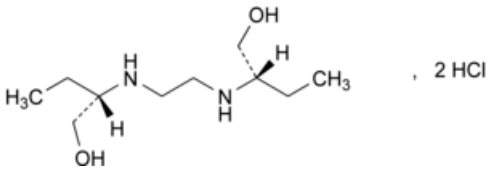
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ethambutol Hydrochloride

General Notices

(Ph. Eur. monograph 0553)



$C_{10}H_{26}Cl_2N_2O_2$ 277.2 *1070-11-7*

Action and use

Antituberculosis drug.

Preparations

Ethambutol Oral Solution

Ethambutol Tablets

Ph Eur

DEFINITION

(2*S*,2′*S*)-2,2′-(Ethylenediimino)dibutan-1-ol dihydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder, hygroscopic.

Solubility

Freely soluble in water, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D, E.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ethambutol hydrochloride CRS*.

B. Examine the chromatograms obtained in the test for impurity A.

Results The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (b).

C. Dissolve 0.1 g in 10 mL of *water R*. Add 0.2 mL of *copper sulfate solution R* and 0.5 mL of *dilute sodium hydroxide solution R*; a blue colour is produced.
D. It gives reaction (a) of chlorides (2.3.1).
E. Related substances (see Tests).

TESTS

pH (2.2.3)

3.7 to 4.0.

Dissolve 0.2 g in 10 mL of *carbon dioxide-free water R*.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution (a) Dissolve 0.50 g of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Test solution (b) Dilute 1 mL of test solution (a) to 10 mL with *methanol R*.

Reference solution (a) Dissolve 50.0 mg of *aminobutanol R* (impurity A) in *methanol R* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b) Dissolve 50 mg of *ethambutol hydrochloride CRS* and 5 mg of *aminobutanol R* in *methanol R* and dilute to 10 mL with the same solvent.

Plate *TLC silica gel plate R*.

Mobile phase *concentrated ammonia R*, *water R*, *methanol R* (10:15:75 *V/V/V*).

Application 2 µL.

Development Over 2/3 of the plate.

Drying In air; heat at 110 °C for 10 min.

Detection Cool then spray with *ninhydrin solution R1*; heat at 110 °C for 5 min.

System suitability reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Limit:

— *impurity A*: any spot due to impurity A in the chromatogram obtained with test solution (a) is not more intense than the spot in the chromatogram obtained with reference solution (a) (1.0 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*

Test solution Suspend 4.0 mg of the substance to be examined in 4.0 mL of *acetonitrile R1* and add 100 µL of *triethylamine R*. Sonicate the mixture for 5 min. Add 15 µL of *(R)-(+)-α-methylbenzyl isocyanate R* and heat at 70 °C for 20 min.

Reference solution (a) Dilute 0.50 mL of the test solution to 100.0 mL with *acetonitrile R1*.

Reference solution (b) Treat 4.0 mg of *ethambutol for system suitability CRS* (containing impurity B) as described for the test solution.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *methanol R*, *water R* (50:50 *V/V*);

— *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	71	29
30 - 35	71 → 0	29 → 100
35 - 37	0	100
37 - 38	0 → 71	100 → 29

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 10 µL.

Relative retention With reference to ethambutol (retention time = about 14 min): impurity B = about 1.3.

System suitability Reference solution (b):

— *resolution*: minimum 4.0 between the peaks due to ethambutol and impurity B.

Limits:

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

— *unspecified impurities with a relative retention of 0.75 to 1.5 with reference to ethambutol*: for each impurity, not more than 0.2 times the area of the peak due to ethambutol in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total (impurity B and unspecified impurities with a relative retention of 0.75 to 1.5 with reference to ethambutol)*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the peak due to ethambutol in the chromatogram obtained with reference solution (a) (0.05 per cent).

Impurity D (1,2-dichloroethane) (*2.4.24*)

Maximum 5 ppm.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *water R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 27.72 mg of $C_{10}H_{26}Cl_2N_2O_2$.

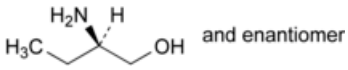
STORAGE

In an airtight container.

IMPURITIES

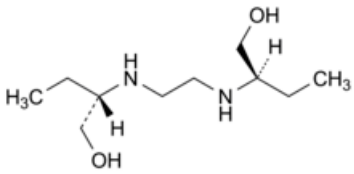
Specified impurities *A, B, D.*

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) C.

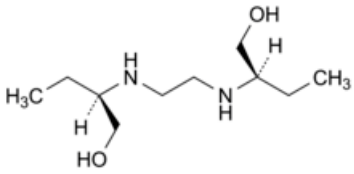


and enantiomer

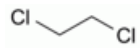
A. 2-aminobutan-1-ol,



B. (2*R*,2′*S*)-2,2′-(ethylenediimino)dibutan-1-ol (meso-ethambutol),



C. (2*R*,2′*R*)-2,2′-(ethylenediimino)dibutan-1-ol ((*R*,*R*)-ethambutol),



D. 1,2-dichloroethane (ethylene chloride).