flask, add 5 mL of nitric acid and 40.0 mL of 0.1 N silver nitrate VS, mix, and dilute with water to volume. Allow it to stand in the dark for 30 minutes, and filter. To 100.0 mL of the filtrate add 5 mL of ferric ammonium sulfate TS, and titrate with 0.1 N ammonium thiocyanate VS (see Residual Titrations under Titrimetry [541]). Calculate the percentage of sodium chloride by the formula:

\[
\frac{5.844(40 N_1 - 2 VN_2)}{W}
\]

in which \(N_1\) and \(N_2\) are the normalities of the silver nitrate VS and the ammonium thiocyanate VS, respectively, \(V\) is the volume, in mL, of ammonium thiocyanate VS used in the titration, and \(W\) is the weight, in g, of Sodium Starch Glycolate taken.

**Assay**—Transfer an accurately weighed portion, \(B\), (about 700 mg) of the dried 80% alcohol-insoluble portion obtained in the test for Sodium–chloride, to a suitable flask, add 80 mL of glacial acetic acid, heat the mixture under reflux, on a boiling water bath, for 2 hours, cool to room temperature, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Calculate the percentage of sodium combined in the form of sodium starch glycolate by the formula:

\[
100\left(\frac{22.99}{V_3 N_3}\right) / B
\]

in which \(V_3\) is the volume, in mL, of the perchloric acid VS, \(N_3\) is the normality of the perchloric acid VS, and \(B\) is the weight, in mg, of the dried alcohol-insoluble residue taken for the Assay.

**Auxiliary Information**—Staff Liaison: Justin Lane, B.S., Scientific Associate

Expert Committee: (EMC) Excipients: Monograph Content

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Phone Number: 1-301-816-8323
Add the following:

- Sodium Starch Glycolate

Starch carboxymethyl ether, sodium salt.

Sodium Starch Glycolate is the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch. It may contain not more than 7.0 percent of Sodium Chloride. The pH and assay requirements for Type A and Type B are set forth in the accompanying table.

<table>
<thead>
<tr>
<th></th>
<th>Type</th>
<th>pH Min.</th>
<th>pH Max.</th>
<th>% Sodium, combined as sodium starch glycolate Min.</th>
<th>% Sodium, combined as sodium starch glycolate Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>5.5</td>
<td>7.5</td>
<td>2.8</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3.0</td>
<td>5.0</td>
<td>2.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Packaging and storage— Preserve in well-closed containers, preferably protected from wide variations in temperature and humidity, which may cause caking.

Labeling— Label it to indicate the botanical source of the starch from which it was derived, the cross-linking agent (if used), the pH range, and whether it is Type A or Type B.

USP Reference standards (11) — USP Sodium Starch Glycolate Type A RS. USP Sodium Starch Glycolate Type B RS.

Identification—

A: Infrared Absorption (197K).

B: A slightly acidified solution of it is colored blue to violet by the addition of iodine and potassium iodide TS 1.

C: A 2-mL portion of the solution prepared for the test for Limit of iron meets the requirements of the potassium carbonate–potassium pyroantimonate test for Sodium (191).

Microbial limits (61) — It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

pH (791) — Disperse 1 g in 30 mL of water: the pH of the resulting suspension is either between 5.5 and 7.5 for Type A or between 3.0 and 5.0 for Type B.

Loss on drying (731) — Dry it at 130° for 90 minutes: it loses not more than 10.0% of its weight.

Heavy metals, Method II (231) : 0.002%.

Limit of iron—
Standard solution— Dissolve 863.4 mg of ferric ammonium sulfate \([\text{FeNH}_4\ (\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}]\) in water, add 25 mL of 2 N sulfuric acid, dilute with water to 500.0 mL, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of 1.0 µg of iron per mL.

Test solution— [ NOTE— Save a portion of this solution for Identification test C. ] Place 2.5 g in a silica or platinum crucible, and add 2 mL of 10 N sulfuric acid. Heat on a water bath, then cautiously raise the temperature progressively over an open flame. Ignite, preferably in a muffle furnace, at 600 ± 25°. Continue heating until all black particles have disappeared. Cool, add a few drops of 2 N sulfuric acid, and heat and ignite as above. Add a few drops of 2 M ammonium carbonate, evaporate to dryness, and ignite as above. Cool, dissolve the residue in 50 mL of water, and mix.

Procedure— Treat the Test solution and the Standard solution as follows. Transfer 10 mL of the solution to a suitable beaker, add 2 mL of citric acid solution (1 in 5) and 0.1 mL of thioglycolic acid, and mix. Render the solution alkaline, using litmus paper as an external indicator, by the addition of ammonium hydroxide, dilute with water to 20 mL, and mix. Allow the solutions to stand for 5 minutes: the color of the solution from the Test solution is a shade of pink no deeper than that of the solution from the Standard solution (0.002%).

Limit of sodium chloride— Transfer to a beaker about 500 mg of Sodium Starch Glycolate, accurately weighed, and suspend in 100 mL of water. Add 1 mL of nitric acid. Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically, using a suitable silver-based indicator electrode and a double-junction reference electrode containing a 10% potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of sodium chloride.

Limit of sodium glycolate— [ NOTE— Conduct this test without exposure to daylight. Use low-actinic glassware. ]

Standard solution— Transfer 310 mg of glycolic acid, previously dried over phosphorus pentoxide in a desiccator at room temperature overnight, to a 500-mL volumetric flask, dissolve in and dilute with water to volume. Transfer 5.0 mL of this solution to a 100-mL beaker, add 4 mL of 6 N acetic acid, and allow to stand for about 30 minutes. Add 50 mL of acetone and 1 g of sodium chloride, mix, and pass through fast filter paper moistened with acetone into a 100-mL volumetric flask. Rinse the beaker and filter paper with acetone. Combine the filtrate and washings, dilute with acetone to volume, and mix. Allow to stand for 24 hours without shaking. Use the clear supernatant as the Standard solution.

Test solution— Transfer 200 mg, accurately weighed, to a 100-mL beaker. Add 4 mL of 6 N acetic acid and 5 mL of water. Stir until dissolution is complete (about 10 minutes). Add 50 mL of acetone and 1 g of sodium chloride, mix, and pass through fast filter paper moistened with acetone into a 100-mL volumetric flask. Rinse the beaker, and filter with acetone. Combine the filtrate and washings, dilute with acetone to volume, and mix. Allow to stand for 24 hours without shaking. Use the clear supernatant as the Test solution.

Procedure— Treat the Test solution and the Standard solution as follows. Heat 2.0 mL of the solution on a water bath for 20 minutes to remove acetone. Cool to room temperature. Prepare a 2,7-dihydroxynaphthalene solution as follows. Dissolve 10 mg of 2,7-dihydroxynaphthalene in 100 mL of sulfuric acid, allow to stand until decolorized, and use within 2 days. Add 20.0 mL of this 2,7-dihydroxynaphthalene solution to the solution under test, mix, and heat on a water bath for 20 minutes. Cool under running water, and transfer quantitatively to a 25-mL volumetric flask. Maintain the flask under running water, and dilute with sulfuric acid to volume. Within 10 minutes determine the absorbance of the solution at 540 nm with a suitable spectrophotometer, using water as the blank: the absorbance of the solution from the Test solution is not more than that of the solution from the Standard solution (2.0%).
Assay— Weigh about 1 g, transfer to a conical flask, add 20 mL of 80% alcohol, stir for 10 minutes, and filter. Repeat the extraction until the chloride has been completely extracted, as shown by a test with silver nitrate. Dry the insoluble portion at 105° to constant weight, and transfer an accurately weighed portion (about 700 mg) of the dried 80% alcohol-insoluble portion to a suitable flask, add 80 mL of glacial acetic acid, heat the mixture under reflux on a boiling water bath for 2 hours, cool to room temperature, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Calculate the percentage of sodium combined in the form of sodium starch glycolate 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 dried alcohol-insoluble residue taken for the Assay.

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