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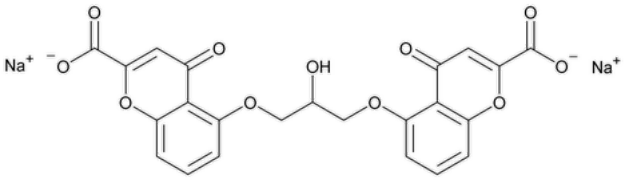
Cromolyn Sodium

Change to read:



$C_{23}H_{14}Na_2O_{11}$ 512.33

4*H*-1-Benzopyran-2-carboxylic acid, 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)▲]▲ (USP 1-Dec-2023) bis[4-oxo-, disodium salt];

Sodium 5,5'-[(2-hydroxypropane-1,3-diyl)bis(oxy)]bis(4-oxo-4*H*-chromene-2-carboxylate) CAS RN®: 15826-37-6; ▲UNII: Q2WXR1I0PK.▲ (USP 1-Dec-2023)

DEFINITION
Cromolyn Sodium contains NLT 98.0% and NMT 101.0% of cromolyn sodium ($C_{23}H_{14}Na_2O_{11}$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K

  Analysis: Dry at 105° to constant weight.

  Acceptance criteria: ▲Meets the requirements▲ (USP 1-Dec-2023)

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Sodium*:** Meets the requirements

ASSAY

- **Procedure**

  Buffer: 2.1 g/L of sodium acetate in water. Adjust with glacial acetic acid to a pH of 5.5.

  Mobile phase: Methanol and *Buffer* (20:80)

  Standard solution: 0.1 mg/mL of USP Cromolyn Sodium RS in water

  Sample solution: 0.1 mg/mL of Cromolyn Sodium in water

  Chromatographic system

  (See *Chromatography ⟨621⟩, System Suitability*.)

  Mode: LC

  Detector: UV 254 nm

  Column: 4.6-mm × 25-cm; 5-µm packing L1

  Column temperature: 35°

  Flow rate: 1.7 mL/min

  Injection volume: 20 µL

  Run time: NLT 2 times the retention time of cromolyn

  System suitability

  Sample: *Standard solution*

  Suitability requirements

  Tailing factor: NMT 2.0

  Relative standard deviation: NMT 0.73%

  Analysis

  Samples: *Standard solution* and *Sample solution*

  Calculate the percentage of cromolyn sodium ($C_{23}H_{14}Na_2O_{11}$) in the portion of Cromolyn Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

  r_U = peak response of cromolyn from the *Sample solution*

r_S = peak response of cromolyn from the *Standard solution*

C_S = concentration of USP Cromolyn Sodium RS in the *Standard solution* (mg/mL)

C_U = concentration of Cromolyn Sodium in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–101.0% on the anhydrous basis

IMPURITIES

Change to read:

• **Organic Impurities**

[Note—The *Sample solution* and *Standard solutions* are stable for 6 h at 4°.]

Diluent A: Acetonitrile and water (20:80)

Diluent B: Methanol and water (30:70)

Buffer: 2.1 g/L of sodium acetate in water. Adjust with glacial acetic acid to a pH of 5.5.

Solution A: Methanol and *Buffer* (20:80)

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
20	43	57
30	43	57
32	100	0
35	100	0

Standard stock solution: 0.15 mg/mL of USP Cromolyn Related Compound A RS and 0.06 mg/mL of USP Cromolyn Related Compound B RS in acetonitrile

Standard solution A: 0.0075 mg/mL of USP Cromolyn Related Compound A RS and 0.003 mg/mL of USP Cromolyn Related Compound B RS from the *Standard stock solution* in *Diluent A*

Standard solution B: 0.0015 mg/mL of USP Cromolyn Sodium RS in *Diluent B*

Sensitivity solution: 0.75 µg/mL of USP Cromolyn Sodium RS from *Standard solution B* in *Diluent B*

Sample solution: 1.5 mg/mL of Cromolyn Sodium in *Diluent B*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 4°

Column: 35°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution A*, *Standard solution B*, and *Sensitivity solution*

▲[Note— The relative retention times in *Table 2* are provided as information that could aid in peak assignment.]

Table 2

Name	Relative Retention Time
Cromolyn	1.0

Name	Relative Retention Time
Cromolyn tricarboxylic acid analog[a]	1.57
2-Acetylresorcinol[b]	2.5
Cromolyn related compound A	4.2
Cromolyn related compound B	4.35▲ (USP 1-Dec-2023)

[a] 5-{3-[(2-Carboxy-4-oxo-4*H*-chromen-5-yl)oxy]-2-hydroxypropoxy}-8-{3-[(2-carboxy-4-oxo-4*H*-chromen-5-yl)oxy]-2-hydroxypropyl}-4-oxo-4*H*-chromene-2-carboxylic acid.

[b] 1-(2,6-Dihydroxyphenyl)ethan-1-one; also known as 2,6-dihydroxyacetophenone.

Suitability requirements

Resolution: NLT 2.5 between cromolyn related compound A and cromolyn related compound B, *Standard solution A*

Relative standard deviation: NMT 5.0%, *Standard solution B*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

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

Calculate the percentage of ▲cromolyn related compound A and cromolyn related compound B▲ (USP 1-Dec-2023) in the portion of Cromolyn Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of cromolyn related compound A or cromolyn related compound B from the *Sample solution*

r_S = peak response of cromolyn related compound A or cromolyn related compound B from *Standard solution A*

C_S = concentration of the corresponding cromolyn related compound in *Standard solution A* (mg/mL)

C_U = concentration of Cromolyn Sodium in the *Sample solution* (mg/mL)

Calculate the percentage of ▲cromolyn tricarboxylic acid analog,▲ (USP 1-Dec-2023) 2-acetylresorcinol, ▲and any▲ (USP 1-Dec-2023) unspecified impurity in the portion of Cromolyn Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of cromolyn tricarboxylic acid analog, 2-acetylresorcinol, or ▲any▲ (USP 1-Dec-2023) unspecified impurity from the *Sample solution*

r_S = peak response of cromolyn from *Standard solution B*

C_S = concentration of USP Cromolyn Sodium RS in *Standard solution B* (mg/mL)

C_U = concentration of Cromolyn Sodium in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Acceptance Criteria, NMT (%)
Cromolyn tricarboxylic acid analog	0.25
2-Acetylresorcinol	0.10
Cromolyn related compound A	0.10
Cromolyn related compound B	0.10

Name	Acceptance Criteria, NMT (%)
Any ▲▲ (USP 1-Dec-2023) unspecified impurity	0.10
Total impurities	0.5

• **Limit of Oxalate**

Standard solution: To 0.35 mg of oxalic acid in 20 mL of water, add 5.0 mL of iron salicylate TS and dilute with water to 50 mL.

Sample solution: To 100 mg of Cromolyn Sodium in 20 mL of water, add 5.0 mL of iron salicylate TS and dilute with water to 50 mL.

Instrumental conditions

Mode: Vis

Analytical wavelength: 480 nm

Blank: Water

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the absorbance of the *Standard solution* and the *Sample solution* at 480 nm.

Acceptance criteria: The absorbance of the *Sample solution* is no less than that of the *Standard solution* (NMT 0.35% of oxalate).

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I*:** NMT 10.0%

• **Sterility Tests ⟨71⟩:** Where the label states that it is sterile, it meets the requirements.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **Labeling:** Where it is intended for use in preparing sterile dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of sterile dosage forms.

• **USP Reference Standards ⟨11⟩**

USP Cromolyn Sodium RS

USP Cromolyn Related Compound A RS

1,3-Bis(2-acetyl-3-hydroxyphenoxy)propan-2-ol.

$C_{19}H_{20}O_7$ 360.36

USP Cromolyn Related Compound B RS

Diethyl 5,5'-[(2-hydroxypropane-1,3-diyl)bis(oxy)]bis(4-oxo-4*H*-chromene-2-carboxylate).

$C_{27}H_{24}O_{11}$ 524.48

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
CROMOLYN SODIUM	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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