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Thyroid Tablets

DEFINITION

Thyroid Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of levothyroxine and liothyronine, the labeled amounts being 38 µg of levothyroxine and 9 µg of liothyronine for each 65 mg of the labeled content of thyroid.

IDENTIFICATION

• **A.** The retention times of the peaks for liothyronine and levothyroxine of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• **Procedure**

Mobile phase: Acetonitrile, water, and phosphoric acid (350:650:5), filtered and degassed

Reducing buffer solution: Freshly prepare 0.04 M tris(hydroxymethyl)aminomethane and 0.05 M methimazole in 0.11 M sodium chloride. Adjust, if necessary, with 6 N hydrochloric acid or 0.1 N sodium hydroxide to a pH of 8.4 ± 0.05.

Proteolytic enzyme: Freshly prepare a solution containing 3 mg/mL of bacterial protease[1] in *Reducing buffer solution*.

Enzyme deactivating solution: Phosphoric acid in acetonitrile (1:99)

Standard stock solution: Transfer accurately weighed quantities of about 9 mg of USP Liothyronine RS and about 38 mg of USP Levothyroxine RS to a 100-mL volumetric flask, add 50 mL of a mixture of acetonitrile, water, and ammonium hydroxide (500:500:1) and swirl to dissolve. Dilute with a mixture of acetonitrile and water (1:1) to volume, and mix. [Note—Protect solutions from light.]

Standard solution: Pipet 5 mL of the freshly prepared *Standard stock solution* into a 250-mL volumetric flask, dilute with *Reducing buffer solution* to volume, and mix to obtain a solution having known concentrations of about 1.8 µg/mL of liothyronine and 7.6 µg/mL of levothyroxine. Pipet 5 mL of this solution into a screw-capped 16- × 125-mm culture tube. Pipet 2 mL of *Enzyme deactivating solution* into the tube, place the cap on the tube, and shake the mixture vigorously. [Note—Prepare on the day of use.]

Sample solution: Weigh and finely powder NLT 20 Tablets. Transfer an accurately weighed portion of finely powdered Thyroid, equivalent to about 38 µg of levothyroxine, to a screw-capped 16- × 125-mm culture tube that has been flushed previously with nitrogen. Taking precautions to avoid unnecessary exposure to air, pipet 5 mL of *Proteolytic enzyme* into the tube. Allow nitrogen to flow gently over the mixture for 5 min. Place the cap on the tube, mix to disperse the contents, and place in a covered water bath maintained at a temperature of 37 ± 1° for 28 h. [Note—Protect the contents of the tubes from light.]

Examine occasionally, and mix as necessary to ensure dispersion. At the end of the incubation period, pipet 2 mL of *Enzyme deactivating solution* into the tube, place the cap on the tube, mix vigorously, and centrifuge at about 2000 rpm for 5 min. Pass the supernatant through a filter of 0.45-µm pore size, discarding the first 1 mL of the filtrate.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: ▲4.6-mm▲ (ERR 1-Apr-2023) × 25-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 200 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.8 for liothyronine and levothyroxine

Relative standard deviation: NMT 2.0% for replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in µg, of liothyronine ($C_{15}H_{12}I_3NO_4$) and levothyroxine ($C_{15}H_{11}I_4NO_4$) in the portion of Tablets taken:

$$\text{Result} = (V \times C) \times (r_U/r_S)$$

V = volume of *Sample solution*, 7 mL

C = concentration of the corresponding Reference Standards in the *Standard solution* (µg/mL)

r_U = peak response of the corresponding analytes from the *Sample solution*

r_S = peak response of the corresponding analytes from the *Standard solution*

Acceptance criteria: 90.0%–110.0% of the labeled amounts of liothyronine ($C_{15}H_{12}I_3NO_4$) and levothyroxine ($C_{15}H_{11}I_4NO_4$)

PERFORMANCE TESTS

- **Disintegration ⟨701⟩**

Time: 15 min, with disks

- **Uniformity of Dosage Units ⟨905⟩**

Standard stock solution: Accurately weigh 1.69 g of potassium iodate and transfer to a 1-L volumetric flask. Dissolve in about 200 mL of water, dilute with water to volume, and mix. This is a stock solution having a concentration of about 1 mg/mL with respect to iodine.

Standard solution: Pipet 8 mL of the *Standard stock solution* into a 250-mL volumetric flask, dilute with water to volume, and mix. Transfer an appropriate aliquot, based on the dosage being analyzed (i.e., ¼ grain, 1 mL; ½ grain, 2 mL; 1 grain, 4 mL; 1½ grains, 6 mL; 2 grains, 8 mL; 2½ grains, 10 mL; 3 grains, 12 mL; 4 grains, 16 mL; 5 grains, 20 mL), to a 100-mL volumetric flask containing 8 g of anhydrous potassium carbonate dissolved in 70 mL of water. Add 1 mL of bromine TS, mix, add sufficient sodium sulfite (about 20 mg) until the solution becomes colorless, and dilute with water to volume, and mix.

Sample solution: Crush 1 Tablet in a porcelain crucible with a glass rod. Remove any sample adhering to the glass rod with a spatula, and add it to the crucible. Add 4 g of anhydrous potassium carbonate, mix carefully, and gently tap the crucible several times to compact the mixture. Overlay with 4 g more of anhydrous potassium carbonate, and again compact the material thoroughly by tapping. Place the crucible in a preheated muffle furnace, and ignite at 675°–700° for 25 min. Cool, add 30 mL of water, carefully heat on a hot plate to dissolve the residue, and pass through a funnel with a glass wool plug into a 100-mL volumetric flask. Repeat the heating and filtration with two additional 30-mL portions of water, and add these filtrates to the volumetric flask. Add 1 mL of bromine TS, mix, add sufficient sodium sulfite (about 20 mg) until the solution becomes colorless, and mix. Dilute with water to volume, and mix.

Blank solution: Add 8 g of anhydrous potassium carbonate into a 100-mL volumetric flask, and dissolve it in 70 mL of water. Add 1 mL of freshly prepared bromine TS, mix, add sufficient sodium sulfite (about 20 mg) until the solution becomes colorless, and dilute with water to volume, and mix.

Analysis: Transfer 10 mL of the *Sample solution* to a dry polarographic cell. Bubble nitrogen through the solution for 5 min, then direct the stream of nitrogen above the solution. Use a suitable differential pulse polarograph equipped with a saturated calomel reference electrode and a dropping mercury electrode with a 1-s drop time. Scan from −0.8 V to −1.5 V at the rate of 5 mV/s, and 50-mV pulses. Record the polarogram of the *Sample solution*, the *Standard solution*, and the *Blank solution*. At the peaks near −1.18 V in the polarograms from the *Standard solution* and the *Sample solution*, measure the heights from the baseline, as established by the *Blank solution*.

Calculate the amount of iodine, in µg, in the Tablet taken:

$$\text{Result} = (A_{r1}/A_{r2}) \times (r_U/r_S) \times (C \times V)$$

A_{r1} = atomic weight of iodine (I), 126.90

A_{r2} = atomic weight of potassium iodate (KIO_3), 214.00

r_U = peak height from the *Sample solution*

r_S = peak height from the *Standard solution*

C = concentration of the aliquot portion of potassium iodate solution used to prepare the *Standard solution*, 54.08 µg/mL

V = volume of the aliquot portion of potassium iodate solution used to prepare the *Standard solution* (mL)

Proceed as directed for *Uniformity of Dosage Units ⟨905⟩, Content Uniformity*, using the results obtained by this procedure to determine the total iodine content of individual Tablets, and use the *Sample solution* from the *Assay* to perform the composite determination for iodine.

Acceptance criteria: The amount of iodine in each Tablet is within 85.0%–115% of the composite assay for iodine, with a relative standard deviation of NMT 6.0%.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** Meet the requirements of the tests for the absence of *Salmonella* species and *Escherichia coli*

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **Labeling:** Label the Tablets to indicate the amount of thyroid in either mg or grain, or both.

• **USP Reference Standards ⟨11⟩**
USP Levothyroxine RS
USP Liothyronine RS

[1] A suitable grade is available as "Pronase" (Catalog number 53702) from Calbiochem-Behring, P.O. Box 12087, San Diego, CA 92112.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
THYROID TABLETS	Jennifer Tong Sun Senior Scientist II	BIO32020 Biologics Monographs 3 - Complex Biologics and Vaccines
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	BIO32020 Biologics Monographs 3 - Complex Biologics and Vaccines

Chromatographic Database Information: Chromatographic Database

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