Levothyroxine Sodium Tablets

DEFINITION

Levothyroxine Sodium Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of levothyroxine sodium (C15H10I4NNaO4).

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

<table>
<thead>
<tr>
<th>Tablet Strength (µg/Tablet of Levothyroxine Sodium)</th>
<th>Number of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 100</td>
<td>20</td>
</tr>
<tr>
<td>At least 100 but less than 200</td>
<td>15</td>
</tr>
<tr>
<td>200 or more</td>
<td>10</td>
</tr>
</tbody>
</table>

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 (C15H10I4NNaO4) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_0}{r_s} \times \frac{C_s}{C_U} \times \frac{M_1}{M_2} \times 100 \right)
\]

where:

- \( r_0 \) = 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)
- \( M_1 \) = molecular weight of levothyroxine sodium, 798.85 g/mol
- \( M_2 \) = molecular weight of levothyroxine, 776.87 g/mol

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 L10

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 (C15H10I4NNaO4) dissolved.

Tolerances: NLT 70% (Q) of the labeled amount of levothyroxine sodium (C15H10I4NNaO4) 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 (C15H10I4NNaO4) dissolved.

Tolerances: NLT 80% (Q) of the labeled amount of levothyroxine sodium (C15H10I4NNaO4) is dissolved.
Levothyroxine

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 (C15H11I3NNaO4) dissolved.

Tolerances: NLT 80% (Q) of the labeled amount of levothyroxine sodium (C15H11I3NNaO4) 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 (C15H11I3NNaO4) dissolved.

Tolerances: NLT 80% (Q) of the labeled amount of levothyroxine sodium (C15H11I3NNaO4) 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.]


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

Analysis
Samples: Sample solution and Liothyronine standard solution (RA 1-Sep-2016)

Calculate the percentage of liothyronine sodium (C13H11I4NNaO4) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_d}{r_i} \right) \times \left( \frac{C_d}{C_0} \right) \times \left( \frac{M_{w1}}{M_{w2}} \right) \times 100
\]

\[r_d\] = peak response of liothyronine from the Sample solution

\[r_i\] = peak response of liothyronine from the Liothyronine standard solution (RA 1-Sep-2016)

\[C_d\] = concentration of USP Liothyronine RS in the Liothyronine standard solution (µg/mL)

\[C_0\] = nominal concentration of liothyronine sodium in the Sample solution (µg/mL)

\[M_{w1}\] = molecular weight of liothyronine sodium, 672.46

\[M_{w2}\] = 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