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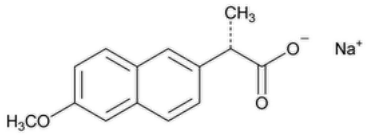
Naproxen Sodium

Change to read:

▲



▲ (USP 1-Aug-2024)

$C_{14}H_{13}NaO_3$ 252.24

2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-;

(-)-Sodium (*S*)-6-methoxy-α-methyl-2-naphthaleneacetate;

▲Sodium (*S*)-2-(6-Methoxynaphthalen-2-yl)propanoate▲ (USP 1-Aug-2024) CAS RN®: 26159-34-2; UNII: 9TN87S3A3C.

DEFINITION

Naproxen Sodium contains NLT 98.0% and NMT 102.0% of naproxen sodium ($C_{14}H_{13}NaO_3$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-Aug-2024)

Change to read:

• **B.** ▲The retention time of the major peak of the *Sample solution* corresponds to that of the naproxen peak in the *System suitability solution*, as obtained in the *Enantiomeric Purity Test*.▲ (USP 1-Aug-2024)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** 0.1% glacial acetic acid in water

Solution B: 0.01% glacial acetic acid in methanol

Mobile phase: See *Table 1*. The recommended equilibration time after the gradient is 5–10 min.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	45	55
20	45	55
27	20	80
32	20	80
32.1	45	55
35	45	55

Diluent: Methanol and water (50:50)

Standard solution: 110 µg/mL of USP Naproxen Sodium RS in *Diluent*

Sample solution: 110 µg/mL of Naproxen Sodium in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 272 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 20 µL

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 naproxen sodium ($C_{14}H_{13}NaO_3$) in the portion of Naproxen Sodium taken:

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

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

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

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

C_U = concentration of Naproxen Sodium in the *Sample solution* (µg/mL)▲ (USP 1-Aug-2024)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

Change to read:

• **Organic Impurities**

▲**Solution A, Solution B, Mobile phase,** and **Diluent:** Prepare as directed in the *Assay*.

System suitability solution: 110 µg/mL of USP Naproxen Sodium RS and 0.5 µg/mL each of USP Naproxen Related Compound K RS, USP Naproxen Related Compound A RS, and USP Naproxen Related Compound L RS in *Diluent*

Standard solution: 0.1 µg/mL each of USP Naproxen Sodium RS, USP Naproxen Related Compound E RS, USP Naproxen Related Compound A RS, and USP Naproxen Related Compound L RS in *Diluent*

Sensitivity solution: 0.05 µg/mL each of USP Naproxen Sodium RS, USP Naproxen Related Compound A RS, USP Naproxen Related Compound L RS, and USP Naproxen Related Compound E RS in *Diluent* from *Standard solution*

Sample solution: 110 µg/mL of Naproxen Sodium in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*

[Note—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between naproxen related compound K and naproxen related compound A; NLT 2.0 between naproxen related compound L and naproxen, *System suitability solution*

Relative standard deviation: NMT 5.0% for each peak, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of naproxen related compound E, naproxen related compound A, and naproxen related compound L in the portion of Naproxen Sodium taken:

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

r_U = peak response of naproxen related compound E, naproxen related compound A, or naproxen related compound L from the *Sample solution*

r_S = peak response of naproxen related compound E, naproxen related compound A, or naproxen related compound L from the *Standard solution*

C_S = concentration of USP Naproxen Related Compound E RS, USP Naproxen Related Compound A RS, or USP Naproxen Related Compound L RS in the *Standard solution* (µg/mL)

C_U = concentration of Naproxen Sodium in the *Sample solution* (µg/mL)

Calculate the percentage of naproxen related compound K and any unspecified impurity in the portion of Naproxen Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of naproxen related compound K or any unspecified impurity from the *Sample solution*

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

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

C_U = concentration of Naproxen Sodium in the *Sample solution* (µg/mL)

F = relative response factor, 0.71 for naproxen related compound K and 1.0 for unspecified impurity

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Naproxen related compound K, if present	0.66	0.10
Naproxen related compound A	0.71	0.06
Naproxen related compound L	0.88	0.1
Naproxen	1.0	—
Naproxen related compound E	1.63	0.1
Any unspecified impurity	—	0.10
Total impurities	—	0.5▲ (USP 1-Aug-2024)

Change to read:

• **▲LIMIT OF▲ (USP 1-AUG-2024) FREE NAPROXEN**

Sample: 5.0 g

Analysis: Transfer the *Sample* to a separator and add 25 mL of water. Extract the solution with three 15-mL portions of chloroform. Evaporate the combined extracts on a steam bath to dryness. Dissolve the residue in 10 mL of a mixture of methanol and water (3:1), previously neutralized with 0.1 N sodium hydroxide to the phenolphthalein endpoint. Add phenolphthalein TS, and titrate with 0.10 N sodium hydroxide.

Acceptance criteria: NMT 2.2 mL is consumed (1.0%)

Add the following:

▲• ENANTIOMERIC PURITY TEST

[NOTE—Protect solutions containing naproxen from light.]

Mobile phase: Hexane, isopropanol, acetonitrile, and glacial acetic acid (84.5: 10: 5: 0.5)

System suitability solution: 25 µg/mL each of USP Naproxen Sodium RS and USP Naproxen Related Compound G RS in *Mobile phase*

Standard solution: 1.25 µg/mL of USP Naproxen Related Compound G RS in *Mobile phase*

Sample stock solution: Equivalent to 500 µg/mL of Naproxen in tetrahydrofuran prepared as follows. Dissolve 25 mg of naproxen sodium in 15 mL of water and add 1 mL of hydrochloric acid. Add 10 mL of ethyl acetate and shake well to extract the free naproxen. Separate the ethyl acetate layer and repeat the extraction with an additional 10 mL of ethyl acetate. Combine the two ethyl acetate extractions and evaporate to dryness under vacuum. Dissolve the residue in 50 mL of tetrahydrofuran.

Sample solution: Equivalent to 50 µg/mL of Naproxen in *Mobile phase* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 263 nm

Column: 4.6-mm × 25-cm; 5-µm packing L102

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of the naproxen peak

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for naproxen related compound G and naproxen are approximately 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between naproxen related compound G and naproxen, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of naproxen related compound G in the portion of Naproxen Sodium taken:

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

r_U = peak response of naproxen related compound G from the *Sample solution*

r_S = peak response of naproxen related compound G from the *Standard solution*

C_S = concentration of USP Naproxen Related Compound G RS in the *Standard solution* (µg/mL)

C_U = concentration of Naproxen Sodium in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 2.5%▲ (USP 1-Aug-2024)

SPECIFIC TESTS

Delete the following:

▲• **OPTICAL ROTATION** ⟨781S⟩, *Procedures, Specific Rotation*▲ (USP 1-AUG-2024)

Change to read:

• **LOSS ON DRYING** ⟨731⟩

Analysis: ▲Dry in vacuum at 105° for 3 h.▲ (ERR 1-Aug-2024)

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Naproxen Sodium RS

▲USP Naproxen Related Compound A RS

6-Methoxy-2-naphthoic acid.

$C_{12}H_{10}O_3$ 202.21

USP Naproxen Related Compound E RS

(*S*)-Methyl 2-(6-methoxynaphthalen-2-yl)propanoate.

$C_{15}H_{16}O_3$ 244.29

USP Naproxen Related Compound G RS

(*R*)-2-(6-Methoxynaphthalen-2-yl)propanoic acid.

$C_{14}H_{14}O_3$ 230.26

USP Naproxen Related Compound K RS

1-(6-Methoxynaphthalen-2-yl)ethanol.

$C_{13}H_{14}O_2$ 202.25

USP Naproxen Related Compound L RS

1-(6-Methoxynaphthalen-2-yl)ethanone.

$C_{13}H_{12}O_2$ 200.24▲ (USP 1-Aug-2024)

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

Topic/Question	Contact	Expert Committee
NAPROXEN SODIUM	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 47(4)
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