Levothyroxine Sodium Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	28–Feb–2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 3

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 3 Expert Committee intends to revise the Levothyroxine Sodium Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Levothyroxine Sodium Tablets monograph to add *Dissolution Test 6*.

- *Dissolution Test 6* was validated using a Zorbax Eclipse XDB C18 brand of 4.6-mm x 15-cm column with 5-µm L1 packing. The typical retention time for levothyroxine is about 7 min.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Andrea F. Carney, Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8155 or afc@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

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.

▲**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

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

Apparatus 1: 75 rpm

Time: 30 min

Solution A: 1 mL of trifluoroacetic acid in 1000 mL of water

Solution B: 0.2 mL of trifluoroacetic acid in 1000 mL of methanol

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	35	65
7	35	65
9	30	70
11	10	90
12	35	65
15	35	65

Diluent: 0.01 N sodium hydroxide and methanol (50:50)
Standard stock solution: 0.03 mg/mL of USP Levothyroxine RS in *Diluent*. Sonicate, as needed, to dissolve.
Standard solution: USP Levothyroxine RS in *Medium* from *Standard stock solution* at a concentration similar to that of the *Sample solution*
Sample solution: Using a glass pipette, pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding NLT 5 mL.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Autosampler: 20°
Column: 30°
Flow rate: 1.5 mL/min
Injection volume: 300 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
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. ▲ (TBD)

- **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