Levothyroxine Sodium Powder

Dissolution <*6.10*> Peform the test with an accurately weighed quantity of Levothyroxine Sodium Powder, equivalent to about 0.1 mg of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) according to the labeled amount, at 100 revolutions per minute according to the Paddle method (drop the sample so that it disperses in the medium) using 900 mL of water as the dissolution medium. Withdraw not less than 5 mL of the medium at the specified minute after starting the test, centrifuge, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 27 mg of Levothyroxine RS, previously dried in vacuum with phosphorus (V) oxide at 60ºC for 4 hours, and dissolve in methanol to make exactly 200 mL. To exactly 2 mL of this solution add methanol to make exactly 50 mL. Further, pipet 2 mL of this solution, add water to make exactly 100mL, and use this solution as the standard solution. Perform the test with exactly 200 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, A_T and A_S, of levothyroxine in each solution.

The requirements are met if Levothyroxine Sodium Powder conforms to the dissolution requirements.

Dissolution rate (%) with respect to the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$)
$= M_S/M_T \times A_T/A_S \times 1/C \times 9/25 \times 1.028$

M_S: Amount (mg) of Levothyroxine RS

M_T: Amount (g) of sample

C: Labeled amount (mg) of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$) in 1 g

Operating conditions —

Detector: An ultraviolet absorption photometer (wavelength: 223 nm).

Column: A stainless steel column 4 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35ºC.

Mobile phase: A mixture of methanol, water and phosphoric acid (1200:800:1).

Flow rate: Adjust the flow rate so that the retention time of levothyroxine is about 8 minutes.

System suitability —

System performance: When the procedure is run with 200 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of levothyroxine are not less than 2000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 200 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of levothyroxine is not more than 3.0%.

Dissolution Requirements

Labeled amount	Specified minute	Dissolution rate
0.1 mg/g	60 minutes	Not less than 70%

Levothyroxine RS $C_{15}H_{11}I_4NO_4$:776.87 *O*-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-L-tyrosine. It meets the following requirements. Purify by the following method if needed.

Purification method—Dissolve 1 g of levothyroxine in 25 mL of a mixture of ethanol (99.5) and a solution of 2-aminoethanol (61 in 500) (5:2), and filter. Adjust the pH of the filtrate to 4 to 5 with 2 mol/L hydrochloric acid TS, cool with ice for 1 hour, and centrifuge. Wash the precipitate 3 times with 25 mL each of a mixture of ethanol (95) and water (5:2), and dry in vacuum over phosphorus (V) oxide at 60ºC for 4 hours.

Description—Levothyroxine RS occurs as a white to light yellow-brown powder.

Identification—Determine the absorption spectrum of diluted sodium hydroxide TS (1 in 10,000) of Levothyroxine RS as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: it exhibits a maximum between 323 nm and 327 nm.

Related substances—To 0.10 g of Levothyroxine RS add exactly 10 mL of a mixture of ethanol (95) and ammonia water (28) (14:1) to dissolve, and use this solution as the sample solution. Perform the test with these solutions as directed under Thin-layer Chromatography <*2.03*>. Spot 2 μL of the sample solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of *t*-butyl alcohol, *t*-amyl alcohol, water, ammonia water (28) and 2-butanone (59:32:17:15:7) to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution prepared by dissolving 0.3g of ninhydrin in 100 mL of a mixture of 1-butanol and acetic acid (100) (97:3), and heat at 100ºC for 3 minutes: no red-purple spots other then principal spot appear.

Loss on drying <*2.41*>: not more than 1.0% (0.5g, in vacuum, phosphorus (V) oxide, 60ºC, 4 hours).

Content: not less than 99.0%. Assay—Prepare the test solution with accurately 25 mg of Levothyroxine RS, previously dried, as directed under Oxygen Flask Combustion Method <*1.06*> using a mixture of 10 mL of a solution of sodium hydroxide (1 in 100) and 1 mL of a freshly prepared solution of sodium bisulfate (1 in 100) as the absorbing liquid. Apply a small amount of water to the upper part of the Apparatus A, pull out C carefully, wash C, B and the inner side of A with 40 mL of water. To the test solution add 1 mL of bromine-acetic acid TS, insert the stopper C, and shake vigorously for 1 minute. Wash C, B and the inner side of A with 40 mL of water, add 0.5 mL of formic acid, stopper the flask with C again, shake vigorously for 1 minute, and wash C, B and the inner side of A with 40 mL of water. Bubble the solution with enough nitrogen gas in A to remove the oxygen and excess bromide, add 0.5 g of potassium iodide to dissolve. Add immediately 3 mL of dilute sulfuric acid, mix, and allow to stand for 2 minutes. Titrate <*2.50*> the solution with 0.02 mol/L sodium

thiosulfate VS (indicator: 3 mL of starch TS). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 0.02 mol/L sodium thiosulfate VS
= 0.6474 mg of $C_{15}H_{11}I_4NO_4$