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Levothyroxine Sodium Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-levothyroxine-caps-20220527.

DEFINITION
Levothyroxine Sodium Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$).

IDENTIFICATION
• **A.** The retention time of the major peak of the *Sample solution* corresponds to the levothyroxine peak of the *Standard solution*, as obtained in the *Assay*.

ASSAY
• **Procedure**
[Note—Use *Sample solution 2* for Tablets labeled to meet the requirements of *Dissolution Test 3*. For all other products, use the *Sample solution*.]

Mobile phase: Acetonitrile and water (4:6) containing 0.5 mL of phosphoric acid per liter of mixture

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

Diluent: Methanol and water (6:4) containing 0.5 mL of phosphoric acid per liter of mixture

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

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

Standard solution: 10 µg/mL of levothyroxine from *Levothyroxine stock solution* and 0.2 µg/mL of liothyronine from *Liothyronine stock solution*, in *Mobile phase*

Sample solution: Transfer an equivalent to about 100 µg of levothyroxine sodium, from finely powdered Tablets (NLT 20), to a centrifuge tube, add two glass beads, pipet 10 mL of *Mobile phase* into the tube, and mix on a vortex mixer for 3 min. Centrifuge to obtain a clear supernatant, filtering if necessary.

Sample solution 2 (for Tablets labeled to meet the requirements of *Dissolution Test 3*): Place the appropriate number of Tablets (see *Table 1*) into a suitable container, add 100.0 mL of *Diluent*, and shake by mechanical means for at least 30 min, or until the Tablets are fully disintegrated. Pass through a PTFE filter of 0.45-µm pore size.

Table 1

Tablet Strength (µg/Tablet of Levothyroxine Sodium)	Number of Tablets
Less than 100	20
At least 100 but less than 200	15
200 or more	10

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 liothyronine and levothyroxine

Relative standard deviation: NMT 2.0% for the levothyroxine peak

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

C_U = nominal concentration of levothyroxine 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: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

[Note—All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass.]

Test 1

Medium: 0.01 N hydrochloric acid containing 0.2% sodium lauryl sulfate; 500 mL

Apparatus 2: 50 rpm

Time: 45 min

Mobile phase: Methanol and 0.1% phosphoric acid (6:4)

Standard stock solution: 0.1 mg/mL of USP Levothyroxine RS in methanol

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a solution having a concentration similar to that expected in the *Sample solution*.

Sample solution: Pass a portion of the solution under test through a suitable filter. [Note—Before use, check the filters for absorptive loss of drug.]

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 800 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 4.0% for levothyroxine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) dissolved.

Tolerances: NLT 70% (*Q*) of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium, Apparatus 2, Mobile phase, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed for *Test 1*.

Time: 15 min

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) dissolved.

Tolerances: NLT 80% (*Q*) of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, Apparatus 2, Time, Standard solution, and **Sample solution:** Proceed as directed for *Test 1*. [Note—Filter the *Standard solution* in a manner identical to that used for the *Sample solution*.]

Mobile phase: Acetonitrile and water (35:65) that contains 0.5 mL of phosphoric acid per liter of mixture

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing L10

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 4.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) dissolved.

Tolerances: NLT 80% (*Q*) of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) is dissolved.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

[NOTE—Do not use paddle stirrers with synthetic coating.]

Medium: 0.01 N hydrochloric acid; 500 mL for Tablets labeled to contain between 25 and 175 µg of levothyroxine sodium; and 900 mL for Tablets labeled to contain 200 or 300 µg of levothyroxine sodium

Apparatus 2: 75 rpm

Time: 45 min

Mobile phase: Acetonitrile, water, and phosphoric acid (500:700:2)

Standard stock solution: Transfer about 100 mg of USP Levothyroxine RS to a 100-mL volumetric flask. Add 80 mL of alcohol and 1 mL of 1 N hydrochloric acid, sonicate for 2 min, dilute with alcohol to volume, and mix.

Standard solution: Dilute the *Standard stock solution* with a mixture of alcohol and water (1:1) to obtain a concentration of 0.01 mg/mL of levothyroxine. Dilute the resulting solution with *Medium* to obtain a final concentration similar to that expected in the *Sample solution*.

Sample solution: Sample per *Dissolution* ⟨711⟩. Centrifuge the solution under analysis.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.0-mm × 12.5-cm; packing L7

Flow rate: 1.5 mL/min

Injection volume: 500 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 4.0% of levothyroxine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) dissolved.

Tolerances: NLT 80% (*Q*) of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) is dissolved.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: 0.01 N hydrochloric acid containing 0.2% sodium lauryl sulfate; 500 mL

Apparatus 2: 50 rpm

Time: 30 min

Mobile phase: Acetonitrile, water, and phosphoric acid (32: 68: 0.05)

Standard stock solution: Transfer about 25 mg of USP Levothyroxine RS to a 250-mL volumetric flask. Add 50 mL of methanol, sonicate to dissolve, and dilute with methanol to volume.

Standard solution: 0.0004 mg/mL of USP Levothyroxine RS from *Standard stock solution* in *Medium*

Sample solution: Collect the sample using a suitable glass syringe and cannula.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 7.5-cm; 5-µm packing L10

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 1 mL/min

Injection volume: 80 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 4.0% for levothyroxine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) dissolved.

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

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

M_{r2} = molecular weight of levothyroxine, 776.87

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) is dissolved.

▲**Test 7:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

Medium: 0.01 N hydrochloric acid containing 0.2% sodium lauryl sulfate; 500 mL

Apparatus 2: 75 rpm

Time: 15 min

Solution A: 0.1% (v/v) phosphoric acid in water

Mobile phase: Methanol and *Solution A* (63:37)

Sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first few milliliters.

Standard stock solution: 0.1 mg/mL of USP Levothyroxine RS in methanol. Sonicate as needed to dissolve.

Standard solution: USP Levothyroxine RS in *Medium*, from the *Standard stock solution* at a concentration similar to that of the *Sample solution*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 10-µm packing L1

Temperatures

Autosampler: 12°

Column: 25°

Flow rate: 2 mL/min

Injection volume: 800 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 4.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

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

M_{r2} = molecular weight of levothyroxine, 776.87

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) is dissolved.▲ (RB 1-Jun-2022)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Limit of Liothyronine Sodium**

[Note—Use *Sample solution 2* for Tablets labeled to meet the requirements of *Dissolution Test 3*. For all other products, use the *Sample solution*.]

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

Liothyronine standard solution: 0.2 µg/mL of liothyronine from *Liothyronine stock solution*, in *Mobile phase*

Analysis

Samples: *Sample solution* and *Liothyronine standard solution*

Calculate the percentage of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$) in the portion of Tablets 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 *Liothyronine standard solution*

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

C_U = nominal concentration of levothyroxine sodium in the *Sample solution* (µg/mL)

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

M_{r2} = molecular weight of liothyronine, 650.98

Acceptance criteria: NMT 2.0% of liothyronine sodium

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

• **USP Reference Standards ⟨11⟩**

USP Levothyroxine RS

USP Liothyronine RS

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

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

Chromatographic Database Information: Chromatographic Database

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