Levothyroxine Sodium Tablets

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* below) 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

- **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.

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

- **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,**• (IRA 1-Sep-2016) **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*• (IRA 1-Sep-2016)
Analysis
•**Samples:** *Sample solution* and *Liothyronine standard solution*• (IRA 1-Sep-2016)
Calculate the percentage of levothyroxine 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*• (IRA 1-Sep-2016)
C_S = concentration of USP Liothyronine RS in the •*Liothyronine standard solution*• (IRA 1-Sep-2016) (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