Levothyroxine Sodium Tablets

Type of Posting	Revision Bulletin
Posting Date	27–Sep–2019
Official Date	01–Oct–2019
Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Levothyroxine Sodium Tablets monograph. The purpose for the revision is to add *Dissolution Test 5* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

• *Dissolution Test 5* was validated using a Waters XSelect HSS Cyano brand 4.6-mm x 7.5-cm column with 5-µm packing L10. The typical retention time for levothyroxine is about 6.5 min.

The Levothyroxine Sodium Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Andrea F Carney, Scientific Liaison (301-816-8155 or afc@usp.org).

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*) 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.▲ (RB 1-Oct-2019)

• **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