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.

Metoprolol Succinate Extended-Release Tablets

» Metoprolol Succinate Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$.

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

Labeling—Label it to indicate the content of metoprolol succinate and its equivalent, expressed as metoprolol tartrate $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$.

USP Reference standards ⟨11⟩**—**
USP Metoprolol Succinate RS

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Transfer one or more Tablets, equivalent to about 200 mg of metoprolol succinate, to a stoppered centrifuge tube. Add about 40 mL of pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*) and 40 mL of methylene chloride, and shake for 5 minutes. Centrifuge, filter, and use the aqueous phase as the *Test solution*. Transfer 3 mL of the *Test solution* to a separator, add 2 mL of ammonium hydroxide, and extract with 20 mL of methylene chloride. Filter the methylene chloride phase. Grind 1 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 USP Metoprolol Succinate RS (*presence of metoprolol*).

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%.

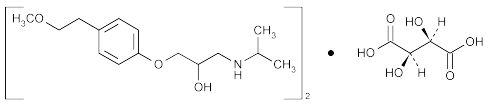
Procedure—Separately inject equal volumes (about 40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of metoprolol succinate $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ in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