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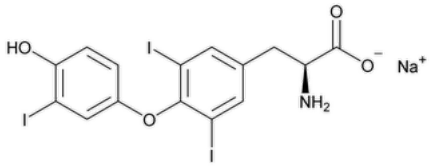
Liothyronine Sodium



$C_{15}H_{11}I_3NNaO_4$ 672.96

L-Tyrosine, *O*-(4-hydroxy-3-iodophenyl)-3,5-diiodo-, monosodium salt;

Monosodium L-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]alanine CAS RN®: 55-06-1; UNII: GCA9VV7D2N.

DEFINITION

Change to read:

Liothyronine Sodium is the sodium salt of L-3,3',5-triiodothyronine. It contains NLT 95.0% and NMT ▲102.0%▲ (USP 1-May-2021) of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$), calculated on the dried basis.

IDENTIFICATION

Delete the following:

▲• **A.**

Diluent: Solution of hydrochloric acid in 80% alcohol (1 in 50)

Sample solution: 0.1-mg/mL solution in *Diluent*

Acceptance criteria: The UV absorption spectrum of the *Sample solution* exhibits maxima at the same wavelengths as those of a similar solution of USP Liothyronine RS, concomitantly measured; and the respective absorptivities, both calculated on the dried basis in terms of the acid at the wavelength of maximum absorbance at about 297 nm, do not differ by more than 5.0%.▲ (USP 1-May-2021)

Add the following:

▲• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K or 197A▲ (USP 1-May-2021)

Change to read:

• **B.** ▲The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

• **C.** **Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Sodium*:** The residue from the ignition of Liothyronine Sodium meets the requirements.

Delete the following:

▲• **D.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

Mobile phase: Mixture of acetonitrile and water (40:60) that contains 0.5 mL of phosphoric acid in each liter of the mixture

Solution A: Dissolve 400 mg of sodium hydroxide in 500 mL of water. Cool and add 500 mL of methanol.

Levothyroxine stock solution: 0.4 mg/mL of USP Levothyroxine RS in *Solution A*. Make a dilution (1:100) of this solution using *Mobile phase*.

Liothyronine stock solution: 0.4 mg/mL of USP Liothyronine RS in *Solution A*

Standard solution: 10 µg/mL of liothyronine from *Liothyronine stock solution* and 0.5 µg/mL of levothyroxine from *Levothyroxine stock solution*, in *Mobile phase*

Sample solution: 10 µg/mL of Liothyronine Sodium in *Mobile phase*. [Note—A small amount of 0.01 M methanolic sodium hydroxide can be used to facilitate the dissolution of the sample.]

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; packing L10

Flow rate: 1.5 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 5.0 between levothyroxine and liothyronine

Relative standard deviation: NMT ▲0.73%▲ (USP 1-May-2021) for liothyronine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$) in the portion of Liothyronine Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of liothyronine sodium, 672.96

M_{r2} = molecular weight of liothyronine, 650.97

Acceptance criteria: 95.0%–▲102.0%▲ (USP 1-May-2021) on the dried basis

IMPURITIES

Change to read:

• **Chloride Content**

▲**Sample solution:** Dissolve 500 mg of Liothyronine Sodium in 100 mL of a 2-g/L solution of sodium hydroxide.

Analysis: Add 25 mL of diluted nitric acid to the *Sample solution*, and titrate with 0.05 N silver nitrate VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary corrections. Each milliliter of 0.05 N silver nitrate is equivalent to 1.77 mg of chloride.

Acceptance criteria: NMT 1.2% on the dried basis (equivalent to NMT 2.0% of sodium chloride)▲ (USP 1-May-2021)

Delete the following:

▲• **Limit of Levothyroxine Sodium**

Mobile phase, Levothyroxine stock solution, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Levothyroxine standard solution: 0.5 µg/mL of levothyroxine from *Levothyroxine stock solution*, in *Mobile phase*

Analysis

Samples: *Levothyroxine standard solution* and *Sample solution*

Calculate the percentage of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) in the portion of Liothyronine Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

r_S = peak response of levothyroxine from the *LevothyroxineStandard solution*

C_S = concentration of USP Levothyroxine RS in the *LevothyroxineStandard solution* (µg/mL)

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

M_{r1} = molecular weight of levothyroxine sodium, 798.85

M_{r2} = molecular weight of levothyroxine, 776.87

Acceptance criteria: NMT 5.0% of levothyroxine sodium▲ (USP 1-May-2021)

Add the following:

▲• **Organic Impurities**

Solution A: 4.9 g/L of sulfamic acid and 0.75 g/L of sodium hydroxide in water. Adjust with 2 N sodium hydroxide to a pH of 2.0.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
2	75	25
20	20	80
22	20	80
23	75	25
28	75	25

Diluent 1: Methanol and *Solution A* (90:10)

Diluent 2: Acetonitrile, *Solution A*, and *Diluent 1* (15:35:50)

Standard solution: 0.1 µg/mL of USP Liothyronine RS in 20% of the volume of *Diluent 1*. Dilute with *Diluent 2* to volume.

Sensitivity solution: 0.05 µg/mL of USP Liothyronine RS from *Standard solution* in 20% of the volume of *Diluent 1*. Dilute with *Diluent 2* to volume.

Sample solution: 100 µg/mL of Liothyronine Sodium in 20% of the volume of *Diluent 1*. Dilute with *Diluent 2* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.0-mm x 15-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Liothyronine Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

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

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

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

M_{r1} = molecular weight of liothyronine sodium, 672.96

M_{r2} = molecular weight of liothyronine, 650.97

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

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Diotyrosine[a]	0.25	0.3
Diiodothyronine[b]	0.75	0.5
Liothyronine	1.00	—
Levothyroxine	1.15	1.0
Triiodothyroacetic acid[c]	1.69	0.3
Tetraiodothyroacetic acid[d]	1.93	0.2
Any unspecified impurity	—	0.10
Total impurities	—	2.0

[a] 3,5-Diiodo-L-tyrosine.

[b] *O*-(4-Hydroxyphenyl)-3,5-diiodo-L-tyrosine.

[c] [4-(4-Hydroxy-3-iodophenoxy)-3,5-diiodophenyl]acetic acid.

[d] [4-(4-Hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetic acid.

▲ (USP 1-May-2021)

SPECIFIC TESTS

Delete the following:

▲• **Sodium Content**

Analysis: Transfer 100 mg, previously dried, into a platinum dish. Add 8–10 drops of sulfuric acid, and ignite to constant weight, taking care to avoid spattering. Each mg of residue is equivalent to 0.324 mg of sodium (Na).

Correct the result for the quantity of sodium equivalent to the sodium chloride (NaCl) found in the test for *Chloride Content*.

Acceptance criteria: 2.9%–4.0%▲ (USP 1-May-2021)

• **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

Diluent: Alcohol and 1.2 N hydrochloric acid (80:20)

Sample solution: 20 mg/mL in *Diluent*

Acceptance criteria: +18° to +22°

• **Loss on Drying** ⟨731⟩

Analysis: Dry at 105° for 2 h.

Acceptance criteria: NMT 4.0%

ADDITIONAL REQUIREMENTS

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

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Levothyroxine RS

USP Liothyronine RS

▲ USP Liothyronine Sodium RS▲ (USP 1-May-2021)

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

Topic/Question	Contact	Expert Committee
LIOTHYRONINE SODIUM	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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