Levothyroxine Sodium Tablets

» Levothyroxine Sodium Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$).

(Official until October 3, 2009)

Change to read:

» Levothyroxine Sodium Tablets contain ▲not less than 95.0 percent and not more than 105.0 percent▲*USP32* of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$).

(Official October 3, 2009)

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*.

Change to read:

Identification—■The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to the levothyroxine peak in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.■2S *(USP32)*

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 minutes.

Determine the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of methanol and 0.1% phosphoric acid (60 : 40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a stock solution of USP Levothyroxine RS in methanol having a known concentration of about 0.1 mg per mL. Dilute this stock solution with *Medium* to obtain a solution having a concentration similar to that expected in the *Test solution*.

Test solution—[NOTE—Prior to use, check the filters for absorptive loss of drug.] Use a filtered portion of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation is not more than 4.0%.

Procedure—Separately inject equal volumes (about 800 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 45 minutes.

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

Medium, Apparatus, Mobile phase, Standard solution, Test solution, Chromatographic system, and *Procedure*—Proceed as directed for *Test 1.*

Time: 15 minutes.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 15 minutes.

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

Medium, Apparatus, Time, Standard solution, and *Test solution*—Proceed as directed for *Test 1*. [NOTE—Filter the *Standard solution* in a manner identical to the *Test solution*.]

Determine the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (65 : 35) with 0.5 mL of phosphoric acid per L. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L10. The column temperature is maintained at 30°. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation is not more than 4.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 45 minutes.

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 µg and 175 µg of levothyroxine sodium; 900 mL for Tablets labeled to contain 200 µg or 300 µg of levothyroxine sodium.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Determine the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and 85% orthophosphoric acid (700 : 500 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a stock solution by transferring about 100 mg of USP Levothyroxine RS, accurately weighed, to a 100-mL volumetric flask. Add 80 mL of alcohol and 1 mL of 1 N hydrochloric acid, sonicate for about 2 minutes, dilute with alcohol to volume, and mix. Dilute this stock solution with a mixture of alcohol and water (1 : 1) to obtain a solution having a concentration of 0.01 mg of levothyroxine per mL. Dilute this intermediate solution with *Medium* to obtain a solution having a concentration similar to that expected in the *Test solution.*

Test solution—Use a centrifuged portion of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.0-mm × 12.5-cm column that contains packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation is not more than 4.0%.

Procedure—Separately inject equal volumes (about 500 µL) of the *Standard solution* and the *Test solution* into the chromatograph,

record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Change to read:

Limit of liothyronine sodium—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay* under *Levothyroxine Sodium*.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—•Use *Assay preparation 2* for Tablets labeled to meet the requirements of *Dissolution Test 3*. For all other products,•(RB 1-Feb-2010) use the *Assay preparation.*

Procedure—Proceed as directed in the *Assay* under *Levothyroxine Sodium*. Calculate the percentage of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$) in the portion of Tablets taken by the formula:

$$\bullet 100(672.96/650.98)(C_S / C_U)(r_U / r_S \bullet_{\text{(RB 1-Feb-2010)}})$$

in which 672.96 and 650.98 are the molecular weights of liothyronine sodium and liothyronine, respectively; $\bullet C_S \bullet_{\text{(RB 1-Feb-2010)}}$ is the concentration, in µg per mL, of USP Liothyronine RS in the *Standard solution;* $\bullet C_U$ is the concentration, in µg per mL, of levothyroxine sodium in the *Test solution*, based on the label claim;• (RB 1-Feb-2010) and r_U and r_S are the liothyronine peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 2.0% of liothyronine is found.

Change to read:

Assay—•[NOTE—Use *Assay preparation 2* for Tablets labeled to meet the requirements of *Dissolution Test 3*. For all other products, use the *Assay preparation*.]•(RB 1-Feb-2010)

Mobile phase, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Levothyroxine Sodium*.

•*Diluent*—Prepare a mixture of methanol and water (6 : 4), containing 0.5 mL of phosphoric acid per L of the mixture.•(RB 1-Feb-2010)

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 µg of levothyroxine sodium, to a centrifuge tube, add 2 glass beads, pipet 10 mL of *Mobile phase* into the tube, and mix on a vortex mixer for 3 minutes. Centrifuge to obtain a clear supernatant, filtering if necessary.

•*Assay preparation 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, accurately add 100.0 mL of *Diluent*, and shake by mechanical means for at least 30 minutes, or until the Tablets are fully disintegrated. Pass through a 0.45-µm PTFE filter.

Table 1

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

• (RB 1-Feb-2010)

Procedure—Proceed as directed in the *Assay* under *Levothyroxine Sodium*. Calculate the •percentage of the labeled amount• (RB 1-Feb-2010) of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) in the portion of Tablets taken by the formula:

$$\bullet 100(798.85/776.87)(C_S / C_U)(r_U / r_S)\bullet_{\text{(RB 1-Feb-2010)}}$$

in which 798.85 and 776.87 are the molecular weights of levothyroxine sodium and levothyroxine, respectively; $\bullet C_S \bullet_{\text{(RB 1-Feb-2010)}}$ is the concentration, in µg per mL, of USP Levothyroxine RS in the *Standard preparation;* $\bullet C_U$ is the concentration, in µg per mL, of levothyroxine sodium in the *Assay preparation*, based on the label claim;• (RB 1-Feb-2010) and r_U and r_S are the levothyroxine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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