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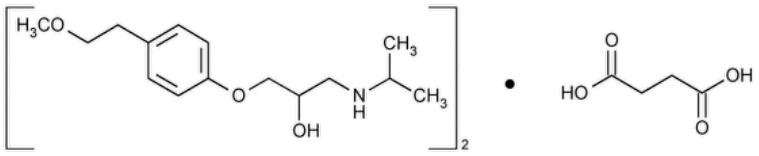
Metoprolol Succinate



$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ 652.82

2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, (±)-, butanedioate (2:1) (salt).

(±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt) CAS RN®: 98418-47-4; UNII: TH25PD4CCB.

» Metoprolol Succinate contains not less than 98.0 percent and not more than 102.0 percent of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers at controlled room temperature.

Change to read:

USP Reference standards ⟨11⟩—

USP Metoprolol Related Compound A RS

(±)1-Ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol.

$C_{14}H_{23}NO_3$ 253.34

USP Metoprolol Related Compound B RS

(±)1-Chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane.

$C_{12}H_{17}ClO_3$ 244.71

USP Metoprolol Related Compound C RS

▲4-[2-Hydroxy-3-(isopropylamino)propoxy]benzaldehyde hydrochloride.▲ (ERR 1-Jun-2020)

$C_{13}H_{19}NO_3$▲ · HCl 273.76▲ (ERR 1-Jun-2020)

USP Metoprolol Related Compound D RS

▲*N,N*-Bis{2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl}isopropylamine hydrochloride; also known as (±) *N,N*-Bis[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine hydrochloride.▲ (ERR 1-Jun-2020)

$C_{27}H_{41}NO_6$▲ · HCl 512.08▲ (ERR 1-Jun-2020)

USP Metoprolol Succinate RS

Clarity and color of solution—A solution of Metoprolol Succinate having a concentration of 20 mg per mL is not less clear than an equal volume of water in a test tube of similar size. The absorbance of the solution determined at 440 nm in a 5-cm cell, using water as the blank, is not more than 0.1.

Identification, *Spectroscopic Identification Tests* ⟨197⟩*, Infrared Spectroscopy: 197K*.

pH ⟨791⟩**:** between 7.0 and 7.6, in a solution containing 65 mg per mL.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 4 hours: it loses not more than 0.2% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Related compounds—

TEST 1—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Dissolve an accurately weighed quantity of Metoprolol Succinate in methanol to obtain a solution containing 50 mg per mL.

Standard solution—Dilute the *Test solution* quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of 0.1 mg per mL.

Application volume: 10 µL.

Developing solvent system: a mixture of ethyl acetate and methanol (80:20).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Place two 50-mL beakers, each containing 30 mL of ammonium hydroxide, on the bottom of a chromatographic chamber that is lined with filter paper and contains the *Developing solvent system,* and allow to equilibrate for 1 hour. Position the plate in the chromatographic chamber, and develop the chromatogram until the solvent front has moved about two-thirds of the length of the plate. Remove the plate from the chamber, mark the solvent front, and dry the plate for 3 hours in a current of warm air. Place the plate in a chamber containing iodine vapor, and allow to react for at least 15 hours.

Compare the intensities of the brown spots appearing on the chromatogram: any secondary spot obtained from the *Test solution* is not more intense than the corresponding spot obtained from the *Standard solution.* Not more than 0.2% is found.

TEST 2—

Sodium dodecyl sulfate solution, Mobile phase, and *Resolution solution*— Prepare as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Metoprolol Succinate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.0 µg per mL.

Test solution—Transfer about 50 mg of Metoprolol Succinate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see Chromatography ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between metoprolol related compound A and metoprolol related compound B is not less than 2.5; and the resolution, *R,* between metoprolol related compound B and metoprolol related compound C is not less than 1.5. [Note—The relative retention times are about 0.6 for metoprolol related compound C, 0.7 for metoprolol related compound B, 0.8 for metoprolol related compound A, 1.0 for metoprolol, and 5.0 and 5.2 for the two diastereomers of metoprolol related compound D.] Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Metoprolol Succinate taken by the formula:

$$100(C_S/C_T)(r_i/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Metoprolol Succinate RS in the *Standard solution;* C_T is the concentration of metoprolol succinate in the *Test solution;* r_i is the individual peak response of related impurities; and r_S is the peak response obtained from the *Standard solution:* not more than 0.1% of any single impurity is found, and not more than 0.5% of total impurities is found. [Note—The sum of the peak responses for the two diastereomers of metoprolol related compound D is used in the above calculation to report the amount of metoprolol related compound D.]

Assay—

Sodium dodecyl sulfate solution—Add 1.3 g of sodium dodecyl sulfate to 1 L of aqueous phosphoric acid, 0.1% (w/v).

Mobile phase—Prepare a filtered and degassed mixture of *Sodium dodecyl sulfate solution* and acetonitrile (60:40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution in *Mobile phase* containing about 5 µg each of USP Metoprolol Succinate RS, USP Metoprolol Related Compound A RS, USP Metoprolol Related Compound B RS, USP Metoprolol Related Compound C RS, and USP Metoprolol Related Compound D RS per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Metoprolol Succinate RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.08 mg per mL.

Test preparation—Transfer about 80 mg of Metoprolol Succinate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see Chromatography ⟨621⟩)—The liquid chromatograph is equipped with a 223-nm detector and a 4-mm × 12.5-cm column that contains 4-µm packing L7. The column temperature is maintained at 30°. The flow rate is about 0.9 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between metoprolol related compound A and metoprolol related compound B is not less than 2.5; and the resolution, *R,* between metoprolol related compound B and metoprolol related compound C is not less than 1.5. [Note—The relative retention times are about 0.6 for metoprolol related compound C, 0.7 for metoprolol related compound B, 0.8 for metoprolol related compound A, 1.0 for metoprolol, and 5.0 and 5.2 for the two diastereomers of metoprolol related compound D.] Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Inject equal volumes (about 10 µL) of the *Standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms for at least 1.5 times the retention of the metoprolol peak, and measure the peak responses. Calculate the quantity, in mg, of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ in the portion of Metoprolol Succinate taken by the formula:

$$1000C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Metoprolol Succinate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Test preparation* and the *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
METOPROLOL SUCCINATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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