Edition: BP 2025 (Ph. Eur. 11.6 update)

Liothyronine Tablets

General Notices

Action and use

Thyroid hormone replacement.

DEFINITION

Liothyronine Tablets contain Liothyronine Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of liothyronine sodium, $C_{15}H_{11}I_3NNaO_4$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

In the test for Uniformity of content, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Plastic containers must not be used to prepare and store solutions.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.
(c) Place a number of tablets containing 40 µg of Liothyronine Sodium in the dissolution vessel.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

(1) After 45 minutes withdraw a sample of the medium and filter (a GMF filter is suitable), discarding the first 6 mL of the filtrate. To 10 volumes of the resulting solution, add 0.25 volume of a 2% v/v solution of *diethylamine* and 0.4 volume of 0.1 M *sodium hydroxide*.
(2) 0.004% w/v of *liothyronine sodium EPCRS* in 0.001M *sodium hydroxide*. Dilute with *water* to produce a solution containing 0.000008% w/v of *liothyronine sodium EPCRS*. To 10 volumes of the resulting solution, add 0.25 volume of a 2% v/v solution of *diethylamine* and 0.4 volume of 0.1M *sodium hydroxide*.
(3) 0.004% w/v of *liothyronine sodium EPCRS* in 0.001M *sodium hydroxide* and 0.004% w/v of *levothyroxine sodium EPCRS* in *water*. Dilute with *water* to produce a solution containing 0.000008% w/v of *liothyronine sodium EPCRS*. To 10 volumes of the resulting solution, add 0.25 volume of a 2% v/v solution of *diethylamine* and 0.4 volume of 0.1M *sodium hydroxide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 100 volumes of *acetonitrile R1* and 900 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of liothyronine is about 6 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and levothyroxine is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of liothyronine sodium, $C_{15}H_{11}I_3NNaO_4$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{11}I_3NNaO_4$ in *liothyronine sodium EPCRS*.

LIMITS

The amount of liothyronine sodium released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A. Prepare the solutions immediately before use and protect from light.

Solution A 25 volumes of *methanol* and 75 volumes of 0.1M *sodium hydroxide*.

(1) To a quantity of powdered tablets containing 0.25 mg of Liothyronine Sodium add 20 mL of solution A. Shake for about 45 minutes and then mix with the aid of ultrasound. Dilute to 25 mL, centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.0002% w/v of *liothyronine sodium impurity standard BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Phenomenex Gemini NX C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 200 µL of each solution.

MOBILE PHASE

Mobile phase A 0.136% w/v of *potassium dihydrogen orthophosphate* in *water*, adjusted to pH 2.2 with *orthophosphoric acid*.

Mobile phase B 100 volumes of mobile phase A, 400 volumes of *methanol* and 500 volumes of *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	70	30	isocratic
5-30	70→35	30→65	linear gradient
30-42	35→25	65→75	linear gradient
42-47	25→5	75→95	linear gradient
47-52	5	95	isocratic
52-53	5→70	95→30	linear gradient
53-62	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to liothyronine (retention time about 21 minutes) are: impurity E, about 0.6; impurity 1, about 0.9; impurity A, about 1.2; impurity C, about 1.7 and impurity D, about 1.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between liothyronine and impurity A is at least 10.0;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (4) is at least 25.

LIMITS

Identify any peak corresponding to impurity 1 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (6%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks*, excluding impurity 1, is not greater than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3.5%);

the sum of the areas of all *secondary peaks*, is not greater than 8 times the area of the principal peak in the chromatogram obtained with solution (2) (8%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Liothyronine Sodium comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 0.05M *sodium hydroxide*. Carry out the test protected from light.

(1) To one tablet, add 1 mL of 0.05M *sodium hydroxide* and mix with the aid of ultrasound until the tablet is fully dispersed, cool and shake for 2 minutes. Add sufficient 0.05M *sodium hydroxide* to produce a solution containing 0.0005% w/v of Liothyronine Sodium, filter through a glass microfibre filter paper (Whatman GF/C is suitable) and use the filtrate.
(2) 0.00055% w/v of *liothyronine sodium EPCRS*.
(3) 0.0005% w/v of *liothyronine sodium EPCRS* and 0.0005% w/v of *levothyroxine sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Nucleosil 5 CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile R1* and 700 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention time of liothyronine is about 7 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and levothyroxine is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}I_3NNaO_4$ in each tablet using the declared content of $C_{15}H_{11}I_3NNaO_4$ in *liothyronine sodium EPCRS*.

ASSAY

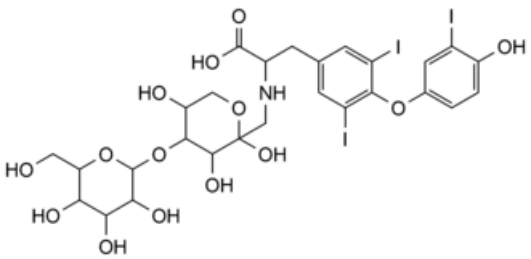
Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

Liothyronine Tablets should be protected from light.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Liothyronine Sodium and:



1. 3-(4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl)-2-(((4,5,6-trihydroxy-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)amino)propanoic acid (Liothyronine-lactose maillard impurity).