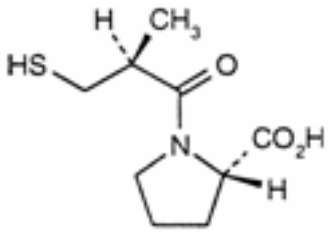
Captopril (Captoprilum)



$C_9H_{15}NO_3S$

Relative molecular mass. 217.3

Chemical name. 1-[(2*S*)-3-Mercapto-2-methylpropionyl]-L-proline; 1-[(2*S*)-3- mercapto-2-methyl-1-oxopropyl]-L-proline; CAS Reg. No. 62571-86-2.

Description. A white or almost white, crystalline powder.

Solubility. Freely soluble in water, dichloromethane R, and methanol R.

Category. Cardiovascular agent; angiotensin-converting enzyme inhibitor.

Storage. Captopril should be kept in a tightly closed container, protected from light.

Additional information. Captopril may exist in different polymorphic forms.

Requirements

Captopril contains not less than **98.0%** and not more than **102.0%** of $C_9H_{15}NO_3S$, calculated with reference to the dried substance.

Identity tests

• Either tests A and D or tests B, C, and D may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from captopril RS or with the *reference spectrum* of captopril.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R4 as the coating substance and a mixture of 75 volumes of toluene R, 25 volumes of glacial acetic acid R, and 1 volume of methanol R as the mobile phase. Apply separately to the plate 2 µl of each of 2 solutions in dichloromethane R containing (A) 5.0 mg of Captopril per mL, and (B) 5.0 mg of captopril RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in air, and spray with 5,5¢- dithiobis-2-nitrobenzoic acid/methanol TS. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. Dissolve 25 mg in 2 mL of ethanol (~750 g/l) TS, add a few crystals of sodium nitrite R and 10 mL of sulfuric acid (~100 g/l) TS, and shake; a red colour is produced.

D. Melting temperature, about 107 °C.

Specific optical rotation. Use a 10 mg/mL solution in dehydrated ethanol R and calculate with reference to the dried substance; $[\alpha]_D^{20\,°C}$ = -125° to -134°.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 20 µg/g.

Sulfated ash. Not more than 2.0 mg/g.

Loss on drying. Dry at 60°C under reduced pressure (not exceeding 0.6kPa or about 5mm of mercury) for 3 hours; it loses not more than 10 mg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (12.5cm × 4mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). Prepare the following solution to be used as the mobile phase: mix 0.05 volumes of phosphoric acid

(~1440 g/l) TS with 50 volumes of methanol R and 50 volumes of water.

Prepare the following solutions in the mobile phase: solution (A) 0.5 mg of Captopril per mL; solution (B) 10µg of Captopril per mL; and for solution (C) dissolve 10 µg of Captopril in the mobile phase, add 1 mL of iodine (0.05 mol/l) VS, and dilute to 100 mL with the mobile phase; further dilute 10 mL of this solution to 100 mL with the mobile phase.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 220nm.

Inject 20 µl of solution B and adjust the sensitivity of the system so that the height of the principal peak is not less than 40% of the full scale of the recorder. Inject 20 µl of solution C. The test is not valid unless three peaks are obtained and the resolution between the last two eluting principal peaks is at least 2.0.

Inject alternately 20 µl each of solutions A and B. Continue the chromatography for three times the retention time of the principal peak obtained with solution A.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution A, the area of any peak, other than the principal peak, is not greater than half the area of the principal peak obtained with solution B (1.0%). The sum of the areas of all the peaks, other than the principal peak, is not greater than the area of the peak obtained with solution A (2.0%). Disregard any peak with a retention time of less than 1.4 minutes or with an area less than 0.1 times that of the peak obtained with solution B.

Assay. Dissolve about 0.3 g, accurately weighed, in 100 mL of water, add 10ml of sulfuric acid (~190 g/l) TS and 1 g of potassium iodide R. Mix and titrate with potassium iodate (0.01 mol/l) VS, using starch TS as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of potassium iodate required.

Each mL of potassium iodate (0.01 mol/l) VS is equivalent to 13.04mg of $C_9H_{15}NO_3S$.