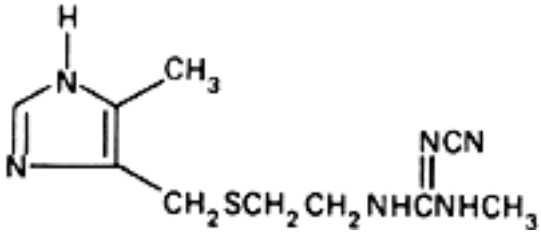
Cimetidine (Cimetidinum)

Molecular formula. $C_{10}H_{16}N_6S$

Relative molecular mass. 252.3

Graphic formula.



Chemical name. 2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]-thio]ethyl]guanidine; *N″*-cyano-*N*-methyl-*N′*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]guanidine; 1-cyano-2-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]guanidine; *N*-cyano-*N′*-methyl-*N″*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]guanidine; CAS Reg. No. 51481-61-9.

Description. A white to off-white powder; odourless or with a faint odour.

Solubility. Sparingly soluble in water; very soluble in methanol R.

Category. Antiulcer drug.

Storage. Cimetidine should be kept in a well-closed container.

Additional information. Cimetidine exists in three polymorphic forms. The polymorph specified in the monograph corresponds to the crystal form of cimetidine RS.

Requirements

Definition. Cimetidine contains not less than 98.5% and not more than 101.0% of $C_{10}H_{16}N_6S$, calculated with reference to the dried substance.

Identity tests

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum obtained from the solid state without prior solvent treatment is concordant with the spectrum similarly obtained from cimetidine RS or with the *reference spectrum* of cimetidine; no shoulder or peak is discernible at 1180 cm^{-1} (confirmation of polymorphic form).

B. Melting temperature, about 142°C.

Heavy metals. Use 1.0 g for the preparation if 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 1.0 mg/g.

Loss on drying. Dry to constant weight at 105°C; it loses not more than 10.0 mg/g.

pH value. pH of a 5.0 mg/mL solution in carbon-dioxide-free water R, 8.0-9.5.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a column 25 cm long and 4.6 mm internal diameter, packed with particles of porous silica gel or ceramic, 5-10 µm in diameter, the surface of which has been modified with chemically bonded octadecylsilyl groups. Prepare the following solvent mixture: Dilute 1 mL of glacial acetic acid R with sufficient water to produce 200 mL. To 190 mL of this solution add 10 mL of ammonium acetate (2 g/l) TS. As the mobile phase use a degassed and filtered mixture of 84 volumes of the above solvent mixture and 16 volumes of acetonitrile R. For the system suitability test prepare a solution containing 18 µg of cimetidine RS and 24 µg of caffeine RS per mL of the above solvent mixture (solution A). Further prepare a solution of the substance to be examined containing 18 µg per mL of solvent mixture (solution B). Operate with a flow rate of about 1 mL per minute. As detector use an ultraviolet spectrophotometer at a wavelength of about 228 nm, fitted with a suitable recorder. Make 6 replicate injections, each of 10 µl of solution A. Measure the peak responses; the relative standard deviation of the ratio of the responses from cimetidine to the sum of all the responses in the chromatogram, excluding any from the solvent mixture, is not more than 2.0%, and the resolution between caffeine and cimetidine is not less than 3.0. The relative retention times are about 1.0 for caffeine and 1.4 for cimetidine. Then inject 10 µl of solution B and measure the peak responses: the ratio of the response from cimetidine to the sum of all the responses in the chromatogram, excluding any from the solvent mixture, is not less than 0.99.

Assay. Dissolve about 0.25 g, accurately weighed, in 30 mL of glacial acetic acid R1, and titrate with perchloric acid (0.1 mol/l)

VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/l) VS is equivalent to 25.23 mg of $C_{10}H_{16}N_6S$.

Additional requirement for Cimetidine for parenteral use

Complies with the monograph for "Parenteral preparations".