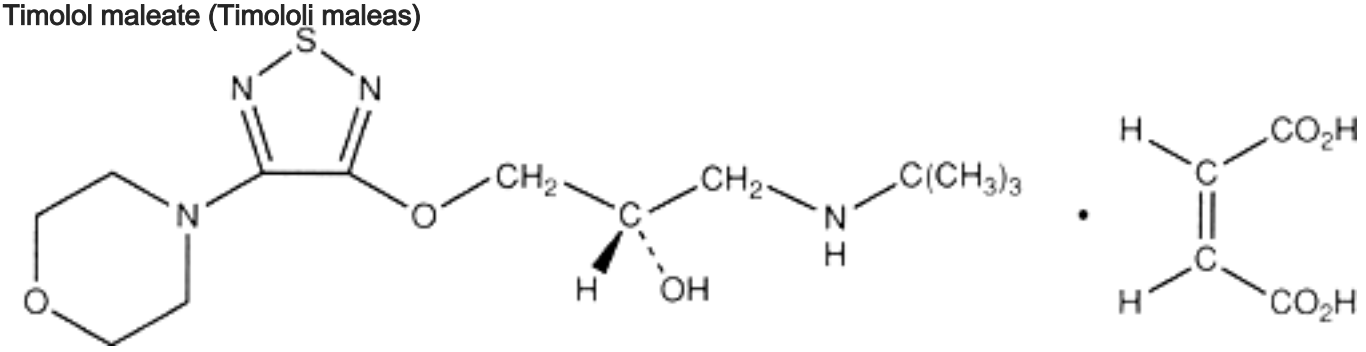
Timolol maleate (Timololi maleas)



$C_{13}H_{24}N_4O_3S,C_4H_4O_4$

Relative molecular mass. 432.5

Chemical name. (-)-(*S*)-1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt); (*S*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) (salt); CAS Reg. No. 26921-17-5.

Description. A white or almost white powder; odourless or almost odourless.

Solubility. Soluble in water, methanol R, and ethanol (~750 g/l) TS; practically insoluble in ether R.

Category. Antiglaucoma drug.

Storage. Timolol maleate should be kept in a well-closed container, protected from light.

Requirements

Timolol maleate contains not less than **98.0%** and not more than the equivalent of **101.0%** of $C_{13}H_{24}N_4O_3S,C_4H_4O_4$, calculated with reference to the dried substance.

Identity tests

• Either test A alone or tests B and C 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 timolol maleate RS or with the *reference spectrum* of timolol maleate.

B. The absorption spectrum of a 25 µg/mL solution in sulfuric acid (0.05 mol/l) VS, when observed between 230 nm and 350 nm, exhibits a maximum at about 295 nm; the absorbance of a 1-cm layer at this wavelength is about 0.52.

C. Dissolve 0.2 g in 3 mL of water, add 2 mL of sodium hydroxide (~200 g/l) TS, and shake with three quantities, each of 3 mL, of ether R. Warm the aqueous layer in a water-bath for 10 minutes, add 2 mL of bromine TS1, boil, and cool. Add 0.2 mL of this solution to 10 mg of resorcinol R dissolved in 3 mL of sulfuric acid (~1760 g/l) TS, and heat in a water-bath for 15 minutes; a bluish black colour is produced.

Specific optical rotation. Use a 50 mg/mL solution in hydrochloric acid (1 mol/l) VS; $[\alpha]_D^{20\,°C}$ = -11.7° to -12.5°.

Clarity and colour of solution. A solution of 0.2 g in 10 mL of water is clear and colourless.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry to constant mass at 100 °C under reduced pressure (not exceeding 0.6 kPa or 5 mm of mercury); it loses not more than 5.0 mg/g.

pH value. pH of a 20 mg/mL solution, 3.8-4.3.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance (a precoated plate from a commercial source is suitable) and a mixture of 80 volumes of dichloromethane R, 20 volumes of methanol R, and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of three solutions in methanol R containing (A) 50 mg of Timolol maleate per mL, (B) 0.2 mg of Timolol maleate per mL, and (C) 0.1 mg of Timolol maleate per mL. After removing the plate from the chromatographic chamber, allow it to dry in air, and examine the chromatogram in ultraviolet light (254 nm). Then expose the plate to iodine vapours for 2 hours and examine the chromatogram in daylight.

Using both methods of visualization, any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution B, and not more than two such spots are more intense than that obtained with solution C.

Assay. Dissolve about 0.85 g, accurately weighed, in 90 mL of glacial acetic acid R1, add 3 drops of 1-naphtholbenzein/acetic acid TS as indicator, and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A.

Each mL of perchloric acid (0.1 mol/l) VS is equivalent to 43.25 mg of $C_{13}H_{24}N_4O_3S,C_4H_4O_4$.

Additional requirement for Timolol maleate for sterile use

Complies with 3.2 Test for sterility.