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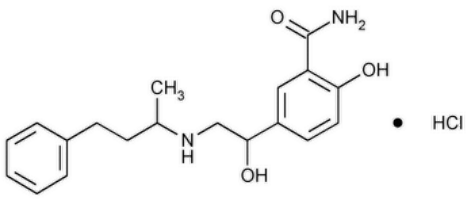
Labetalol Hydrochloride



$C_{19}H_{24}N_2O_3 \cdot HCl$ 364.87

Benzamide, 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride.

5-[1-Hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide monohydrochloride CAS RN®: 32780-64-6; UNII: 1GEV3BAW9J.

» Labetalol Hydrochloride contains not less than 97.5 percent and not more than 101.0 percent of $C_{19}H_{24}N_2O_3 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—

USP Labetalol Hydrochloride RS

Identification—

Change to read:

A: ▲*Spectroscopic Identification Tests* ⟨197⟩*, Infrared Spectroscopy: 197M*▲ (CN 1-May-2020) ·

B: It responds to the tests for *Chloride* ⟨191⟩.

pH ⟨791⟩**:** between 4.0 and 5.0, in a solution (1 in 100).

Loss on drying ⟨731⟩**:** Dry it in a vacuum at 105° for 4 hours: it loses not more than 1.0% of its weight.

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

Chromatographic purity—

Detection reagent—Transfer 2.5 g of cadmium acetate to a 500-mL volumetric flask, add 10 mL of glacial acetic acid, dilute with alcohol to volume, and mix. Just prior to use, prepare a 0.2 in 100 solution of ninhydrin in the cadmium acetate solution for use as the *Detection reagent.*

Solvent mixture—Prepare a solution of methanol and water (4:1), and mix.

Ammonium chloride reference solution—Dissolve 60 mg of ammonium chloride in 10.0 mL of water, and mix.

Standard stock solution—Dissolve USP Labetalol Hydrochloride RS in *Solvent mixture,* and mix to obtain a solution having a known concentration of 40 mg per mL.

Standard solution 1—Quantitatively dilute a portion of the *Standard stock solution* with *Solvent mixture* to obtain a solution having a known concentration of 0.2 mg per mL.

Standard solution 2—Quantitatively dilute a portion of the *Standard solution 1* with *Solvent mixture* to obtain a solution having a known concentration of 0.1 mg per mL.

Test solution—Dissolve 200 mg of Labetalol Hydrochloride in 5.0 mL of *Solvent mixture,* and mix.

Procedure I—Apply separately 5-µL portions of the *Standard stock solution, Standard solution 1, Standard solution 2,* and the *Test solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatograms in a solvent system consisting of a mixture of dichloromethane, methanol, and ammonium hydroxide (15:5:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light: the R_F value of the principal spot from the *Test solution* corresponds to that of the principal spot from the *Standard stock solution.*

Spray the plate with *Detection reagent,* heat the plate at 105° for 15 minutes, cool to room temperature, and examine the chromatogram: no individual secondary spot observed in the chromatogram of the *Test solution* is greater in size or intensity than the principal spot observed in the chromatogram of *Standard solution 1* (0.5% each). [Note—The spots appear as dark orange spots on a light orange to yellow background. A "negative image" spot (white) near the origin may be observed in the chromatogram of the *Test solution.* This is due to the formation of ammonium chloride during the chromatographic procedure and may be ignored.]

Procedure II—Apply separately 10-µL portions of the *Ammonium chloride reference solution*, the *Standard stock solution, Standard solution 1, Standard solution 2,* and the *Test solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩), coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatograms in a solvent system consisting of a mixture of ethyl acetate, isopropyl alcohol, water, and ammonium hydroxide (25:15:8:2) until the solvent front has moved about three-

fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light: no individual secondary spot (other than that due to ammonium chloride) observed in the chromatogram of the *Test solution* is greater in size or intensity than the principal spot observed in the chromatogram of *Standard solution 1* (0.5% each).

Total impurities—The sum of the intensities of all secondary spots (other than those due to ammonium chloride) observed in the chromatograms of the *Test solution* from both *Procedure I* and *Procedure II* does not exceed 1.0%.

Diastereoisomer ratio—

1-Butaneboronic acid solution—Dissolve 1-butaneboronic acid in pyridine, previously dried over a suitable molecular sieve, and mix to obtain a solution having a known concentration of 20 mg per mL.

System suitability solution—Dissolve an accurately weighed quantity of USP Labetalol Hydrochloride RS in *1-Butaneboronic acid solution,* and dilute quantitatively and stepwise with *1-Butaneboronic acid solution* to obtain a solution having a known concentration of about 1.4 mg of USP Labetalol Hydrochloride RS per mL. Allow the solution to stand at room temperature for 20 minutes before using.

Test solution—Transfer about 1 mg of Labetalol Hydrochloride to a 1-mL reaction vial, add 0.7 mL of *1-Butaneboronic acid solution,* and mix until the labetalol hydrochloride is completely dissolved. Allow the solution to stand at room temperature for 20 minutes before using.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 1.8-m glass column packed with 10% phase G3 on 100- to 120-mesh support S1AB. The column temperature is maintained at about 320°, and the injection port and the detector block temperatures are maintained at about 340°. Nitrogen is used as the carrier gas at the flow rate of about 30 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for the diastereoisomer B 1-butaneboronate derivative and 1.0 for the diastereoisomer A 1-butaneboronate derivative; the resolution, *R,* between the diastereoisomer A 1-butaneboronate derivative and diastereoisomer B 1-butaneboronate derivative peaks is not less than 1.5; and the relative standard deviation of the ratios of the peak areas of the diastereoisomers for replicate injections is not more than 2.0%.

Procedure—Inject about 2 µL of the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the diastereoisomer A content, in percentage, taken by the formula:

$$100 r_A/(r_A + r_B)$$

in which r_A is the peak area of the diastereoisomer A 1-butaneboronate derivative peak; and r_B is the peak area of the diastereoisomer B 1-butaneboronate derivative peak. The diastereoisomer A content is not less than 45.0% and not more than 55.0%.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of 0.1 M monobasic sodium phosphate and methanol (65:35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Labetalol Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.4 mg per mL.

Assay preparation—Transfer about 40 mg of Labetalol Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 20-cm column that contains packing L1 and is maintained at 60 ± 1°. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency determined from the analyte peak is not less than 700 theoretical plates; the tailing factor for the analyte peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of labetalol hydrochloride ($C_{19}H_{24}N_2O_3 \cdot HCl$) in the portion of Labetalol Hydrochloride taken by the formula:

$$100C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Labetalol Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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

Topic/Question	Contact	Expert Committee
LABETALOL HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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