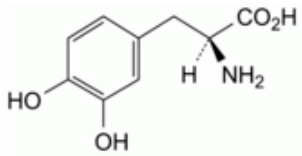
Edition: BP 2025 (Ph. Eur. 11.6 update)

Levodopa

General Notices

(Ph. Eur. monograph 0038)



$C_9H_{11}NO_4$ 197.2 *59-92-7*

Action and use

Dopamine precursor; treatment of Parkinson's disease.

Preparations

Co-beneldopa Capsules

Co-beneldopa Dispersible Tablets

Co-beneldopa Prolonged-release Capsules

Co-careldopa Tablets

When L-dopa is prescribed or demanded, Levodopa shall be dispensed or supplied.

Ph Eur

DEFINITION

(2*S*)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Slightly soluble in water, practically insoluble in ethanol (96 per cent). It is freely soluble in *1 M hydrochloric acid* and sparingly soluble in *0.1 M hydrochloric acid*.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *levodopa CRS*.

TESTS

Appearance of solution

The solution is not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 1.0 g in a 103 g/L solution of *hydrochloric acid R* and dilute to 25 mL with the same solution.

pH (*2.2.3*)

4.5 to 7.0.

Shake 0.10 g with 10 mL of *carbon dioxide-free water R* for 15 min.

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions.*

Solution A 10.3 g/L solution of *hydrochloric acid R*.

Test solution Dissolve 0.100 g of the substance to be examined in solution A and dilute to 25 mL with solution A.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with solution A. Dilute 5.0 mL of this solution to 100.0 mL with solution A.

Reference solution (b) Dissolve 8 mg of *tyrosine R* (impurity B) and 4 mg of *3-methoxy-L-tyrosine R* (L-isomer of impurity C) in 2 mL of the test solution and dilute to 50 mL with solution A. Dilute 5 mL of this solution to 100 mL with solution A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *di-isobutyloctadecylsilyl silica gel for chromatography R* (5 µm) with a pore size of 8 nm.

Mobile phase:

— *mobile phase A*: 0.1 M phosphate buffer solution pH 3.0 R;

— *mobile phase B*: *methanol R*, 0.1 M phosphate buffer solution pH 3.0 R (18:85 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	90	10
18 - 22	90 → 0	10 → 100
22 - 35	0	100

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to levodopa (retention time = about 6 min): impurity A = about 0.7; impurity B = about 2; impurity C = about 3.5.

System suitability Reference solution (b):

— *resolution*: minimum 10 between the peaks due to levodopa and impurity B.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 2.2;

— *impurity B*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— *total*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Enantiomeric purity

Liquid chromatography (2.2.29). *Use freshly prepared solutions*.

Test solution Dissolve 25 mg of the substance to be examined in the mobile phase and dilute to 25 mL with the mobile phase.

Reference solution (a) Dilute 5.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 50.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of *D-dopa R* (impurity D) in 10 mL of the test solution. Dilute 1 mL of this solution to 100 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve separately 200 mg of *copper acetate R* and 387 mg of *N,N-dimethyl-L-phenylalanine R* in 250 mL of *water R*; mix the 2 solutions and adjust immediately to pH 4.0 with *acetic acid R*; add 50 mL of *methanol R* and dilute to 1000 mL with *water R*; mix and filter.

Flow rate 1 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time Twice the retention time of levodopa.

Relative retention With reference to levodopa (retention time = about 7 min): impurity D = about 0.4.

System suitability Reference solution (b):

— *resolution*: minimum 5 between the peaks due to impurity D and levodopa.

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Loss on drying (*2.2.32*)

Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g, heating if necessary, in 5 mL of *anhydrous formic acid R*. Add 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

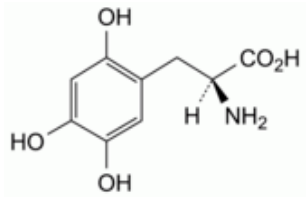
1 mL of *0.1 M perchloric acid* is equivalent to 19.72 mg of $C_9H_{11}NO_4$.

STORAGE

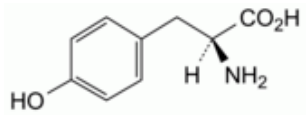
Protected from light.

IMPURITIES

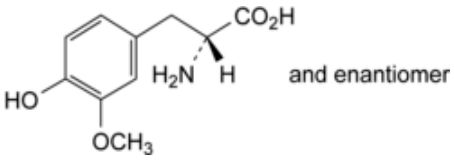
Specified impurities *A, B, C, D.*



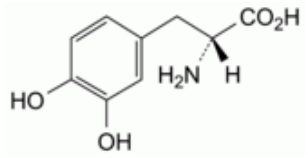
A. (2*S*)-2-amino-3-(2,4,5-trihydroxyphenyl)propanoic acid,



B. (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid (tyrosine),



C. (2*RS*)-2-amino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid (3-methoxy-DL-tyrosine),



D. (2*R*)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (D-dopa).

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