B: *Infrared Absorption* ⟨197K⟩—

Test specimen—Transfer 5 mL of the *Test solution* prepared as directed for *Identification* test *A* to a glass-stoppered test tube, add 2 mL of 5 N hydrochloric acid, and extract with 5 mL of ether. Filter the ether phase. Grind 2 mL of the filtrate with 300 mg of potassium bromide, dry in a current of warm air, and prepare a disk: the IR spectrum of the *Test specimen* exhibits maxima only at the same wavelengths as that obtained from a similar preparation of succinic acid (*presence of succinate*).

Dissolution ⟨711⟩**—**

Medium: pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 500 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, 8, and 20 hours.

Determine the amount of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ dissolved by employing the following method.

pH 3.0 Phosphate buffer, Mobile phase, and *Standard solution*—Proceed as directed in the test for *Uniformity of dosage units.*

Procedure—Proceed as directed in the test for *Uniformity of dosage units,* except to use 5.0 mL of a filtered portion of the solution under test as the *Test solution,* and *Medium* as the blank, in comparison with a Standard solution having a known concentration of USP Metoprolol Succinate RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	not more than 25%
4	between 20% and 40%
8	between 40% and 60%
20	not less than 80%

Uniformity of dosage units ⟨905⟩: meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

pH 3.0 Phosphate buffer—Mix 50 mL of 1 M monobasic sodium phosphate and 8.0 mL of 1 M phosphoric acid, and dilute with water to 1000 mL. If necessary, adjust with 1 M monobasic potassium phosphate or 1 M phosphoric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *pH 3.0 Phosphate buffer* and acetonitrile (375:125). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve a quantity of USP Metoprolol Succinate RS, accurately weighed, in *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Test stock solution—Transfer 1 Tablet, accurately weighed, to a volumetric flask of suitable capacity to obtain a solution having a concentration of about 1 mg per mL of metoprolol succinate. Add about 5 mL of water, and allow the Tablet to disintegrate. Add a volume of alcohol such that when diluted to volume, the concentration of alcohol is 30%. Shake for 30 minutes. Add a portion of 0.1 N hydrochloric acid equivalent to about one half of the flask volume, and shake for 30 minutes. Dilute with 0.1 N hydrochloric acid to volume, and mix.

Test solution—Filter the *Test stock solution,* and discard the first 10 mL of the filtrate. Dilute the filtrate quantitatively with *Mobile phase* to obtain a solution containing about 0.05 mg per mL of metoprolol succinate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4-mm × 12.5-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

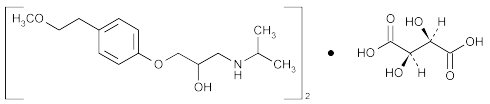
Procedure—Separately inject equal volumes (about 40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of metoprolol succinate $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ in the Tablet taken by the formula:

$$20CV(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Metoprolol Succinate RS in the *Standard solution; V* is the volume of the *Test stock solution* used to prepare the *Test solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Assay—Determine the mean value of the quantity, in mg, of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ in the Tablets analyzed in the test for *Uniformity of dosage units.*

Metoprolol Tartrate



$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$ 684.81

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

(±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt).

1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol (2:1) *dextro*-tartrate salt [56392-17-7].

» Metoprolol Tartrate contains not less than 99.0 percent and not more than 101.0 percent of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$, 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 Metoprolol Tartrate RS

Identification, *Infrared Absorption* ⟨197M⟩.

Specific rotation ⟨781S⟩**:** between +6.5° and +10.5° (*t* = 20°).

Test solution: 20 mg per mL, in water.

pH ⟨791⟩**:** between 6.0 and 7.0, in a solution (1 in 10).

Loss on drying ⟨731⟩**—**Dry it in vacuum at 60° for 4 hours: it loses not more than 0.5% of its weight.

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

Heavy metals, *Method I* ⟨231⟩**:** 0.001%.

Chromatographic purity—

Standard solution and *Standard dilutions*—Dissolve a suitable quantity of USP Metoprolol Tartrate RS, accurately weighed, in methanol, and dilute quantitatively and stepwise with methanol to obtain solutions having known concentrations of 1.0, 0.5, 0.2, and 0.1 mg per mL, respectively.

Test solution—Dissolve a quantity of Metoprolol Tartrate in methanol to obtain a solution containing 100 mg per mL.

Chromatographic chamber—Line a suitable chamber (see *Chromatography* ⟨621⟩) with absorbent paper, and pour into the chamber 250 mL of a mixture of chloroform, methanol, and ammonium hydroxide (80:15:2). Saturate the chamber for 1.5 hours before using.

Detecting reagent—Prepare separate solutions of potassium iodide (1 in 100) and soluble starch (prepared by triturating 3 g in 10 mL of cold water and adding the mixture to 90 mL of

boiling water with constant stirring). Just prior to use, mix 10 mL of each solution with 3 mL of alcohol.

Procedure—Apply separately 5-µL portions of the *Test solution* and each of the *Standard dilutions* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Place the plate in the *Chromatographic chamber,* seal the chamber, and allow the chromatogram to develop until the solvent front has moved about three-fourths of the length of the plate. Remove the plate, and dry in a current of warm air until the odor of ammonia is no longer perceptible (about 45 minutes). Place a beaker containing 0.5 g of potassium permanganate in a chamber. Add 5 mL of 6 N hydrochloric acid to the beaker, and allow to equilibrate for 5 minutes. Place the plate in the chamber for 5 minutes. Remove the plate from the chamber, allow to stand in a current of cool air for 1 hour, and spray with *Detecting reagent.* If spots other than the principal spot are observed in the lane of the *Test solution,* estimate the concentration of each by comparison with the *Standard dilutions:* the spots from the 1.0, 0.5, 0.2, and 0.1 mg per mL *Standard dilutions* correspond to 1.0%, 0.5%, 0.2%, and 0.1% of impurities, respectively; and the sum of any observed impurities in the *Test solution* is not greater than 1.0%.

Assay—Dissolve about 280 mg of Metoprolol Tartrate, accurately weighed, in 20 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using a glass electrode and a calomel electrode containing glacial acetic acid saturated with lithium chloride (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 34.24 mg of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$.

Metoprolol Tartrate Injection

» Metoprolol Tartrate Injection is a sterile solution of Metoprolol Tartrate in Water for Injection. It contains Sodium Chloride as a tonicity-adjusting agent. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$.

Packaging and storage—Preserve in single-dose, light-resistant containers, preferably of Type I or Type II glass.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS
USP Metoprolol Tartrate RS
USP Oxprenolol Hydrochloride RS

Identification—Place a volume of Injection, equivalent to about 40 mg of metoprolol tartrate, in a separator, add 4 mL of dilute ammonium hydroxide (1 in 3), and extract with 20 mL of chloroform, filtering the chloroform extract through chloroform-pre-rinsed anhydrous sodium sulfate. Evaporate the chloroform to dryness, and place in a freezer to congeal the residue: the IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Metoprolol Tartrate RS.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 25.0 USP Endotoxin Units per mg of metoprolol tartrate.

Sterility ⟨71⟩**—**It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined.*

pH ⟨791⟩: between 5.0 and 8.0.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Prepare a degassed solution by dissolving 961 mg of 1-pentanesulfonic acid sodium salt (monohydrate) and 82 mg of anhydrous sodium acetate in a mixture of 550 mL of methanol and 470 mL of water and adding 0.57 mL of glacial acetic acid.

Internal standard solution—Dissolve USP Oxprenolol Hydrochloride RS in freshly prepared *Mobile phase* to obtain a solution containing about 720 µg per mL.

Sodium chloride solution—Dissolve 9.0 g of sodium chloride in water to make 1000 mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Metoprolol Tartrate RS in *Sodium chloride solution* to obtain a stock solution having a known concentration of about 1000 µg per mL. Mix equal volumes, accurately measured, of this stock solution and of *Internal standard solution*.

Assay preparation—Dilute an accurately measured volume of Injection, if necessary, quantitatively with *Sodium chloride solution* to obtain a stock solution having a concentration of about 1000 µg per mL. Mix equal volumes, accurately measured, of this stock solution and of *Internal standard solution*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph three replicate injections of the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative standard deviation is not more than 2.0%, and the resolution factor between metoprolol tartrate and oxprenolol hydrochloride is not less than 2.0.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.8 for metoprolol tartrate and 1.0 for oxprenolol hydrochloride. Calculate the quantity, in mg, of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ in each mL of the Injection taken by the formula:

$$(L / D)(C)(R_U / R_S)$$

in which L is the labeled quantity, in mg, of metoprolol tartrate in the Injection; D is the concentration, in µg per mL, of metoprolol tartrate in the *Assay preparation,* on the basis of the labeled quantity in each mL of Injection taken and the extent of dilution; C is the concentration, in µg per mL, of USP Metoprolol Tartrate RS in the *Standard preparation;* and R_U and R_S are the peak response ratios of metoprolol tartrate to oxprenolol hydrochloride obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Metoprolol Tartrate Oral Solution

» Metoprolol Tartrate Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$. Prepare Metoprolol Tartrate Oral Solution 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Metoprolol Tartrate Oral Suspension*):

Metoprolol Tartrate powder	1 g
Vehicle for Oral Solution (regular or sugar-free), *NF*, a sufficient quantity to make	100 mL